TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

ANESTHESIOLOGY AND RESPIRATORY THERAPY

DEVICES PANEL MEETING

OPEN SESSION

This transcript has not been edited and FDA makes no representation regarding its accuracy

Pages 1 thru 137

Rockville, Maryland
December 18, 1998

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

ajh

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

12 58 '98 DEC 28 P2:46

ANESTHESIOLOGY AND RESPIRATORY THERAPY

DEVICES PANEL MEETING

OPEN SESSION

Friday, December 18, 1998

12:25 p.m.

Room 020B
9200 Corporate Boulevard
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002

PARTICIPANTS

Arthur Slutsky, M.D., Chairman
Michael Bazaral, M.D., Ph.D., Executive Secretary

MEMBERS

Lois Bready, M.D.
Robert Kacmarek, Ph.D.
Terri G. Monk, M.D.
Donald S. Prough, M.D.
Catherine S.H. Sassoon, M.D.
Michael T. Amato, Industry Representative
Ellen Rosenthal, Consumer Representative

PANEL CONSULTANTS

Reese H. Clark, M.D.
Franklin Dexter, M.D., Ph.D.
Michael Roizen, M.D.

INVITED SPEAKER

Avi Nahum, M.D.

FDA

Thomas P. Callahan, M.D.

C O N T E N T S

	Page No.
Conflict of Interest Statement, Introductions, Announcements	4
Presentation of Year 2000 Software Problems Donna-Bea Tillman, Ph.D.	7
Presentation of a Certificate of Appreciation to Michael Roizen, M.D. Thomas Callahan, Ph.D.	13
Presentation on Recognized Standards Emil Wang	14
Open Public Hearing	19
Brief Presentation of five FDA Questions on Tracheal Gas Insufflation Christy Foreman	20
Summary of Tracheal Gas Insufflation Avi Nahum, M.D.	22
Prepared Public Comments on Tracheal Gas Insufflation Adi Miro, M.D.	61
Peter M. Fitzgerald	73
Panel Discussion of each of Five Questions on Tracheal Gas Insufflation	81

1 P R O C E E D I N G S

2 DR. SLUTSKY: We are in open session. My name is
3 Art Slutsky. I am chairing this session today. It is an
4 open panel session that covers a few areas.
5 We are going to start first with the conflict of
6 interest statement by Mike Bazaral from the FDA.

7 **Conflict of Interest Statement**

8 **Introductions, Announcements**

9 DR. BAZARAL: The following announcement addresses
10 conflict of interest issues associated with this meeting and
11 is made a part of the record to preclude even the appearance
12 of an impropriety.
13 To determine if any conflict existed, the Agency
14 reviewed the submitted agenda and all financial interests
15 reported by the committee participants. The conflict of
16 interest statutes prohibit special government employees from
17 participating in matters that could affect their or their
18 employer's financial interests. However, the Agency has
19 determined that participation of certain members and
20 consultants, the need for whose services outweighs the
21 potential conflict of interest involved, is in the best
22 interests of the government.
23 For participation in today's discussion, all the
24 panelists have been granted limited waivers of their
25 employment or their financial interests in firms that could

1 potentially be affected by the panel's decisions. This
2 includes Drs. Lois Bready, Robert Kacmarek, Terri Monk,
3 Donald Prough, Catherine Sassoon, Arthur Slutsky, Reese
4 Clark, Franklin Dexter, Michael Roizen, and Ms. Ellen
5 Rosenthal.
6 Copies of these waivers may be obtained from the
7 Agency's Freedom of Information Office, Room 12A-15 of the
8 Parklawn Building.
9 In the event that the discussions involve any
10 other products or firms not already on the agenda for which
11 an FDA participant has a financial interest, the participant
12 should excuse him or herself from such involvement and the
13 exclusion will be noted for the record.
14 With respect to all other participants, we ask in
15 the interest of fairness that all persons making statements
16 or presentations disclose any current or previous financial
17 involvement with any firm whose products they may wish to
18 comment on.
19 DR. SLUTSKY: Thanks very much, Mike.
20 Next, we will have introductions. You have met
21 Mike Bazaral. You have met myself. We will move to the
22 right.
23 DR. CLARK: I am Reese Clark from Fort Lauderdale
24 where I work for Pediatrix Medical Group as Director of
25 Research and also hold an appointment as Associate

1 Consulting Professor at Duke University.

2 DR. DEXTER: Frank Dexter, University of Iowa. I

3 am an anesthesiologist.

4 DR. SASSOON: Catherine Sassoon, adult

5 pulmonologist, from the University of California, Irvine,

6 and Long Beach Medical Center.

7 MR. AMATO: Michael Amato, Senior Vice President,

8 Monaghan Medical Corporation.

9 DR. CALLAHAN: Tom Callahan, Director of

10 Cardiovascular and Respiratory here at the FDA.

11 MS. ROSENTHAL: Ellen Rosenthal. I am the

12 consumer representative. I have a background in

13 engineering.

14 DR. KACMAREK: Bob Kacmarek, Director of

15 Respiratory Care at Massachusetts General Hospital.

16 DR. MONK: I am Terri Monk. I am an

17 anesthesiologist at the University of Florida.

18 DR. ROIZEN: I am Mike Roizen. I am an

19 anesthesiologist and internist at the University of Chicago.

20 DR. PROUGH: Don Prough. I am an anesthesiologist

21 and intensivist at the University of Texas Medical Branch at

22 Galveston.

23 DR. BREADY: Lois Bready. I am an

24 anesthesiologist. I am on the faculty at the University of

25 Texas Health Science Center in San Antonio.

1 DR. SLUTSKY: Thanks very much.

2 You all have probably received or picked up a copy
3 of the agenda. There is only one slight change. We are
4 going to move the second speaker, Donna-Bea Tillman. She is
5 going to speak first, and is going to talk about the
6 presentation on Year 2000 software problems.

7 **Presentation on Year 2000 Software Problems**

8 DR. TILLMAN: I am here to just give you a little
9 bit of an update on what CDRH is doing to address the Year
10 2000 date problem with medical devices.

11 [Slide.]

12 I hope that most of you have heard about what the
13 Year 2000 problem is by now. It has certainly been in the
14 press enough. The problem basically is that there is a
15 failure of some computer systems to properly process dates
16 representing the year, and especially when they only use two
17 digits for the date.

18 So, for example, when it becomes 2000, the
19 question is does 00 refer to 2000 or 1900.

20 [Slide.]

21 Medical devices can be subject to Year 2000
22 problems. Over the past 10 years or so, we have seen a
23 dramatic increase in the number of microprocessors or PC-
24 controlled medical devices, so there is certainly the
25 potential for medical devices to be subject to this problem.

1 There are also software applications that you may
2 be using in your clinical practice that could potentially be
3 impacted by the Year 2000 problem. There is device
4 interfaces to databases, patient recordkeeping systems, and
5 then there are a lot of devices that may have
6 microprocessors in them where you really don't even know
7 that there is a microprocessor in them.
8 A lot of the lights and a lot of the equipment
9 that are used in ORs nowadays have embedded chips in them,
10 that people probably aren't even aware of.
11 [Slide.]
12 So, what is FDA doing to address this problem? We
13 have taken a couple of different approaches. We have sent
14 several letters to manufacturers. We have provided guidance
15 to manufacturers reminding them this is a problem they need
16 to do something about.
17 We have established a database of product
18 information that's available through the Internet. We have
19 done monitoring and assessment activities out in the field,
20 and we have also tried to educate the public, the
21 clinicians, and manufacturers about this problem. That is
22 one of the reasons I am talking to you today.
23 [Slide.]
24 FDA started working on the Year 2000 problem back
25 in around 1997. In that year, we sent our first letter to

1 manufacturers where we advised them of the problem, and we
2 told them that if they went out and modified their devices
3 to address the Year 2000 problem, they would not need to
4 submit a new submission to us, and that as long as they
5 fixed the problem before Year 2000, we wouldn't consider it
6 to be a recall. Obviously, most of the manufacturer
7 community is quite interested in having to have massive
8 recalls.
9 [Slide.]
10 We are also participating in a biomedical
11 equipment working group that is governmentwide, and it is
12 chaired by our department. That group is focusing on sort
13 of broad issues across the health community with Year 2000.
14 In the spring of this year, we established a web
15 site that I am going to talk briefly about, and we have
16 issued guidance to the industry on what our expectations
17 are, as well.
18 [Slide.]
19 The Biomedical Equipment database is on FDA's
20 worldwide web site. I will give you the address in the next
21 slide. Basically, what happens is that manufacturers
22 voluntarily submit information that tells us to what extent
23 their products are Year 2000 compliant.
24 They certify that groups of devices are Year 2000
25 compliant, and then they tell you which ones may not be.

1 This web site is continuously updated. You can search it by
2 the manufacturer's name, and the information can be
3 downloaded off of the web site.
4 [Slide.]
5 That is the address for the FDA web site, and you
6 can find Year 2000 right on the home page there.
7 [Slide.]
8 We have also sent additional letters to
9 manufacturers, and I am not going to go into all the gory
10 details, but we have basically reminded them that this
11 problem is getting closer and closer, and we have also
12 reminded them that the Year 2000 problem could potentially
13 impact on their manufacturing processes, because a lot of
14 manufacturing processes nowadays are computer controlled,
15 and we want to make sure that there aren't any problems with
16 lack of availability of critical devices or device
17 components.
18 [Slide.]
19 The database on the web site, as I said before,
20 the manufacturer lists their products that are noncompliant
21 with the Year 2000, and then they certify that the rest are
22 compliant.
23 The other useful thing is many medical device
24 manufacturers have their own web sites that talk about the
25 Year 2000 problem. So, if you go onto our web site and you

1 find a manufacturer, you will often find a link to their web
2 site, and you can go and find more detailed information
3 about Year 2000 compliance.
4 [Slide.]
5 Basically, the other important thing to keep in
6 mind here is what do we mean when we say Year 2000
7 compliant. It basically means that the equipment will
8 process the dates correctly now and into the future.
9 The important thing that we want to drive home is
10 just because a product is not compliant with the Year 2000,
11 it doesn't necessarily mean it is a risk to the public
12 health.
13 A lot of the equipment out there that may use date
14 information may use it in such a way that is obvious to you
15 or that really doesn't significantly impact the public
16 health, but we are still trying to get people to get this
17 cleared up as quickly as possible.
18 [Slide.]
19 What has our product database shown us? Many of
20 the companies haven't reported their information to the
21 database yet. We are continuing to try and urge them to
22 update it. Most of the noncompliant products have to do
23 with date stamping, and these are really the low risk issues
24 where it is going to be pretty obvious to you if you see the
25 date that it is not what it should be.

1 There has only been a limited number of products
2 that we have identified that have significant operational
3 problems, and the manufacturers of those devices are aware
4 of the problems and are working to provide solutions.
5 [Slide.]
6 We can require a recall of a device which we think
7 presents a significant risk to the public health, and we
8 will continue to monitor reports of Year 2K problems that we
9 see. We have people on our staff who are continuously
10 looking at the web site to see what products are being
11 reported, and we will be very active in trying to make sure
12 that we take action where appropriate.
13 [Slide.]
14 What do we want you to do and why have we bothered
15 to waste your busy time with this? We are trying to get
16 some additional information about this problem from our
17 panels, and we would like to have you provide us with advice
18 regarding any problematic devices that you may know of.
19 If you know of any devices that you think could
20 potentially have a Year 2K problem, we would really like to
21 hear about it. We are especially interested in classes or
22 groups of devices that you are familiar with where you think
23 the dates could present risk to the patients if they are not
24 addressed.
25 If you have any other ideas about things we can do

1 to reduce risks from the Year 2000 problem, we would love to
2 hear from you.
3 [Slide.]
4 The person who is in charge of this program is Tom
5 Shope. You can also address your comments to your panel
6 exec. sec., Dr. Bazaral, and he can forward them on to the
7 appropriate people.
8 I thank you for your attention.
9 DR. SLUTSKY: Thanks very much.
10 Any questions from the panel? I think in terms of
11 specific advice, this is not the appropriate place for that.
12 We will send those in to whatever that address was or to
13 Mike.
14 DR. TILLMAN: You can send them to Mike.
15 DR. SLUTSKY: Okay.
16 The next speaker is Tom Callahan, Director of the
17 Division of Cardiovascular, Respiratory, and Neurological
18 Devices.
19 **Presentation of Certificate of Appreciation**
20 **to Michael Roizen, M.D.**
21 DR. CALLAHAN: Thank you. I would like to ask Dr.
22 Roizen, if you would just come up here for a minute.
23 You may or may not know, Dr. Roizen has been a
24 voting panel member for four years, and his actual voting
25 status runs out, and for one of those four years he was

1 actually a panel chairperson.

2 Dr. Alpert mentioned this morning how much we

3 value all of your input, and to do it for four years in this

4 forum I think is commendable. I know you all participate in

5 other governmental activities or advisory boards, but I

6 think these kinds of activities, where you actually sit in

7 front and make controversial decisions in an open session,

8 in front of sometimes protagonists that are looking for an

9 alternate decision.

10 So, on behalf of the Commissioner of FDA, there is

11 a Notice of Appreciation here from Dr. Freedman and also a

12 Certificate of Appreciation from the Center and the Center

13 for Devices and Radiologic Health, and we hope that you

14 continue in an advisory capacity now that your voting status

15 has ceased.

16 DR. ROIZEN: I would be privileged to.

17 DR. CALLAHAN: Thank you very much.

18 DR. ROIZEN: Thank you.

19 [Applause.]

20 DR. SLUTSKY: Thanks very much.

21 The next speaker is Emil Wang, FDA reviewer, who

22 is going to give us a presentation on recognized standards.

23 **Presentation on Recognized Standards**

24 MR. WANG: Good afternoon. My name is Emil Wang.

25 I am a reviewer in the Anesthesiology and Defibrillator

1 Devices Branch.

2 I would like to give everybody a quick status

3 update on agency reengineering update on the use of

4 consensus standards in the premarket review of medical

5 devices and to relate that to branch activities.

6 [Slide.]

7 The purpose as described in the CDRH guidance on

8 the recognition and use of consensus standards is to provide

9 guidance to industry and FDA reviewers on the voluntary use

10 of FDA recognized national and international consensus

11 standards including declarations of conformity to these

12 recognized standards during the evaluation of premarket

13 submissions for medical devices.

14 The guidance will assist manufacturers who elect

15 to declare conformity with consensus standards to meet all

16 or part of medical device review requirements. FDA believes

17 that conformance with applicable recognized consensus

18 standards can help to simplify their premarket review

19 process by reducing the need for testing information already

20 addressed by an FDA-recognized consensus standard.

21 Consensus standards may address a variety of

22 medical device review requirements, such as

23 biocompatibility, environmental testing, device-specific

24 descriptive tests, specifications, design aspects, and

25 labeling information.

1 [Slide.]

2 I would like to describe some very general

3 limitations and caveats on the use of consensus standards

4 where conformity to consensus standards will not satisfy all

5 requirements or device evaluation in the United States.

6 First of all, use of recognized consensus

7 standards does not affect FDA's ability to obtain any

8 information authorized by statute or regulations.

9 Secondly, a specific device may raise safety or

10 efficacy issues not addressed by a recognized consensus

11 standard.

12 Lastly, each specific recognized consensus

13 standard will specify the extent of recognition, if any.

14 [Slide.]

15 I would like to take this opportunity to provide a

16 brief update on branch consensus standard activities.

17 To date, 22 anesthesia and respiratory consensus

18 standards have been recognized covering devices such as

19 resuscitators, ventilators, anesthesia machines, tracheal

20 tubes, oxygen concentrators, hyperbaric facilities, and so

21 forth.

22 I have listed some examples of anesthesia and

23 respiratory-specific recognized consensus standards.

24 Future branch standards activities include a

25 continuing process for reviewers to review and recognize

1 consensus standard candidates. Modifications to the list of
2 recognized consensus standards will be announced in the
3 Federal Register on a periodic basis.
4 [Slide.]
5 This is an example of a supplemental sheet for a
6 specific anesthesia and respiratory recognized consensus
7 standard. This in particular pertains to ASTM-F920 for
8 resuscitators. You will notice that this supplemental data
9 sheet will specify the standard that is recognized and will
10 reference the address of the national or international
11 standards organization.
12 Some of the relevant points I would like to bring
13 your attention to is the extent of recognition. This
14 particular standard has been completely recognized with no
15 limitations, and the supplemental sheet will also describe
16 the relevant guidance that should be taken in consideration
17 for a premarket submission, as well as a contact person for
18 any questions or additional information.
19 [Slide.]
20 This is another supplemental sheet for ASTM-F1100
21 for ventilators. I would like to bring your attention in
22 particular to the extent of recognition, which lists some
23 limitations and some additional issues that sponsors should
24 address to assure a complete premarket submission.
25 [Slide.]

1 In conclusion, the goal of the consensus standard
2 program is to improve the efficiency of premarket review
3 process whereby declaration of conformity to a recognized
4 consensus standard will eliminate the need for the
5 substantive review of actual test data for those aspects of
6 a device addressed by the standard.
7 I would like to reiterate that this program is a
8 continuous process. Any person may recommend a consensus
9 standard as a candidate for recognition as described in the
10 Federal Register Notice.
11 That concludes my presentation. Thank you very
12 much.
13 DR. SLUTSKY: Emil, I think you answered the
14 question, but I was going to ask you, how does a standard
15 come to be FDA recognized?
16 MR. WANG: Well, the standard is proposed as a
17 candidate for recognition, and the Office of Science and
18 Technology runs this overall program, and they will refer
19 the specific standard to the appropriate review group.
20 The reviewers will then go over each standard and
21 raise any additional issues that aren't addressed by the
22 standard, and those are addressed in the limitations. So,
23 the reviewers will look through the standards individually
24 and to recommend that the standard be adopted.
25 DR. SLUTSKY: Any questions from the panel

1 members?

2 [No response.]

3 DR. SLUTSKY: Thanks very much.

4 **Open Public Hearing**

5 The next part of this meeting is an open public

6 hearing. The idea here is to provide the public the

7 possibility to address any comments, concerns, compliments

8 to the FDA panel, FDA staff for the next half-hour or hour

9 or so.

10 I think it is important that we are going to be

11 talking later on about tracheal gas insufflation, and I

12 think all comments related to TGI, tracheal gas

13 insufflation, should come later.

14 So, if there are any comments, any individuals,

15 anybody from the public want to make any comments?

16 [No response.]

17 DR. SLUTSKY: Have any of the FDA staff heard from

18 anybody who would like to make comments?

19 DR. BAZARAL: Not to my knowledge other than what

20 is on the agenda.

21 DR. SLUTSKY: Let the record show that no one in

22 the public wanted to make any comments.

23 We are now going to proceed with the main topic

24 today, and that is tracheal gas insufflation. The way this

25 is going to work is that Christy Foreman from the FDA will

1 give us a brief presentation of five questions that the FDA
2 would like the panel to address.
3 Avi Nahum, who is an expert in the area, will give
4 us a brief review of tracheal gas insufflation. Then, there
5 are some public comments from the individuals who have
6 requested to speak. We will then go back, review the
7 questions, and then discuss each of the questions
8 individually.
9 Christy.
10 **Brief Presentation of Five FDA Questions on**
11 **Tracheal Gas Insufflation**
12 MS. FOREMAN: Good afternoon. My name is Christy
13 Foreman. I am a reviewer in the Anesthesiology and
14 Defibrillator Devices Branch. That is in the Division of
15 Cardiovascular, Respiratory, and Neurological Devices.
16 We have convened this meeting of the
17 Anesthesiology and Respiratory Therapy Devices Panel to
18 discuss general issues related to tracheal gas insufflation
19 devices used to provide part or all of the breathing gas for
20 the treatment of respiratory failure or respiratory
21 insufficiency.
22 We are aware of publications and research in the
23 area of tracheal gas insufflation, therefore, in the
24 anticipation of future submissions, we would like to define
25 the criteria used to evaluate tracheal gas insufflation

1 systems and define the critical components of TGI systems.

2 We have five questions to pose to the panel

3 specific to TGI. In summary, those questions are:

4 1. For the evaluation of effectiveness of TGI, is

5 reduction of minute ventilation an appropriate endpoint?

6 2. For adults, is there sufficient understanding

7 of TGI to be reasonably sure that TGI will not have worse

8 outcomes? Or, should the FDA review outcome data?

9 3. Are there special considerations in relation

10 to the ventilation of children, infants, newborns, or

11 premature infants?

12 4. What are the minimum system functions such as

13 a gas source, humidification, catheter or other distal

14 delivery device, monitoring and an interface that are

15 essential to provide TGI for clinical use?

16 5. What specific safety provisions, such as

17 distal pressure monitoring, are important or essential?

18 I would like to ask you to think about these

19 questions as you hear presentations from both Dr. Nahum and

20 manufacturers. At the end of the presentations, we will ask

21 you to discuss these five questions.

22 Thank you.

23 DR. SLUTSKY: Thanks, Christy.

24 I should point out in reviewing these, that

25 probably when we go to discuss these, Question 2, we will

1 discuss first. It seems to make more sense to discuss --
2 can you put the questions back up again -- I think it makes
3 more sense to discuss Question No. 2 first, but we will deal
4 with that when we get to that point.
5 Thanks very much.
6 I would like to now introduce Avi Nahum from the
7 University of Minnesota. Avi is Associate Professor and has
8 published widely on tracheal gas insufflation. Avi was
9 asked to review TGI, but not necessarily to specifically
10 address each of the five questions in a point-by-point way.
11 So, he is going to give us a general overview of tracheal
12 gas insufflation.
13 Avi.
14 **Summary of Tracheal Gas Insufflation**
15 DR. NAHUM: Thank you, Arthur.
16 First, let me thank Dr. Bazaral for inviting me to
17 speak in this meeting. It is quite impressive that with one
18 invitation, one becomes an expert.
19 [Slide.]
20 I was asked specifically not to address the
21 questions, so what I will try to do is concentrate on three
22 aspects of TGI: first, how it works; second, what is the
23 clinical applications that are available; and, third, some
24 of the problems associated with TGI.
25 This is the recipes that I developed.

1 DR. SLUTSKY: I think that has been read by people
2 in Washington, Avi.
3 [Laughter.]
4 [Slide.]
5 Let me first start by describing what does TGI do.
6 Well, TGI is a technique, a rather simple technique, and it
7 all consists of introduction of a fresh gas at the tracheal
8 level.
9 In normal ventilation, at the end of expiration,
10 the anatomic dead space has carbon dioxide that has been
11 exhaled from the alveoli, and during the next inspiration
12 this carbon dioxide is recycled. As a result, efficacy of
13 each breath in terms of CO_2 elimination is obviously
14 decreased.
15 What you accomplish with TGI is you flush this
16 anatomic dead space free of carbon dioxide, and also you can
17 enhance some mixing, turbulent mixing in front of the
18 catheter. As a result, when the next inspiratory cycle
19 arrives, the amount of carbon dioxide that is recycled into
20 the lung decreases, and this, of course, increases the
21 efficacy of carbon dioxide elimination.
22 [Slide.]
23 So, the mechanism of action of TGI, in terms of
24 CO_2 clearance is mainly washout of proximal anatomic dead
25 space and then, to a certain extent, there is some turbulent

1 mixing due to the jet that is present in front of the
2 catheter.
3 [Slide.]
4 The TGI can be delivered in a variety of fashions.
5 In its early application, it was a continuous, in other
6 words, it was a constant source of fresh gas that was at the
7 trachea, and later, the investigators started exploring
8 phasing the delivery to either the inspiratory or expiratory
9 phases of the respiratory cycle.
10 Then, of course, you can start playing games with
11 it and put certain delays where you can have it kick in
12 early in expiration or late in expiration or turn off just
13 before expiration, and I will discuss what are some of the
14 ramifications of those delays.
15 [Slide.]
16 In terms of CO_2 elimination, there are certain
17 major factors that play a role. If you want the CO_2
18 elimination efficacy to be highest, then, you need to choose
19 a system where anatomic dead space rather than the alveolar
20 dead space predominates.
21 Number two, there is some kind of a saturation
22 with flow rate. Initially, you get a lot of CO_2
23 elimination, but later the system starts to saturate and
24 increasing the flow rate beyond a certain point usually does
25 not help. These flow rates in clinical practices have been

1 somewhere around 10 to 15 liters per minute.

2 In terms of catheter shape and location, I will

3 show you some of the data that we produce, but it turns out

4 that placing the catheter somewhere closer to main carina

5 seems to give the best application.

6 In terms of monitoring elimination efficacy, you

7 can use end-tidal CO_2 monitoring, and I will show you some

8 data on that, as well.

9 [Slide.]

10 First, let me address the issue of alveolar dead

11 space. As you know, when you have lung injury, you create

12 alveolar dead space, and that dead space will, in turn,

13 decrease the CO_2 that is being exhaled by the alveoli and

14 has the potential to decrease the efficacy of CO_2

15 elimination of TGI.

16 In the study that we perform, I plotted on the y

17 axis the arterial PCO_2 level; under the dotted line,

18 conventional mechanical ventilation before injury, after

19 oleic acid injury, and after oleic acid injury where we

20 increase the tidal volume, so that we match the CO_2 to the

21 level before injury.

22 Now, at each stage, we then apply tracheal gas

23 insufflation, and those are the diamonds that you are

24 seeing, the solid line.

25 As you can see, in a normal animal, the TGI

1 dropped the PCO_2 by about 15 to 20 millimeters of mercury.
2 When the PCO_2 was allowed to rise, despite generating
3 alveolar dead space, since the anatomic dead space now
4 contains more carbon dioxide, the amount of PCO_2 that you
5 decrease by TGI in fact increased.
6 Now, if you bring the PCO_2 to the levels before
7 injury, you can then see that the efficacy of TGI becomes
8 less. So, the point that I am trying to make is yes, in the
9 case of lung injury with alveolar dead space production, you
10 do decrease the efficacy to TGI. However, if you operate at
11 higher PCO_2 levels, then, you regain the efficacy of TGI.
12 [Slide.]
13 A couple words about the position of the catheter.
14 I have here two panels, A and B. If you just concentrate on
15 A, the y axis is again $PaCO_2$, and the x axis is catheter
16 flow rate in terms of liters per minute.
17 In this panel, the position refers to the tip of
18 the catheter in terms of centimeters above the main carina,
19 1, 5, or 10 centimeters above the carina. You can see that
20 at low flow rates, the position is not very important,
21 however, at higher flow rates, the best data is obtained
22 from the position that is closest to the main carina.
23 In the same study, we actually placed catheters
24 beyond the main carina, and there was no additional benefit.
25 So, we believe based on this study that positioning the

1 catheter 1 to 2 centimeters above the main carina pretty
2 much gives you optimum CO_2 clearance.
3 [Slide.]
4 A couple of words about end-tidal CO_2. You can
5 monitor how much CO_2 elimination you are achieving by TGI by
6 just simply looking at the capnogram.
7 Here again I have, on the y axis, the CO_2
8 concentration as measured by a capnogram at the tip of the
9 endotracheal tube, and on the x axis I have time.
10 I have plotted capnograms superimposed at TGI
11 catheter flow rates of zero, in other words, during
12 conventional mechanical ventilation, at flow rates of 2, 6,
13 and 10 liters per minute.
14 If you look at zero, which is conventional
15 mechanical ventilation, you have a slope on the end-tidal
16 CO_2, because this is an injured dog. As you start to
17 perform TGI and increase the flow rate, you notice two
18 things.
19 Number one, the concentrations, of course, come
20 down because there is now fresh gas diluting the carbon
21 dioxide. Number two, the end-tidal CO_2 starts to come down,
22 and the efficacy of TGI turns out to be proportional to how
23 much you can decrease the end-tidal CO_2.
24 [Slide.]
25 This is a study from Kuo, et al., and we have

1 actually done this in animals. You get very similar
2 results. As you can see, in 20 ARDS patients, the amount of
3 CO_2 reduction in terms of percent $PaCO_2$ change, was
4 dependent on how much there was a drop in the end-tidal CO_2.
5 So a simple device, a capnogram, which is in
6 clinical practice today, can be used to predict how much CO_2
7 elimination you can achieve by TGI, and also to optimize the
8 system in terms of TGI flow rate.
9 [Slide.]
10 One of the problems with TGI is, of course, it
11 introduces a bias flow into the circuit, which the
12 ventilator is not designed to cope with. That flow, since
13 it exists throughout expiration, also causes dynamic
14 hyperinflation or, in other words, it produces intrinsic
15 PEEP or auto-PEEP.
16 This is dependent on the catheter shape and, of
17 course, has certain characteristics that depend on the flow
18 properties. If the catheter is straight, in other words,
19 the flow is directed towards the alveoli, then, TGI does
20 cause dynamic hyperinflation, and in most clinical studies,
21 the change in lung volume is modest, in the order of 50 to
22 100 ml's at flow rates of around 10 to 15 liters per minute.
23 You can pretty much eliminate this by changing the
24 direction of the flow, in other words, inverting the
25 catheter and directing towards the mouth. By certain

1 designs like the annular catheter that Dr. Kolobow has
2 designed, you can actually have now the opposite problem
3 where you start decreasing an expiratory lung volume.
4 So, depending on the catheter flow shape and the
5 flow properties, you can have different results.
6 [Slide.]
7 Just to get you oriented, I will show you our data
8 from animals. On the y axis is the change in lung volume.
9 On the x axis you catheter flow rate at 5, 10, and 15 liters
10 per minute.
11 The solid circles are obtained data from six dogs
12 with a straight catheter, whereas, the open circles are same
13 animals, same location, but this time the catheter is
14 inverted with the flow directed to the mouth. You can see
15 that the change in lung volume is much less with the
16 inverted catheter.
17 Since the study, there have been other catheter
18 designs where the change in lung volume is actually zero
19 with the inverted catheter.
20 [Slide.]
21 TGI also poses some problems in terms of
22 monitoring, and the main problem is tidal volume. In
23 continuous TGI, there are three sources for tidal volume
24 delivery -- actually, two sources for tidal volume delivery.
25 One is ventilator-delivered tidal volume, and the

1 other one is catheter-delivered tidal volume. You can
2 eliminate the change in tidal volume either by decreasing
3 the ventilator set tidal volume, in other words,
4 compensating for the catheter-delivered tidal volume, or you
5 can time the TGI to occur only during expiration.
6 In this way, the catheter can no longer deliver a
7 tidal volume during inspiration because it is not
8 operational. However, during expiratory TGI, there is some
9 tidal volume delivered to the circuit because of TGI circuit
10 decompression.
11 Now, this depends on the resistance properties and
12 the compressibility of the TGI circuit, and in most cases it
13 is very small, in the order of 10 to 20 ml's at best.
14 Another benefit of expiratory TGI is in terms of
15 dynamic hyperinflation. However, in order to eliminate
16 dynamic hyperinflation during expiratory TGI, you need to
17 turn off expiratory TGI at certain period before the next
18 inspiration, so that you can allow the system to decompress.
19 [Slide.]
20 Now pressure control ventilation poses certain
21 special characteristics in terms of TGI and tidal volume
22 delivery, and let me discuss that briefly.
23 Usually, in pressure control ventilation, when you
24 apply TGI, what you see is that the total tidal volume
25 delivered to the patient or to the animal remains constant.

1 However, the ventilator-delivered portion starts to
2 decrease.
3 Yet, if you have a long inspiratory time or a high
4 catheter flow rate, you can end up with a condition where
5 the circuit is now overpressurized above the set pressure.
6 [Slide.]
7 An example is shown in this slide, where this is
8 now a patient. We have four breaths, these are four
9 consecutive breaths. The first two breaths have TGI on.
10 This breath, here is the TGI flow rate here. In the second
11 breath, the TGI flow has been turned off. The third and
12 fourth breaths are administered without any TGI, and you can
13 see that in the expiratory flow.
14 The expiratory flow is here, about 10 or 15 liters
15 per minute, the TGI is turned off, so now it comes down to
16 zero.
17 If you look at the pressure profile, these two
18 breaths are standard pressure-controlled breaths, where it
19 rises from a PEEP to a set pressure. In this case, I
20 believe it was somewhere around 35, 36 cm of water.
21 In the first two breaths, however, you can see
22 that it is not a full pressure-controlled breath. This is a
23 hybrid of pressure control and constant flow breath, and the
24 reason the pressure is increasing here is because during
25 continuous TGI, the tidal volume is much higher.

1 [Slide.]

2 What I would like to do is take this information
3 and try to sort of force-fit it into clinical practice. I
4 shouldn't use the word "force-fit," but it fits better with
5 the joke slide.

6 [Slide.]

7 What do I see as the role of TGI? I consider TGI
8 as an adjunct to mechanical ventilation, and the major
9 applicability in my mind is the first two with a lot of
10 potential in the last three.

11 You can use TGI either to decrease tidal volume
12 while keeping the arterial CO_2 constant, or you can keep
13 tidal volume constant and use it to decrease arterial CO_2.
14 Of course, you can do a combination of both if you want.

15 TGI also has the potential as a tool to facilitate
16 weaning. I think it has a potential for a novel drug
17 delivery technique, but that has not been investigated to my
18 knowledge, and it can be used in combination of other
19 modalities. By that, I mean you can use it with high
20 frequency ventilation, you can use it with nitric oxide, you
21 can use it with partial liquid ventilation, and the list
22 goes on and on.

23 [Slide.]

24 A couple words about effect of TGI in oxygenation.
25 If you actually keep all the ventilatory parameters the same

1 when you turn TGI on, and by that I mean if you keep tidal
2 volume the same, and if you keep an expiratory lung volume
3 the same, the net effect of TGI on oxygenation is simply due
4 to a drop in PCO_2. In other words, in lung injury models
5 and in patients, the PO_2 really doesn't change much, but you
6 have to pay attention to tidal volume and expiratory lung
7 volume.
8 This is just a study that we did. Just
9 concentrate on this panel. Baseline mechanical ventilation,
10 TGI, and again going back to baseline mechanical
11 ventilation. We kept the FRC the same by adjusting
12 ventilator-set PEEP, and we also adjusted ventilator-set
13 tidal volume to keep the tidal volume the same, and at even
14 two levels of FRC, low and high, the oxygenation really did
15 not change when we went to TGI.
16 [Slide.]
17 Instead of showing you a lot of data, what I
18 decided to do was show you one data and summarize all the
19 other data in one slide. The effect of TGI on gas exchange
20 during acute lung injury I believe can be summarized as
21 shown in this slide.
22 First, there is no change in oxygenation when the
23 tidal volume and FRC is kept constant when you turn TGI.
24 Second, when you apply it, keeping tidal volume constant,
25 you can decrease PCO_2 anywhere from 10 to 30 percent, and

1 this depends on the flow rate used, the alveolar dead space
2 component, as well as what was the initial PCO_2 when you
3 applied the TGI.
4 DR. SLUTSKY: Is that patients or animals?
5 DR. NAHUM: Both. Both actually show pretty much
6 identical numbers. So, you can forget the animals for this
7 discussion and say this is patient data, making the point
8 you can actually get a higher number here if you start from
9 a higher PCO_2 number when you turn the TGI on.
10 Similarly, there is one data from Greece, from
11 Nakos and colleagues, that shows that if you keep the PCO_2
12 constant, now you can drop the pressures that you are
13 operating by about 10 to 30 percent.
14 A point that I tried to make, you get better
15 efficacy if you apply it in the setting of hypercarbia.
16 [Slide.]
17 After having talked about this, let me try to make
18 a case for a clinical utility.
19 [Slide.]
20 There has been in the last five to 10 years
21 increasing discussion about a lung protective strategy, and
22 in a nutshell, what the lung protective strategy tells us,
23 in animals at least, is that we need to pay attention to two
24 things. I apologize for oversimplifying here to make my
25 point.

1 The first one is that we should really operate the
2 ventilator in such a way that we do not overdistend the
3 alveoli. The second point is that we should protect an
4 expiratory lung volume, such that there is no repeated
5 opening and closure of airways and alveoli that will amplify
6 sheer forces and promote lung injury.
7 Now, if you apply this strategy to patients, you
8 very quickly realize that you have to let go of something,
9 and what you have to let go is PCO_2, and therefore, the name
10 permissive hypercapnia. It is really not permissive, it is
11 an outcome of the chosen ventilatory strategy if you try to
12 apply this concept to patients with ARDS.
13 [Slide.]
14 There are five studies out there that look at
15 ventilatory strategies. Three of them are published. The
16 one from Brazil, Amoto and colleagues, from Dr. Stewart from
17 Slutsky's group, so if I say anything wrong, Arthur can
18 correct me, and from the French group, this was a European-
19 North American combined group.
20 There are two more. One is from Dr. Brower's
21 group from Johns Hopkins, which I don't have the data,
22 pointed here, and the other one is there is an ongoing NIH
23 trial, which I don't know any of the results for that trial
24 since it's an ongoing study.
25 The point I like to make is that only one study

1 showed any positive outcome, and that is the Brazilian
2 study. The other two studies, for that matter, Dr. Brower's
3 study, which is very similar to these, were all negative.
4 In other words, whether you do a low tidal volume or a high
5 tidal volume strategy, it didn't seem to make a difference.
6 [Slide.]
7 However, remember from my previous slide that you
8 needed two conditions, one was the upper bound, and the
9 other one was the lower one, in other words, you had a
10 ceiling and a basement.
11 These two studies only paid attention to the
12 ceiling. They really did not do anything about the
13 basement. You can see the PEEP values between the control
14 and treatment arms are about the same.
15 The only study that really paid attention to both
16 were the Marcello study. Now, if you do that, you very
17 quickly find out that the PCO_2 has become quite high, and
18 you have to let the PCO_2, you have to accept the PCO_2's to
19 rise.
20 In these studies, since they had more pressure for
21 delivery of tidal volume, the PCO_2's were not as high.
22 [Slide.]
23 However, when they looked at the functional status
24 of their patients in terms of certain parameters like
25 Spitzer function, emotional function, and mastery -- and I

1 cannot quite tell you what these mean since this was an
2 abstract, and I was not there to discuss it with Dr.
3 Ferguson, this again comes from Dr. Slutsky's group -- what
4 they showed is that in 70 percent of the patients who were
5 available for this kind of analysis, the patients who had a
6 lung protective strategy with hypercarbia, had worse outcome
7 in terms of mental function. Now, that is, to me, is
8 worrisome.
9 [Slide.]
10 On top of it there are certain contraindications
11 to acute hypercarbia in this intensive care unit. The first
12 clear one is hypoxia, a combination of acute hypercarbia
13 with hypoxia can be quite deadly, and the second one, of
14 course, as we all know, is if there is any intracranial
15 pathology.
16 There is also some relative contraindications, and
17 this is when the patients have heart problems, such as right
18 ventricular dysfunction. As acute hypercarbia increases,
19 right ventricular afterload due to increases in pulmonary
20 artery pressure. Patients with arrhythmia, hypovolemic
21 patients, and patients I believe with beta-adrenergic
22 blockade are at specific risk because what protects the
23 hemodynamics is the sympathetic discharge that the acute
24 respiratory acidosis produces.
25 [Slide.]

1 So, we do take care of patients in the ICU that
2 allowing the PCO_2 to rise may not be a wise option. Now, if
3 you look at one of the early articles, where the concept of
4 permissive hypercapnia was developed, and you look at the
5 PCO_2 ranges, in this study, Dr. Hickling basically targeted
6 a peak airway opening pressure of less than 40 cm of water,
7 and he accomplished that by using small tidal volumes, on
8 the order of 5 to 8 ml per kilo.
9 The conventional strategy here would say the tidal
10 volume should be double that, 10 to 12 ml per kilo. You can
11 see that there are some patients who are above 120 in terms
12 of PCO_2.
13 So, if you look at this data, and if you use a
14 cutoff for PCO_2, then, you can get an idea of how many
15 patients will benefit from TGI, and I really don't know
16 exactly where to set the threshold, but I used to believe 80
17 as the threshold, but looking at the recent data from
18 Slutsky's group, I might reconsider that and set it at 60,
19 and if you put it at 60 with this strategy, about 20 to 25
20 percent of the patients may actually benefit from TGI.
21 [Slide.]
22 All the studies that are currently available in
23 the literature in terms of application of TGI in ARDS, did
24 not utilize this lung protective strategy, and did not
25 really increase the respiratory rate to the limit as defined

1 by development of auto-PEEP, because after all, if I can
2 increase the respiratory rate, and don't cause any auto-
3 PEEP, I can still cycle between those two limits that I
4 showed you, but my PCO_2 would be less.
5 I was lucky enough about a couple months ago to
6 review a paper from Jean Jacques Rouby's group, where they
7 did exactly that, and I was lucky enough also for Jean
8 Jacques Rouby to give me permission to show these slides
9 here.
10 He studied six patients. These are ARDS patients.
11 In each ARDS patient, they did basically the pressure volume
12 curve, and set the ventilator according to the study that
13 was done in Dr. Amato's study that I showed you.
14 [Slide.]
15 Moreover, they then increased the respiratory rate
16 until there was auto-PEEP development in the study. So,
17 what they have is control group, in other words, optimized
18 mechanical ventilation with a chosen respiratory rate.
19 Then, they have expiratory TGI. Then, they go
20 back to conventional or to this lung protective strategy,
21 but they increased the respiratory rate until there is auto-
22 PEEP development in the study. Then, with these settings
23 they reapply expiratory TGI.
24 Since they adjust the tidal volume and their FRC
25 by decreasing PEEP, when they turned the TGI on, their

1 plateau pressures in the system remain constant across all
2 conditions.
3 If you look at their PCO_2, it falls when you turn
4 the TGI on, but that is no different if you just turned the
5 respiratory rate. You can pretty much achieve what the TGI
6 achieved by turning the respiratory rate, but you still get
7 an effect of TGI under those conditions, and you can pretty
8 much take somebody's PCO_2, who is around 80, and almost
9 normalize it, bring it down to 50.
10 Now, this is lung protective strategy, optimized
11 respiratory rate plus TGI. So, I think this is the true
12 test of the effect of TGI in the lung protective strategy.
13 There was a very small and statistically
14 insignificant drop in PO_2 in this study, as well.
15 [Slide.]
16 Let me change gears and proceed to other uses of
17 TGI. TGI, I believe can be a novel weaning modality. I
18 believe it will be most useful when the anatomic dead space
19 is high, such as in muscular weakness.
20 If it is not incorporated into the ventilator,
21 there can be some trigger problems, which I will demonstrate
22 for you. There is still the problem of dynamic
23 hyperinflation which can be solved with some novel
24 applications.
25 The trigger problem can pretty much solve if you

1 integrate it into the ventilator by a flow-by system, and
2 there are some issues in terms of conditioning the gas,
3 which I think can be solved, as well.
4 [Slide.]
5 Let me first demonstrate what I mean by the
6 trigger problem. Here is a patient. This was a
7 tracheostomized patient that we studied, a long-term
8 ventilator-dependent due to a muscular weakness. He is
9 being ventilated on a pressure support of 4 cm of water, and
10 there is a TGI flow of 8 liters per minute that is only on
11 during expiration.
12 The top panel is flow at the airway versus time.
13 The bottom panel is actually a Respitrace. It is an
14 inductive plethysmography. It shows you what happens to
15 lung volume changes in terms of time, of synchronized.
16 If you look at the top panel, you can see there is
17 five breaths that has been delivered by the ventilator. If
18 you look at the bottom panel, you will see that there is
19 indeed, in fact, 11.
20 What is happening is here, here, here, here, here,
21 and here, the patient is simply breathing from the TGI. In
22 order for the patient to trigger the ventilator, first, the
23 patient's effort has to outstrip the TGI flow, such that it
24 can decrease the airway opening pressure, and then the
25 ventilator can see it as a trigger signal.

1 When the patient cannot do it, or chooses not to
2 do it, there is no trigger, but there is a volume delivery
3 to the patient.
4 [Slide.]
5 Now, we actually looked at this in terms of an
6 animal model, where if you take anesthetized normal dogs and
7 use conventional mechanical ventilation here, then, turn TGI
8 on at 5 liters per minute, 10 liters per minute, what the
9 normal dog chooses to do is it keeps their PCO_2 pretty much
10 constant, but decreases their minute ventilation.
11 This is also true in patients that received
12 intratracheal oxygen through a mini-tracheostomy. So, what
13 a normal dog does, it breathes less because it needs less
14 minute ventilation, but maintains the PCO_2 the same.
15 [Slide.]
16 Now, if you take the same dog, give him some
17 Pavulon at very low doses, such that now you make him
18 weaker, before, the dog's negative inspiratory force was
19 minus 50 cm of water, now it is minus 25 cm of water.
20 Here, you can see that the dog is having some
21 problems by itself through the ventilator, but when you turn
22 the TGI on, as you increase the flow, the dog can no longer
23 trigger the ventilator, and the PCO_2 rises.
24 We actually matched end-tidal expiratory volume,
25 such that when you turn the TGI, there is no change in the

1 end expiratory lung volume. So, this is just the inability
2 of a weak dog, and it may translate into a weak patient to
3 trigger the ventilator at this point.
4 [Slide.]
5 In the last 10 to 15 minutes, what I would like to
6 then discuss is some of the problems associated with the
7 TGI. This slide I have to confess is about seven years old.
8 When we first started, we tried to come up with every
9 problem that we can think of in TGI, and there may be some
10 other problems that the panel members or other people can
11 tell me about, but I must admit that most of the problems
12 have been addressed one way or another.
13 Number one, there is pressure and volume
14 monitoring. The ventilator monitoring system breaks down
15 because the ventilator is not designed to accept a bias
16 flow. There are some problems that I will discuss.
17 We discussed the problem in pressure control of
18 over-pressurizing the system, so you can institute a
19 pressure popoff mechanism, and I believe that has been
20 demonstrated by Dr. Pinsky's group to overcome that problem.
21 There is a problem of humidification. Most
22 commercially available ventilators cannot withstand the
23 pressures that you need to drive flows in a TGI circuit, but
24 there are now some new humidification systems available that
25 can actually withstand those pressures.

1 There is also a concern that if you have a
2 catheter sitting at the trachea, you may cause bronchial
3 injury either by the impact of the jet directly to the
4 bronchial mucosa or by the tube sort of swinging in the air
5 and hitting the mucosa itself.
6 These problems can be solved by incorporating the
7 TGI system into the endotracheal tube, as I will show to
8 you.
9 In early studies, the TGI was applied by putting a
10 catheter directly through the endotracheal tube and, of
11 course, as you can imagine, that made suctioning the patient
12 quite problematic. Again, this problem can be solved by
13 incorporating the TGI into the endotracheal tube.
14 I believe we know quite a bit more about optimal
15 catheter configuration and flow rates, but I have to admit
16 that every endotracheal tube that I have seen, that has
17 incorporated TGI into its walls, has a different design, and
18 I don't have any data that compares different endotracheal
19 tubes.
20 Lastly, there is this problem of the bias flow and
21 how it will interact with the mechanical ventilator.
22 [Slide.]
23 Certain problems with the TGI ventilator
24 interactions due to the bias flow, there is always going to
25 be some expiratory flow in the circuit. This makes the

1 exhaled volume measurement of the ventilator really
2 inaccurate, and under certain conditions you get a
3 continuous alarm which can be quite irritating.
4 There may be problems with detection of leaks and
5 there may be problems with absence of a pressurized breath.
6 I mentioned the problems of triggering, and another problem
7 that I want to draw your attention to is that we usually, at
8 the bedside, measure mechanics by doing an inspiratory and
9 an expiratory pauses.
10 Now, if you have a bias flow in the circuit,
11 number one, the measurement becomes useless. Number two, it
12 can be dangerous. So, you have to have a way to turn the
13 flow off when you want to make these measurements, and
14 certain TGI phasing systems actually accomplish this task.
15 Of course, lastly, which is quite obvious to
16 everyone, is that you need to blend oxygen to the same
17 concentration that you are using in the ventilator,
18 otherwise, the FiO_2 that you delivered to the patient is
19 going to be different.
20 [Slide.]
21 As far as design modifications, incorporating the
22 TGI catheter into the endotracheal tube will solve the
23 problem of bronchial injury as you can have the outlet a
24 little bit proximal to the tip of the endotracheal tube, and
25 then you can freely suction these patients.

1 What is more, there is at least one study in the
2 literature with the Boussignac tube that shows that you can
3 prevent lung collapse during suctioning if you applied this
4 endotracheal tube.
5 Incorporating the TGI into a ventilator where the
6 TGI becomes an integral part of the ventilator will solve
7 gas conditioning problems, will solve monitoring problems,
8 if you have a pressure popoff, will solve over-
9 pressurization. If you put it part of a flow-by system,
10 will solve the triggering problems, and I believe the phasic
11 delivery can also be accomplished in a very easy manner.
12 [Slide.]
13 For the sake of time, I will go very quickly over
14 the last couple of slides that I have. This is just to give
15 you an idea of the pressures we are talking that requires to
16 generate flows through the very small tubes that we use as
17 TGI's.
18 This is an 8 French catheter, 10 and 14 French
19 catheters. So, if you had a flow rate of 10, you are
20 talking quite high pressures, and this pressure, remember,
21 is not in the patient. This is at the tip, at the proximal
22 end of the catheter.
23 So, these pressures are going to be seen by the
24 humidifier -- that is why I put this slide on -- but not by
25 the patient. So, if you want to have a humidification

1 system, you have to have a system that would stand these
2 pressures. I proved this point very nicely in the lab by
3 having a lot of water all over the place.
4 [Slide.]
5 TGI will also cool the airway, so you need to
6 heat, not only humidify the system.
7 [Slide.]
8 A couple of words about modified endotracheal
9 tubes. Here is a Boussignac tube. It has these channels,
10 capillary channels that are actually extruded into the tube
11 wall itself, and as you can see here, the site of air
12 injection happens inside the endotracheal tube, and this
13 will prevent any kind of bronchial injury, and you can also
14 suction the patient.
15 [Slide.]
16 The other possible benefits of TGI can be in terms
17 of clearance of the endotracheal tube of mucus and other
18 stuff, and I think this is an unexplored area. You can make
19 an argument that TGI may decrease incidence of nosocomial
20 pneumonia, but I might be stretching it over there.
21 [Slide.]
22 So, what is the future of TGI? I couldn't help
23 put this slide. Initially, it has to be stand-alone,
24 because right now there is not many ventilators out there
25 that the TGI system is integrated into. However, if it is

1 going to become a modality that we are going to use in the
2 intensive care unit in the future, it has to be ventilator-
3 integrated in one form or another.
4 [Slide.]
5 Well, since this is Washington, I tried to make
6 this joke. I don't know whether you agree or disagree.
7 I always get asked this question. Is TGI ready
8 for prime time? About seven years ago, I would have said
9 no. About two years ago or a year ago, I would have said
10 maybe, and I am not oscillating between maybe and yes, and
11 favoring yes more than maybe.
12 Thank you for your attention.
13 [Applause.]
14 DR. SLUTSKY: Thanks very much, Avi, for a very
15 comprehensive review.
16 I would like to now open your presentation up to
17 the panel members for questions, not necessarily
18 specifically addressing the five questions, because we can
19 get back to that, and you told me you would be able to stay,
20 Avi, but just general questions.
21 Michael.
22 DR. ROIZEN: Avi, if permissive hypercapnia,
23 whatever you want to call that form of ventilation that is
24 known as permissive hypercapnia, proves not to be an
25 effective mode for outcome, will TGI not have a sizable role

1 or even any role?

2 DR. NAHUM: I think that is an excellent question.

3 It puts me on the spot. It will not have as big a role in

4 management of patients with acute lung injury.

5 DR. ROIZEN: Will it have any role?

6 DR. NAHUM: Well, then, you have to think about it

7 in terms of another modality, what can it accomplish.

8 DR. ROIZEN: But all the others are really

9 experimental. I mean, in other words, the weaning, the drug

10 delivery.

11 DR. NAHUM: Yes, I think we do not have currently

12 enough clinical experience for me to comment on those.

13 DR. CLARK: Getting back to this question, I share

14 your belief that the protective strategy should be one of

15 lung recruitment and avoidance of large tidal volumes.

16 In the animal model that you have looked at, have

17 you been able to demonstrate that using the strategy of

18 tracheal insufflation as a way to reduce tidal volume has

19 actually been associated with decreased lung injury in those

20 particular models, just as maybe your high frequency

21 ventilation or other low tidal volume strategies have been

22 looked at?

23 DR. NAHUM: A simple answer to your question is

24 no, but I don't think the answer is that simple. Number

25 one, it is exceedingly difficult to mimic ARDS in acute lung

1 injury models, and we can have a discussion a whole day, and
2 we probably will still not agree on certain specifics.
3 So, to prove that in an animal model is
4 exceedingly difficult. You can generate ventilator-induced
5 lung injury in animals, but then in dogs, for example, you
6 need 70 ml per kilo tidal volume. Now, what the heck does
7 that mean?
8 We can start arguing, well, this is a normal dog.
9 If you have an ARDS patient, it only has about a third of
10 lung capacity that can be aerated. So, then, you have very
11 small space that can accept the air, and the arguments can
12 go both ways, back and forth.
13 The real test I believe has to come from the
14 clinical arena. Unfortunately, the studies, they answer
15 some questions, but they also raise a lot of other
16 unanswered questions, so there is not a clear-cut consensus
17 on the mechanical ventilation strategy of ARDS.
18 Then, it becomes a philosophical argument, what do
19 we mean by ARDS, and so on, and so forth, which I don't want
20 to go into, but hopefully, maybe the NIH study will give us
21 certain guidelines, and I think there is some impetus in the
22 medical community to do another final study to see, indeed,
23 the lung protective strategy works or doesn't work.
24 My bias is that it does work, but at this point I
25 can only defend it as a bias.

1 DR. SLUTSKY: You also have a signal-to-noise
2 problem in a sense, because if you decrease tidal volume,
3 let's say, by 10 or 15 percent, and you then look to see
4 whether that causes decreased ventilator and lung injury,
5 you are going from 10 ml/kilo to 8 or 9. Even if it does,
6 you have to have a huge n. That is why, when you call it an
7 adjunct, I think that is what it is, and the question that
8 Michael raised, if minimizing tidal volume doesn't prove to
9 be useful, minimizing tidal volume a lot doesn't prove to be
10 useful, then, minimizing a little is unlikely to be very,
11 very helpful in and of itself.
12 DR. NAHUM: I can tell you from our experience
13 that the conventional control strategy, at least I would say
14 internationally, both in U.S. and Europe, has evolved over
15 the last 10 years, and it all started by Hickling's article
16 in 1990.
17 I think there is no longer a conventional
18 mechanical strategy that has been fixed in time, that has
19 evolved such that people started paying a lot more attention
20 to the peak pressures in the system.
21 As a result, when these studies came, the last
22 three studies came, or the last four studies came, their
23 control was a moving target. The control was not fixed.
24 So, in a way to say that that was the control, I think is a
25 little bit misleading because the first patient in the

1 Brazilian study was enrolled in 1990, and I think Dr.
2 Slutsky's study was in, what, 1995?
3 DR. SLUTSKY: 1994-95, I think.
4 DR. NAHUM: By then, permissive hypercapnia was in
5 the literature, there were excellent review articles, and
6 there were a couple of studies out. So, people have changed
7 on how they ventilate a patient. So, this gets to be a very
8 complicated, difficult subject to sort out, at least for me.
9 DR. SLUTSKY: Can I ask you a question about
10 definition, what TGI is. One of your earlier slides, you
11 showed, you had phasic, and you had entering inspiration,
12 does that not make it another ventilator? I mean if you
13 have phasic inspiration, what do you mean exactly and how do
14 we separate this, or how does the FDA look at this in terms
15 of is this ventilator or is this just an adjunct?
16 DR. NAHUM: Actually, we called it inspiratory
17 bypass. Everybody likes to coin words. What you are
18 referring to is what you and Yasha did in late 1980s, in
19 other words, if you just put a catheter into the trachea and
20 somehow find a shutter where you don't allow air to escape,
21 you have a ventilator, that is what you are referring to.
22 DR. SLUTSKY: Yes. That is not my study, but yes,
23 that is what I am referring to.
24 DR. NAHUM: That, I would say, is the end, in
25 other words, you can think of it is a continuum, you can

1 have a ventilator act like a shutter, okay, and you can have
2 the catheter deliver flow only during inspiration, and you
3 can use it as the sole delivery of tidal volume, or you can
4 use a combination, a little it from the ventilator, a little
5 bit from the catheter.
6 But what you are referring to would be the end of
7 the spectrum for inspiratory TGI.
8 DR. SLUTSKY: And that could be jet ventilation.
9 DR. NAHUM: That's correct.
10 DR. SLUTSKY: Cathy.
11 DR. SASSOON: The study of Amato, the lung
12 protected strategy, I don't believe that in the treatment
13 group, any of the patients had any TGI treatment or jumped,
14 so what my question is, when is that going to be used?
15 Another thing, even without TGI, the survival seems to
16 surpass the control group. So, what role does the TGI have?
17 Secondly, at what level of $PaCO_2$ would you
18 recommend TGI to be used, or would you like to look at the
19 pH rather than $PaCO_2$? The study of Hickling, I believe you
20 showed that some of the patients had $PaCO_2$ to 120 or so.
21 DR. NAHUM: 140 was the highest one.
22 DR. SASSOON: So, those are the main two questions
23 I have.
24 DR. NAHUM: If I remember them all, I will go one
25 at a time.

1 First of all, you cannot let PCO_2 to rise acutely
2 in all patients. There are certain clinical
3 contraindications, and I tried to list some of them. Of
4 course, the classic one is if you have a patient with
5 intracranial pathology.
6 Another one that comes up routinely is asthma
7 patients. This is another group of patients, asthma patient
8 who had a respiratory arrest in the field, had maybe some
9 hypoxia, and now you are ventilating this patient, and you
10 are scratching your head and saying how much anoxic brain
11 injury is there, and can I let this PCO_2 go up.
12 I personally get very nervous when I am sort of
13 trying to do this. So, there are certain patients that
14 clinically, the clinician will not be comfortable allowing
15 the PCO_2 to rise, at least quickly. That will be a group of
16 patients where TGI may have a benefit.
17 Another group of patients is if what Dr. Slutsky's
18 group is showing, and that is, that high PCO_2's are
19 tolerated well hemodynamically, but they may have long-term
20 sequela in terms of mental function, then, I think everybody
21 is going to be very nervous having the PCO_2's rise, and I
22 would actually ask Arthur what he thinks about that since
23 the data come from his institution.
24 I can tell you that I have seen this happen
25 anecdotally in asthma patients where we have ventilated them

1 and they had extremely high PCO_2's for a couple days. When
2 they come out, initially, they are crazy, they are really,
3 they are mentally -- and it is very difficult to sort out
4 clinically, because in the meantime, you have paralyzed
5 them, you have sedated them, it becomes clinically a mess
6 trying to sort it out, but it is a concern.
7 DR. SLUTSKY: In our study, actually, Tom Stewart,
8 the principal investigator, small numbers, long-term, 14
9 patients and 7 patients, I think it was, so they are really
10 quite small numbers, and we show differences. We are not
11 sure if it is related to the CO_2 or not. Certainly, by
12 regression, CO_2 doesn't turn out to be an independent
13 variable, but it's small numbers, so it is hard to say.
14 So, at this moment, that is a hypothesis and it is
15 unclear what the mechanism was. We are going to try to sort
16 that out.
17 DR. NAHUM: Cathy, you had one more question, but
18 I forgot.
19 DR. SASSOON: You answered my second one. The
20 first one is the Amato study, even without TGI, the survival
21 surpassed the control group.
22 DR. NAHUM: But the question to me is can it be
23 better.
24 DR. CLARK: One of the questions that was raised
25 from a regulatory standpoint, explain to me the differences

1 in terms of thinking about the engineering of this system,
2 how this is different than, say, the Bunnell jet.
3 If there are lots of similarities, there is a fair
4 amount of information about what that does to the trachea
5 and different things and how to avoid those problems over
6 time. Certainly, 10 years ago, necrotizing tracheal
7 bronchitis was a huge problem in neonates, but those
8 problems disappeared with better humidification systems, at
9 least I haven't heard any more of that in neonates.
10 How would this system be distinct from, with
11 regards to pressure, driving pressures and humidification?
12 DR. NAHUM: I don't think it is going to be very
13 different. I mean I cannot talk about the engineering
14 aspects, but based on what I know in terms of what we have
15 to do to sort of cycle this flow with the vent from a signal
16 from the ventilator, it is rather simple to do. The
17 technical aspects are very simple to do.
18 You can pretty much, using a microchip and some
19 signals, can make this do whatever you design it to do.
20 That is simple. So, the technical aspects are simple. As
21 far as what is available for you from where you are sitting,
22 so that you can make a regulatory decision, I don't know.
23 DR. SLUTSKY: Can I ask you a couple of questions?
24 You ended up by saying you are sort of oscillating between
25 yes and maybe by the use of TGI.

1 Can you tell us why you are oscillating, what is
2 bringing you towards the maybe more than the yes?
3 DR. NAHUM: I should maybe rephrase it. I am more
4 on the yes, and I was trying to make an argument for the yes
5 in the acute lung injury patients, but then, of course, Dr.
6 Roizen, who I also had the privilege of knowing at the
7 University of Chicago, caught me and said what if this
8 ventilatory strategy doesn't show to benefit.
9 Then, I think you have to look at it a little bit
10 differently.
11 DR. SLUTSKY: But let's assume for the moment that
12 decreased tidal volumes is beneficial. We don't have a
13 specific device in front of us, but we are eventually going
14 to have to deal with safety and efficacy.
15 So, what is there that makes you lean towards a
16 maybe, for example? What are the issues, I guess? I guess
17 you have dealt with some of them in terms of the side
18 effects. Is there anything else?
19 DR. NAHUM: The reason I say yes and maybe, I say
20 more yes than maybe, is that when you have an ARDS patient
21 at 2:00 a.m. in the morning that you are trying to stabilize
22 and the PCO_2's are going up, and the pH is coming down, my
23 blood pressure starts going up.
24 But the answer, really, I don't know because what
25 is a safe -- I mean it is not the PCO_2 per se, it's the pH

1 is the essential, and it is the intracellular pH, and what
2 is a safe intracellular pH? I really don't know, but I can
3 tell you that a lot of things happen and change with the
4 intracellular pH, and some of them are good, some of them
5 are bad, and how it affects the patient is difficult to
6 tell.
7 I can assure you that the neurosurgeons are not
8 going to let me do, is ventilate their head trauma patients
9 with PCO_2's of 50. I mean they want it at 30.
10 DR. KACMAREK: I agree with you, but then why the
11 maybe? Everything you are saying says yes, yes, yes, yes,
12 but you still are underlining maybe.
13 DR. NAHUM: I am sort of hedging, and the reason I
14 am hedging is I am convinced that the lung protective
15 strategy works, but I cannot back it up with solid data.
16 Whether that solid data is going to arrive or not is also
17 extremely questionable.
18 DR. KACMAREK: Do you believe that we can design
19 or somebody can design a system, though, that would
20 accomplish the goals that you have outlined in a safe
21 manner?
22 DR. NAHUM: Yes.
23 DR. KACMAREK: Is there any adverse effects
24 specifically associated with TGI assuming we can correct all
25 those problems that you have outlined in your slide?

1 DR. NAHUM: I believe with the proper safety
2 engineered into the TGI ventilator system, it would be a
3 safe modality.
4 DR. KACMAREK: So, if that could be accomplished,
5 would your answer be a yes, and not a yes/maybe?
6 DR. NAHUM: If that would be accomplished, and I
7 can do it very quickly, easily, I think the answer would be
8 yes. As a matter of fact, that is the argument that John
9 Jacques Rouby makes, because he can do it and bring the PCO_2
10 down, and then there is no arguments about the PCO_2 being
11 high, pH being low, and all these things that you have to
12 juggle in your mind.
13 DR. SLUTSKY: Do you think the TGI has to be
14 ventilator integrated? Again, for a regulatory body to
15 approve it.
16 DR. NAHUM: In the future, yes.
17 DR. SLUTSKY: What about in the past? No, in the
18 future.
19 DR. NAHUM: If you are looking down the line, I
20 cannot tell you how many years, but down the line it only
21 makes sense to me that it has to be ventilator integrated.
22 DR. KACMAREK: I think the point of Art's question
23 is do you believe, considering the safeguards and the
24 concerns that you raised, that a system can be designed
25 independent of integration of the mechanical ventilator,

1 provide the efficacy goals, and still maintain the safety
2 that is necessary. I think that is what Art's question is.
3 DR. NAHUM: I think the answer is most probably
4 yes, but it depends on the design of the system, so that you
5 will specifically look for the safety features that are
6 pretty much obvious what they are, that you go down the line
7 and say, yep, check, yep, check, and then you go down the
8 line and do that.
9 Then, I think you can design a stand-alone system
10 that would be safe and efficacious.
11 **Prepared Public Comments on**
12 **Tracheal Gas Insufflation**
13 DR. SLUTSKY: I think we should probably move on
14 because we are addressing a lot of the five questions, and
15 then we are going to get to those specifically. So, we are
16 now going to move on to the public comments on tracheal gas
17 insufflation.
18 There were a couple of individuals who
19 specifically asked to speak during this session. If there
20 are any others in the audience, perhaps they could come up
21 and just let me know.
22 All the speakers who speak during this session,
23 could you please state any corporate sponsorship or
24 financial support that you have had for attending this
25 meeting before you start your presentation.

1 The first speaker will be Adi Miro, University of
2 Pittsburgh. How long do you think you will need,
3 approximately?
4 DR. MIRO: Fifteen minutes I think.
5 DR. SLUTSKY: Okay.
6 DR. MIRO: Thank you very much for the opportunity
7 to present our experience from the University of Pittsburgh.
8 DR. SLUTSKY: I asked the question earlier about
9 any corporate sponsorships or did anybody pay your way here.
10 DR. MIRO: Yes. My transportation was paid by the
11 Spirit Medical Company. Other than that, I have received no
12 other remuneration or anything else from any other corporate
13 sponsor.
14 [Slide.]
15 What I hope to focus on today, and I think I am
16 going to get a little bit of jump start on some of the
17 questions, because my presentation really revolves around
18 addressing the concerns that have been raised by the FDA.
19 At the University of Pittsburgh, we have been
20 using tracheal gas insufflation for about four to five
21 years, and we actually have used it in two settings, both in
22 a research setting, anywhere from an artificial lung model
23 to animal models, as well as in adults with acute lung
24 injury, but we have also had a lot of experience using it
25 clinically, in other words, the doctors that I work with in

1 the Department of Critical Care Medicine, often request
2 tracheal gas insufflation as part of the management of their
3 patients when they believe that this may be useful.
4 So, I would like to share a little bit of that
5 experience with you today, and that is why I have entitled
6 the discussion, "Bridging the Gap Between Research and
7 Clinical Use."
8 [Slide.]
9 The first question I think addresses two issues.
10 One is what is the appropriate endpoint to evaluate the
11 efficacy of tracheal gas insufflation, is CO_2 elimination
12 efficiency enough, and then the second part of the question,
13 at least from the way it was posted on the Internet is what
14 kind of effects does TGI have on end expiratory lung volume.
15 [Slide.]
16 In the first part of the question regarding what
17 is the optimal endpoint to define whether TGI is an
18 efficacious adjuvant therapy, I do believe that the primary
19 effect of TGI is related to its effects on CO_2, as Dr. Nahum
20 has elaborated on, and usually we see that in one of two
21 ways. We either see a lowering of the CO_2 with a constant
22 minute ventilation or we can actually reduce minute
23 ventilation while keeping CO_2 constant.
24 I believe this is the appropriate endpoint for
25 which to judge tracheal gas insufflation because things like

1 survival, total days on mechanical ventilation, days alive
2 and off mechanical ventilation are, in my opinion, somewhat
3 unrealistic endpoints to evaluate one single therapy
4 targeted at one single organ.
5 Critically ill patients, especially those with
6 acute lung injury and ARDS, are very complex. There is many
7 things that affect their outcome, and quite frankly, I don't
8 think TGI is a magic bullet as any other form of therapy
9 that we are doing in the supportive care of these patients.
10 [Slide.]
11 The second part of the question that was raised by
12 the panel is the issue of auto-PEEP or induced by tracheal
13 gas insufflation, and this graph here is taken from a
14 manuscript that we currently have submitted for publication
15 where we looked at the interactions between tracheal gas
16 insufflation and auto-PEEP.
17 What I have depicted here on the left is baseline
18 or this would be conventional ventilation without any TGI,
19 and we have on the y axis airway pressure. The amount of
20 PEEP that is set on the ventilator obviously defined the end
21 expiratory pressure, and then the tidal breath, which is
22 depicted by the height of these two bars, defines the tidal
23 excursion, and we end up with a specific peak airway
24 pressure.
25 What we noticed actually clinically when we first

1 began using this with volume control ventilation, was that
2 even though we reduced the amount of tidal volume that was
3 delivered by the ventilator in order to keep total inspired
4 volume constant, we saw that there was a rise in peak airway
5 pressure above the baseline value, and we postulated that
6 this was due to an increase in auto-PEEP that was produced
7 by tracheal gas insufflation.
8 We also looked at what would happen when tracheal
9 gas insufflation was used in conjunction with pressure
10 control ventilation, and two things are important to mention
11 with respect to that.
12 The first, that Dr. Nahum has already mentioned,
13 is that it is possible that although the ventilator reduces
14 its proportion of tidal volume to each breath, it has only a
15 limited ability to compensate for the extra volume that is
16 in the circuit, so you may actually get an increase in peak
17 airway pressures, as well as inspired volume during pressure
18 control ventilation and TGI.
19 We found a simple solution to that problem that
20 Dr. Nahum also referenced, and I will show you some data
21 with respect to that later, but what we were able to do was
22 we were able to keep airway pressure constant, but what then
23 happened during pressure control, because it's a pressure
24 mode, is that now the driving pressure is reduced, and
25 hence, tidal volume is reduced.

1 In order to offset the additional PEEP that was
2 produced by TGI, we found that if we simply reduced the
3 amount of ventilator PEEP by an equivalent amount of that
4 produced by auto-PEEP, we can certainly restore the same end
5 expiratory lung pressure and volume, we would be able to
6 keep tidal excursions constant, and we would also be able to
7 keep the end inspiratory pressure or volume constant, as
8 well, and also have the extra CO_2 elimination afforded by
9 tracheal gas insufflation.
10 [Slide.]
11 In our research at the University of Pittsburgh,
12 we so far have studied a total of 21 patients with ARDS, and
13 have been doing this over the past four years thanks to a
14 grant by the National Institute of Nursing Research from the
15 NIH with Dr. Leslie Hoffman and myself being the co-
16 principal investigators.
17 We looked at tracheal gas insufflation at 10
18 liters per minute, and we have looked at it using both
19 volume control and pressure control ventilation, and we
20 measured auto-PEEP in each of these patients and found that
21 the average amount of auto-PEEP or extra PEEP that was added
22 by the use of TGI, was on an average of 3.8 cm of water,
23 which is really, at least clinically in adults, not a
24 terribly high amount. Our range was from zero to 10.6.
25 Now, what we do for research purposes is usually

1 very precise, very accurate, and we need to control all
2 variables, which we did for our research project. On the
3 other hand, when we used tracheal gas insufflation
4 clinically, because an intensivist is asking that for one of
5 their patients, what we do, knowing that we obligatorily
6 have an increase in total PEEP, is we simply decrease the
7 ventilator PEEP by approximately 5 cm of water when we are
8 using TGI at 10 liters per minute.
9 Now obviously, we also monitor patients with
10 arterial blood gases, and if changes need to be made to the
11 total PEEP level based on oxygenation, we monitor that, and
12 clinically, we also use the pressure relief mechanism that I
13 will show you in a few slides in order to prevent any over-
14 ventilation or over-distention.
15 [Slide.]
16 The second question asks is there sufficient
17 understanding of TGI to be sure that with adequate
18 monitoring and other safety provisions, we won't have a
19 worse outcome.
20 [Slide.]
21 One of the ways I think that you could cause some
22 deleterious effects on TGI has to do with the excess gas
23 that is delivered into the system that could potentially
24 over-distend and over-pressurize the lungs. I alluded to
25 the pressure relief valve that we use both in the lab, as

1 well as in patient care, and this is the pressure relief
2 valve that we insert in line that is adjustable with a hex
3 screw nut, and we simply have the valve open at the peak
4 airway pressure that we desire.
5 It works 100 percent of the time, and we have had
6 very much success in keeping our airway pressures constant
7 with this insertion of this device in our ventilator
8 circuit.
9 [Slide.]
10 When we looked at this in an artificial lung
11 model, we have airway pressure on the y axis on the top
12 graph, as well as total inspired volume on the y axis of the
13 bottom graph, and if we do nothing at all except add
14 tracheal gas insufflation to the system, as we increase gas
15 flow rate depicted here on the x axis from zero to 6 and 10
16 liters per minute, the white line here represents what
17 happens if we just add TGI, and you can see that airway
18 pressures at end inspiration go progressively higher, and in
19 fact, values become progressively higher, as well, but if we
20 do nothing else but insert the pressure relief valve in
21 line, depicted by the yellow graph, we are able to maintain
22 peak airway pressures completely constant at all TGI flow
23 rates, as well as keep inspired tidal volumes completely
24 constant at all TGI flow rates.
25 [Slide.]

1 Other safety concerns that have been raised, I
2 have described here, and again categorized them as what we
3 do and what we have seen in our research study versus what
4 we do clinically at the bedside.
5 Again, in our 21 patients with ARDS, we have used
6 10 liters per minute, but it is a self-limited study, and it
7 only lasts approximately four to six hours. When we do our
8 short-term studies, we neither heat nor humidify the gas.
9 We do insert the pressure relief valve to keep peak airway
10 pressure and inspired volume constant, and in this group of
11 patients we have seen no hemodynamic or respiratory
12 complications.
13 Clinically, we have actually had quite extensive
14 experience. We estimate that about 30 patients per year we
15 use tracheal gas insufflation on, and we have probably used
16 this on a total of 100 patients. At the University of
17 Pittsburgh, we have over 150 ICU beds with approximately 50
18 different physicians staffing those beds.
19 The indications that people use TGI for are
20 variable, but the two main ones are either ARDS or patients
21 who are having difficulty weaning. Because we used this for
22 a longer period of time, we do humidify this gas with a
23 cascade humidifier, and we do also always insert the
24 pressure relief valve to prevent over-pressurization.
25 The average duration of TGI in these patients is

1 from three to five days, but we have had someone as long as
2 28 days on tracheal gas insufflation, and over the course of
3 three years we have seen basically three major
4 complications.
5 Two of them occurred very early on, and one of
6 them was the same as Avi reported, was the explosion of the
7 cascade humidifier. The second one that we saw was a
8 patient that we had entered in our research study with
9 positive results, and the attending physician wanted to
10 continue the therapy for a longer duration.
11 We actually advised against it because it was
12 certainly one of our earlier studies and we didn't feel that
13 our respiratory therapy department or other people had
14 sufficient expertise to do this safely, but the attending
15 physician insisted that the therapy continue, and four or
16 five hours later, in the middle of the night, there was an
17 accidental disconnection from the tracheal gas insufflation
18 source, and the patient developed hypoventilation,
19 hypercarbia, and at that point it was discontinued.
20 Then, our last serious complication --
21 DR. SLUTSKY: You have got two minutes left.
22 DR. MIRO: Our last complication involved an
23 occlusion of a right mainstem bronchus with mucus plug 10
24 days after someone was on tracheal gas insufflation.
25 As far as long-term safety, I think in Pittsburgh,

1 and I know in other areas, there is other issues that can be
2 translated or transferred onto TGI, and that is a close
3 cousin which is trans-tracheal oxygen delivery.
4 People have been insufflating gas directly into
5 the trachea for a long time in these patients with chronic
6 hypoxemia, and certainly the safety data is out there on
7 that.
8 [Slide.]
9 We don't do children or infants, so that is easy,
10 and then in focusing on what kind of system requirements do
11 we need -- and I think both Questions 4 and 5 address that
12 issue -- and this is the list that I have made with what I
13 consider essential provisions on the left and optional
14 provisions on the right.
15 Heat and humidity are absolutely positively
16 essential, and we need pressure alarms to tell us about
17 disconnects or about over-pressurization injury. We
18 obviously need some type of pressure relief mechanism in the
19 event that there is some type of obstruction, so that gas is
20 not continuously insufflated into the lung.
21 I think it is also essential to have some type of
22 suctioning ability to prevent mucus plugging and
23 obstruction.
24 Contrary to Dr. Nahum, I think ventilator
25 interface is in fact optional, not necessarily mandatory. I

1 think if it built in, that is fine, but if you are an
2 institution that uses more than one ventilator, it would be
3 nice to have a transportable apparatus that would function
4 with more than one ventilator.
5 Then, the issue of tracheal pressure monitoring,
6 whether we need to monitor pressure distally or is it
7 sufficient to monitor it more proximally at the airway, I
8 think is also one of the key questions posed to this
9 committee, and debating it, in fact, moving it from one
10 column to the other, I finally left it under Optional,
11 because quite frankly, I think you can get the same
12 information with pressure monitored proximally at the
13 airway, not necessarily down into the trachea, and I think
14 it is very nice, although not essential, to have a
15 radiopaque catheter to confirm appropriate position.
16 [Slide.]
17 So, in summary, based on our research and clinical
18 experience, we believe that TGI is a useful adjunct to
19 mechanical ventilation with the main endpoint being
20 enhancing CO_2 elimination.
21 We know that auto-PEEP occurs, and we believe that
22 rather than -- at least at our institution -- rather than
23 going to an inverted catheter, which we don't have, we
24 simply counter it by reducing ventilator PEEP.
25 I think that the most important safety provisions

1 that have been very eloquently defined by Dr. Nahum, and
2 that I have touched on, as well, can be very easily
3 incorporated into TGI delivery devices, and I think that
4 there is many publications out there on TGI, as well as
5 other close relatives, so that I think we understand what is
6 it, I think we understand what it does, and the potential
7 safety concerns, and I think those can be addressed, and
8 should be addressed, in the development of these devices.
9 Thank you.
10 [Applause.]
11 DR. SLUTSKY: Thank you.
12 Any questions from the panel?
13 DR. CLARK: I will ask one real quick question.
14 You obviously have had experience with this. You didn't
15 present any data about how well you change CO_2 in these
16 patients, or what the mortality rates or were there any
17 tracheal --
18 DR. MIRO: I didn't present them because I was
19 trying to keep it as brief as possible, which is always hard
20 enough as it is, but certainly we showed decrease in CO_2
21 with tracheal gas insufflation. I think everybody has shown
22 that. That is sort of the easy part.
23 We do not look at mortality as one of our
24 endpoints, and I forgot the third one.
25 DR. CLARK: Tracheal injury.

1 DR. MIRO: We did do this in a dog study that we
2 did. We took all the tracheal specimens and sent them to
3 histopathology, and that was actually published in the
4 Journal of Intensive Care, and there was no
5 histopathological evidence of tracheal injury in short-term
6 TGI, because it is only a matter of hours that we did those
7 dog studies.
8 DR. SLUTSKY: Thanks very much.
9 The next speaker is Peter Fitzgerald from Spirit
10 Medical Systems, Inc.
11 MR. FITZGERALD: Spirit Medical Systems, we are
12 small, start-up company in Denver, Colorado, two of us, and
13 our objective is to develop a tracheal gas insufflation
14 system. We have met with Dr. Bazaral and his group here,
15 along with Dr. Nahum and many other people that are doing
16 tracheal gas insufflation in an attempt to understand all of
17 what is necessary and how we can possibly approach it.
18 I hope that this will come halfway right, but
19 basically, what I want to talk about is our approach, what
20 we have done, and to deal with some of the problems that
21 both Dr. Nahum and Dr. Miro have addressed.
22 [Slide.]
23 We thought that there were three areas that we
24 wanted to look at, and that was clinical problems solved
25 through design, clinical problems -- and these are

1 literature problems, problems that were in the literature
2 that were solved by maybe changing the way that you run
3 your ventilator -- and then third are problems that need to
4 be solved, but they won't be solved in the first round.
5 They are problems that will have to be solved later on, and
6 I think a lot of this interface with ventilators fall into
7 that area.
8 One of the problems -- and this is not the right
9 order obviously, and I am not sure that the right order is
10 forthcoming, but let's start with the way they are right
11 now, and these are design problems.
12 Mucus balls or potential tissue damage resulting
13 from cold, dry TGI gas. Most of the early studies were done
14 with dry gas right from the wall. We provide in our system
15 a high-pressure canister which works with both the two most
16 commonly used heat and humidification systems, the Fisher-
17 Paykel, or the now vital signs SET-3000.
18 It provides heat and humidification for the
19 volumes of gas that we are working with, which range between
20 4 and 10 liters a minute.
21 Dr. Nahum mentioned that that was very necessary,
22 and so did Dr. Miro. FiO_2 changes, we use a blender with
23 our system, so we match FiO_2's with the ventilator.
24 Inability to stop TGI if sudden endotracheal tube
25 occlusion should occur. Having heat and humidification on

1 your gas does a lot towards eliminating that potential, but
2 we also have a high pressure monitor alarm system to deal
3 with that, that measure the distal pressure of the TGI
4 catheter.
5 Potential for continuous TGI to cause ventilator
6 circuit pressures to exceed the peak inspiratory pressure
7 limit during pressure control ventilation. We took the
8 system that was fabricated by the University of Pittsburgh,
9 that particular popoff system, and made it a little bit
10 simpler, but it works exactly the same way, and it works, as
11 Dr. Miro said, very, very well.
12 [Slide.]
13 Take a look at our system here. Our monitor is at
14 top. We got into a TGI pool, a blender. We use a pressure
15 regulator, back pressure compensated flow meter, a heat and
16 humidification system. This one happens to be a Fisher-
17 Paykel series.
18 It is the things that people in the ICU are used
19 to, they have these things in their armamentarium, and there
20 is very little learning curve involved with hooking them up
21 and using them with the system.
22 [Slide.]
23 Clinical instruction. I am going to try and see
24 if I can find the right slide here, and I really apologize.
25 I am sure it is at the very end.

1 Clinical design problems. Inability to suction
2 the patient without tearing down the TGI setup. If you look
3 at the early papers, even some of the later papers, people
4 use fabricated systems that they have to completely take
5 apart to suction the patient.
6 If you suction the patient every two to three
7 hours, this is quite an inconvenience and quite difficult.
8 We have a dual-purpose closed catheter which has been
9 approved now for their use in hypoxemia, but it contains two
10 catheters. One is a 14 French suction catheter, and one is
11 a 8 French TGI catheter.
12 Ultimately, our design was for this system, and
13 its use in this system. You cannot use both catheters at
14 the same time. They have to be used one at a time.
15 Inability to identify the catheter on x-ray. We
16 used the radiopaque catheter for the TGI, which solves that
17 problem.
18 Inability to accurately position. Dr. Nahum spent
19 quite a bit of time determining the ideal position of 1 to 2
20 cm from the carina. We have a very simple method of doing
21 that based on the length of the endotracheal tube and the
22 initial x-ray of the patient after intubation. I think it
23 works over and over again, allows you to take it out and put
24 it back in and replace it, the very same spot.
25 Inability to secure the TGI catheter's position.

1 We use the Touhy-Borst connection to do that. That is very
2 familiar, commonly used in the cardiovascular area, and
3 works very, very well.
4 Let's take a look at our catheter. You can see it
5 has two different catheters. One is a suction, very common,
6 14 French, most preferred. The other is an 8 French,
7 radiopaque catheter.
8 [Slide.]
9 The problem areas. Inability to function, that is
10 a design issue. Inability to identify on the x-ray, that is
11 a design issue. Inability to accurately position, a design
12 issue. Inability to secure, that is a design issue.
13 Mucus balls and tissue damage resulting from cold,
14 dry air, that is also a design issue. FiO_2 change is a
15 design issue.
16 [Slide.]
17 Inability to stop TGI flow if sudden endotracheal
18 tube occlusion should occur, that is also a design issue,
19 and the potential for continuous TGI to cause ventilator
20 circuit pressures to exceed the peak inspiratory pressure
21 limit is also a design issue. We have dealt with all of
22 those issues in our system.
23 Inability of the ventilator to detect circuit
24 leaks, Dr. Nahum mentioned it. We have looked at that, and
25 we have done quite a bit of bench work on that. I think it

1 can be very nicely managed when you change the lower limit
2 of the ventilator on the exhalation side to represent what
3 you are really going to see during continuous. Dr. Nahum
4 mentioned that it would be quite high, and that is correct,
5 so that you have to adjust the ventilator so that it is
6 looking at a realistic volume, and not the volume that is
7 was dealing with, with the tidal volume.
8 Inaccurate calculation of delivered tidal volume.
9 There are formulas for that. There are some caveats also
10 having to do with the type of patient and how the patient
11 reacts as to the accuracy, but you can pretty accurately
12 determine what you are delivering in the way of tidal volume
13 addition during TGI.
14 CO_2 monitoring. Dr. Nahum mentioned looking at
15 the affectivity of TGI by using your capnographer,
16 capnograph system, but also people use the told standard
17 ABG's to look at exactly where they are coming out. Both
18 methods work. It is just that the initial idea of how you
19 are going to use your capnography has changed.
20 Inability to evaluate end inspiratory pause of
21 auto-PEEP values, that is what Dr. Nahum was talking about.
22 On our system, you can flip it into bypass, so you can do
23 that on an every-so-often basis, so you can make those
24 evaluations, but during continuous TGI, that is a
25 difficulty.

1 DR. SLUTSKY: Two minutes.

2 MR. FITZGERALD: I have got one more to go.

3 [Slide.]

4 Reduced ability to trigger the ventilator. I
5 think there is a future solution for that. TGI-induced
6 auto-PEEP, I think Dr. Miro covered that. That is an
7 instruction possibly area, but also can be modified by some
8 design changes.

9 Inability of the ventilator to provide accurate
10 display. That requires the development of communication
11 systems which we anticipate with ventilators, but my belief
12 is that that won't become a reality until there is systems
13 out, being used in the marketplace, and then the ventilator
14 companies would become interested in becoming involved in
15 this, but until that time, I don't think there is any
16 interest on their part.

17 Inability of ventilator to match tidal volume with
18 exhaled volume, again, that is a communications item.

19 In summary, I think that all of the real critical
20 areas can be addressed. There is a lot of people doing TGI,
21 a lot more than I think any of us really would think right
22 off the top of our heads.

23 They are doing it continuously. They are doing it
24 with a lot of systems that aren't so good, and I think that
25 once systems are out, then, the interest will be there, and

1 the industry in general, and more and more sophisticated
2 applications will be possible.
3 Thank you.
4 [Applause.]
5 DR. SLUTSKY: Thank you.
6 Any questions from the panel? I think the
7 questions should be kept to the general issues related to
8 TGI rather than specifics of the system.
9 DR. CLARK: What is your estimate of how many
10 people are using it?
11 MR. FITZGERALD: I think between 5- and 10,000
12 treatments a year. There is a lot of people that we run
13 into that have become aware of us through just word of mouth
14 and call us, and they are doing quite a bit, and they are
15 doing it in all different ways. There is no common
16 methodology.
17 I think what is really critical is you have to use
18 things that the staff is used to using, blenders, common
19 heat and humidification systems, those kinds of things,
20 because then the comfort level is enhanced dramatically, and
21 if you have a catheter that is easy to use, that uses the
22 same type of technology that they are used to with
23 suctioning, I think then you have a good chance at being to
24 do it very, very easily and I think very comfortably and
25 safely.

1 DR. SLUTSKY: Thanks very much.

2 The next is the detailed discussion of those five
3 questions. I think we should take a 10-minute break and be
4 back here at 25 to 3:00.

5 [Recess.]

6 **Panel Discussion on Questions on Tracheal**
7 **Gas Insufflation**

8 DR. SLUTSKY: The first question we are going to
9 address is up here now. It is called Question 2, but is
10 really Question 1, as you know.

11 For ventilation of adults, is there now sufficient
12 understanding of TGI to be reasonably sure that TGI with
13 adequate monitoring and understood safety positions will not
14 have worse outcomes? Or, does TGI raise concerns that will
15 require that FDA review data on patient outcomes?

16 So, really, the question is do we have to look at
17 clinical outcomes, whether it be days of ventilation,
18 mortality, whatever, or is it sufficient for a technique
19 like this, do we know enough about it to be able to look at
20 intermediate outcomes?

21 That is what we want the panel to address. The
22 way I think we will work this is I would like to have the
23 panel address these issues. I will allow some comment or
24 two from the floor. I would like to keep it very short,
25 though, because we have five questions to get through, and

1 then there is going to be time officially for public
2 discussion, as well.
3 Questions, comments from the panel? Bob.
4 DR. KACMAREK: I think that today we have adequate
5 information as has been reviewed to indicate that TGI does
6 do what it is anticipated to do, to alter CO_2 levels or
7 maintain CO_2 at a lower pressure.
8 With the appropriate monitoring and safety
9 provisions, I think that we have sufficient data to not
10 require outcome studies because I don't think there is any
11 data that would imply that the systems have an adverse
12 effect on outcome with the one exception.
13 I am concerned about simply placing a small bore
14 catheter through an endotracheal tube and injecting those
15 high flows in a tube that just flips around inside the
16 trachea, particularly the long-term effects, which I don't
17 think are available in any system.
18 You have seen it, I have seen it, if you take that
19 and you do it in a lung model, and just look at the amount
20 of whip that there potentially can be, it is hard to imagine
21 that there would not be likelihood for adverse effects, and
22 I don't think there is any data to show us that long term
23 that will not be detrimental.
24 Outside of that particular issue, the concept and
25 the way that it has been done seems to me to be reasonably

1 safe.

2 DR. MONK: I guess I would agree that I think it
3 is going to be very difficult to get mortality data, because
4 there are so many confounding factors going on in ICU
5 patient groups, but I am concerned about the tracheal damage
6 that could be caused also, and I would think that a study
7 could be designed where you looked at a subgroup of patients
8 that were quite well matched, say, trauma patients, and if
9 you want to look at outcome.

10 With head trauma, patients with trauma, often they
11 have aspirated, they would have CO_2 levels that would be
12 above a certain level. You could stratify this type of
13 patients, maybe not do huge studies, so that you would get
14 outcomes in terms of mortality, but you might be able to see
15 some differences in the groups in terms of tracheal damage
16 in this type of morbidity data.

17 DR. KACMAREK: The other thing that may be
18 reasonable to look at, I mean we are talking about a gas
19 delivery system, but we are also talking about a potential
20 catheter, endotracheal tube. As Avi has indicated, there
21 are a number of different designs available, and each design
22 may have unique issues associated with it.

23 So, it may be to decouple this and to looking at
24 the issues regarding gas delivery and the issues of how that
25 gas is injected into the airway.

1 It is simply an ancillary catheter placed in the
2 airway, or is it the use of an especially designed
3 endotracheal tube, is it a direct flow towards the carina,
4 is it a reverse flow, you know, back up into the
5 endotracheal tube itself? All of those would have impact on
6 this particular issue.
7 DR. SLUTSKY: So, in terms of advice for the FDA,
8 because that is all we are doing now, we are just discussing
9 -- just to make it clear -- we are just discussing some
10 general advice to FDA staff, not necessarily laying out an
11 exact plan for how this will be done for each submission,
12 clearly, you have to look at each individual device.
13 They are going to have unique specifications, and
14 if it is a single catheter, you are going to worry about
15 whipping. If it is not, you are going to worry about other
16 things. So, clearly, each one of these potential problems
17 that have been brought up would have to be addressed, but it
18 sounds like at least from the two of you that an
19 intermediate endpoint, in other words, efficacy in terms of
20 improving CO_2, what do the other people -- Cathy?
21 DR. SASSOON: Probably, I think the engineering
22 stuff by itself, we will be able to adequately overcome like
23 tidal volume, PEEP, et cetera, but what I am concerned is
24 the bronchial injury.
25 There has not been any long-term study looking at,

1 for example, from bronchial biopsies of these patients or
2 even in animal studies, several days of tracheal gas
3 insufflation, does that result in the bronchial mucosa or
4 would that be a source of additional infection.
5 So, the main thing is to do no additional harm
6 than what we have done or what the patient already has.
7 DR. ROIZEN: But it seems to me you have got to
8 balance this desire we have for additional data with what is
9 going on currently, and by not having anything, will the
10 current policy, which may be worse, continue, and I don't
11 know how the FDA balances the current use of feeding tubes,
12 et cetera, to do this, or if there is a device that may have
13 greater safety than that although we don't have definitive
14 data.
15 DR. SLUTSKY: Does somebody from the FDA want to
16 address that issue that Michael just brought up in terms of
17 -- I guess the question is if people out there are using
18 this now without standardized devices produced by a company
19 that there is no FDA approval, the risk might be greater
20 than a system that has some potential problems that haven't
21 been sorted out, but still be better than what is out there.
22 I guess that is really their question.
23 Does someone from the FDA want to address that?
24 Mike or Tom?
25 DR. CALLAHAN: Well, clearly, it is always a

1 benefit or risk, and if we see major problems out there, we
2 have ways in which to go out and stop it, but clearly, we
3 are trying to be an advocate for getting good products out
4 there, so we don't always have all the answers, but I think
5 what we are asking of you is you can lay out all of the
6 benefit and risks, that will help us make those decisions
7 easier.
8 DR. ROIZEN: Could you put this as part of a
9 postmarketing requirement if this is accepted or if there is
10 some guideline, then, that patients be followed for the
11 degree of injury?
12 DR. CALLAHAN: For a long-term follow-up you mean?
13 DR. ROIZEN: Right.
14 DR. CALLAHAN: That is certainly possible.
15 DR. SLUTSKY: Don.
16 DR. PROUGH: It seems to me the answer to the
17 first part of the question really has to be no, because, in
18 fact, the concerns that tracheal gas insufflation raises are
19 concerns related to whether, in fact, it is possible to
20 adequately engineer and monitoring safety provisions.
21 Most of the issues that have been raised today are
22 not I think sufficient to offset those continuing concerns.
23 DR. SLUTSKY: So, you still think that there is --
24 the other panelists answered yes, just so we get the
25 question right -- you are saying no, that there isn't enough

1 data yet that we could just look at intermediate outcomes
2 and safety outcomes?
3 DR. PROUGH: I am really not comfortable granting
4 the assumption that adequate monitoring and safety
5 provisions are forthcoming.
6 DR. BAZARAL: Having assumed that, I mean suppose
7 that were clearly done, would you address the other question
8 anyway, I mean being uncomfortable as you are with the
9 assumption?
10 DR. SLUTSKY: In other words, when the
11 manufacturers come in -- we are talking now theoretically --
12 but when the manufacturers come in, they are going to
13 address these issues, and they are going to have some data
14 to how they handle each of these questions. Let's assume
15 that they can handle them. If they can't handle them, it is
16 a different issue, but let's assume they can.
17 Is looking at simply PCO_2 or ventilation or tidal
18 volume sufficient, or we do have to do an outcome study?
19 DR. ROIZEN: They are asking you to assume their
20 statement, that there is adequate monitoring and understood
21 safety provisions exist.
22 DR. PROUGH: I would still like to see information
23 that says that a new modality, presumably one that incurs
24 some additional patient care expense, has a positive
25 influence, or at the very least, not a negative influence on

1 outcome, and I think the experience to date is not
2 sufficient to believe that we have identified all of the
3 possible adverse consequences of tracheal gas insufflation.
4 DR. CLARK: Just as a follow-on to exactly what
5 you are saying, there are two issues. Obviously, if we make
6 the statement that you have to have a mortality outcome, you
7 are not going to find a whole lot of people who are willing
8 to invest in the technology in ARDS to try to do that,
9 because that outcome is essentially impossible to measure.
10 However, I want to go on the record as saying that
11 I agree that if we are going to introduce an order of
12 magnitude more complex ventilator into the PICU or to the
13 adult intensive care arena, or the neonatal intensive care
14 unit, I would like to be reassured that that has some
15 patient care benefit, and I think at least with my
16 experience with nitric oxide in a different area of the FDA,
17 physiologic endpoints are not adequate surrogates for long-
18 term outcome, and I think there are ways to look at softer
19 outcomes that we would all consider valuable, whether they
20 be vent days or less frustration on a ventilator because our
21 CO_2 is lower and you are not as anxious, or some other
22 measure that might be a beneficial measure.
23 I am not willing to just jump out and accept
24 adding another layer of complexity to change just CO_2.
25 DR. SLUTSKY: You started off by saying you

1 wouldn't accept, and then you said, well, lower CO_2, that
2 makes you feel more comfortable, would be an adequate --
3 DR. CLARK: Well, the outcome there would not be
4 CO_2, it would be a measure of the patient's comfort. The
5 outcome measure would be patient comfort, not necessarily
6 the CO_2.
7 DR. SLUTSKY: Not physician comfort.
8 DR. CLARK: Right.
9 DR. MONK: Or possibly the sepsis issue or the
10 tracheal damage issue, something like that. I mean there
11 would be intermediate outcomes that you could look at when
12 you look at patients to determine if there were differences
13 in morbidity, and you wouldn't have to rely on mortality
14 outcomes, but you would probably have to look at more than
15 just lowering CO_2.
16 DR. CLARK: It comes back to the CO_2 issue in
17 prematures. I mean there are good data in prematures, that
18 if you drop the CO_2 too quickly, that is not a good thing.
19 I would imagine the same thing with intracranial pressure
20 monitoring, if you quickly drop the CO_2 or let the CO_2 go up
21 very quickly, changes that are occurring quickly may not
22 necessarily always be good for the patient.
23 DR. KACMAREK: We can accomplish changes in CO_2
24 levels by many different mechanisms, mechanically
25 ventilating patients today. We can increase, we can

1 decrease, we can do whatever we want. I mean that is up to
2 the clinician to decide the speed or the rapidity that those
3 changes are made.
4 This system, again assuming adequate monitoring
5 and safety standards, and assuming we avoid the issues of
6 tracheal damage because of an unstable catheter flopping
7 around on the system, I think is a minor additional adjunct
8 to what we do today in mechanically ventilated patients, and
9 although I would agree that the patient data is not
10 overwhelming, that a lung protective ventilatory strategy is
11 going to improve outcome.
12 I submit that if we were to review all the animal
13 data and the preliminary patient data, it is pretty hard not
14 to make a case that that is, if we can design the study
15 properly, going to prove to be of benefit to the patient.
16 I mean even Art's study and Brochard's, and other
17 ones who showed no benefit, I would argue that they show no
18 benefit because the two arms of the study were equivalent,
19 there was no difference, there is not enough separation in
20 the plateau pressures, or high enough PEEP to have any
21 impact.
22 So, it may be difficult, as everybody has seen, to
23 design the study to do that. I think here, the issue is
24 really can this be designed to be done safely, without any
25 adverse impact by the application of this technique to

1 patients, and will it result in the efficacy that has been
2 clearly shown with crude systems, you know, in multiple
3 patient and multiple animal studies.
4 DR. ROIZEN: So, the answer you would like to
5 give, as I hear it, is yes, if we can do it safely enough.
6 DR. KACMAREK: I am not saying we can do it safely
7 enough. I am saying if we can do it safely enough. I think
8 there is adequate data to show that TGI, with the
9 appropriate ability to monitor I think distal airway
10 pressures, to be able to properly adjust PEEP, to maintain
11 peak airway pressures constant to avoid situations where I
12 would have an occlusion in the ventilator circuit from the
13 pressure distally and the lung from excessively increasing
14 because of this flow.
15 If all that type of issues can be worked out, I
16 would say there is sufficient data to go forward with this.
17 Now, that is a big "if."
18 DR. SLUTSKY: Ellen.
19 MS. ROSENTHAL: This question is really a very
20 interesting question. I think it is the wording of it. It
21 sort of says, you know, if we can do everything that TGI is
22 supposed to do without any problem and make it really work
23 well, do you think that this won't be worse than it was
24 before.
25 I think it is sort of like something Bill Clinton

1 would have said to the public.

2 [Laughter.]

3 MS. ROSENTHAL: Maybe what needs to be done, the
4 question just simply is do we have a good goal here. That
5 is really what this is saying if you take all the
6 hypotheticals. I think that is really the question, and
7 maybe what needs to be done is we need some kind of research
8 into making the events occur that are, you know, the events
9 we don't want to occur, which sounds sort of diabolical, but
10 at what point do we really start to run into problem with
11 this little tube that is running through another tube, and
12 that is small, but has high velocity air, gas coming through
13 it, where do we start to really run into trouble, and maybe
14 we have to find out where we run into trouble.

15 There hasn't been enough research to even see
16 that.

17 DR. SLUTSKY: Good point.

18 Lois.

19 DR. BREADY: I am going to reiterate I guess what
20 Bob said to a certain extent. I think there is some
21 interesting data out there. There is a big black box, that,
22 yes, if we can assume that all the safety things can be put
23 into place and functional, I think there is enough
24 interesting positive data to support our supporting the FDA
25 going forward and looking for the technology, but it is a

1 big black box at this point, the safety issues.

2 DR. KACMAREK: Maybe we should look at the big

3 black box with safety issues first, and then come back to

4 this question. Maybe we should define or give our

5 recommendations of what those issues of safety, et cetera,

6 are, and then come back here after we have had that

7 discussion. Maybe this can't be answered until we all fully

8 understand what it is we think are the safety and monitoring

9 issues.

10 DR. NAHUM: Am I part of the panel?

11 DR. SLUTSKY: You can answer. Well, you are part

12 of the panel for this, how is that?

13 DR. BAZARAL: Let me say exactly. You are here,

14 you are a speaker, and we are very grateful for that, and

15 you are cleared to answer any questions related to the

16 subject that you spoke about.

17 DR. NAHUM: I am hearing a very interesting

18 conversation, yet, I cannot help to think about the

19 ventilators that we use, and there hasn't been any outcome

20 data on ventilators that I know of.

21 I mean there are all kinds of new ventilator

22 modalities that are coming out, yet, there are no outcome

23 data on those. Having put that aside, let me address the

24 bronchial injury information.

25 There is some data in the literature in terms of

1 bronchial injury. There is a paper, which I cannot remember
2 exactly the reference, but they did look at it short term by
3 bronchoscopy, no biopsy, and they weren't able to see any
4 damage, but this is short term.
5 DR. SLUTSKY: How short term?
6 DR. NAHUM: I think on the order of hours is my
7 memory, but I would have to dig out the paper, but there is
8 a study --
9 DR. KACMAREK: And what kind of system?
10 DR. NAHUM: This was a catheter that was placed
11 through the endotracheal tube. Your concern would be valid
12 on that one with the flipping.
13 We did a study in constant flow in dogs. We did
14 show some bronchial injury, however, we did not condition
15 the gas, we didn't heat, we didn't humidify. We used
16 extremely high flow rates, about 60 liters per minute.
17 Then, you can demonstrate some injury.
18 DR. SLUTSKY: That was 60 liters per minute,
19 right?
20 DR. NAHUM: Sixty liters per minute.
21 DR. ROIZEN: Can we go to the other questions and
22 come back to this?
23 DR. SLUTSKY: Yes, we will, but let's finish
24 hearing --
25 DR. NAHUM: I will just finish. I think the

1 physiological endpoints, you have enough data for the
2 physiological endpoints in the literature right now. There
3 is enough data to convince at least me that when you turn
4 TGI on, the PCO_2 will come down. That is clear.
5 Now, whether that is going to translate into a
6 patient outcome, is going to be a very tough question to
7 answer.
8 DR. SASSOON: We do have like the data on
9 ventilator-associated pneumonia. After three days, the
10 incidence increases, and from that point of view, when we
11 use TGI, we would not like to see additional infection.
12 DR. DEXTER: It seems that there is a difference
13 between, on the one hand, asking whether the tracheal gas
14 insufflation improves the patient's outcome versus at least
15 making sure that the outcome isn't any worse, and even
16 though there may not be a mortality input, at least at the
17 secondary endpoints, such as ICU time or ventilator time,
18 which may or may not correlate well to long-term outcome, at
19 least the secondary endpoint shouldn't be worse with the
20 treatment.
21 DR. CLARK: Just let me make a comment, that
22 remember that proving safety is much harder than proving
23 efficacy, because the safety endpoints generally occur less
24 frequently and are less likely to be changed, and so let's
25 be careful in that regard.

1 DR. SLUTSKY: Clearly, the issue here is if you
2 had an infinite amount of money, you would want a clinical
3 outcome study, but they are actually quite difficult and
4 expensive to do. Even for ventilator-free days with not
5 mortality, you know, the n you need is actually not that far
6 from what you need for mortality studies if you want to show
7 a clinically important change of ventilator-free days and
8 days off the ventilator.
9 For example, the NIH study's power to have about
10 800 to 1,000 patients to see a difference actually there in
11 mortality, that is a huge study for something that is going
12 to have a small effect here.
13 I mean we all agree that the effect we are going
14 to observe in terms of PCO_2 or tidal volume is going to be
15 relatively small. The question is obviously, I am just
16 rewording it, are the safety features then, we have to be
17 that much more concerned, if you like, or that much more
18 sure that the safety issues are dealt with.
19 If there is no safety issues, then, that small
20 decrease in PCO_2 and tidal volume would be potentially
21 beneficial, and then we sort of have to -- and that is what
22 we are obviously playing with in terms of the safety issues.
23 Any other comments?
24 DR. BAZARAL: Just an analogy. There are any
25 number of studies that are very similar to this, that if you

1 have milrinone, for example, and you can increase the
2 cardiac output very nicely with that drug, and if you treat
3 patients with cardiomyopathy with that drug, you increase
4 the cardiac output, and you increase the morality rate.
5 So, if you use the endpoint of does the drug work,
6 yes, to increase the cardiac output, but what does it do to
7 the outcomes? It is not obvious that that would happen.
8 People have treated patients that way for a long time before
9 the long-term definitive studies.
10 I don't know what the answer to this is, but I was
11 wondering whether we are far enough from worrying about that
12 in this question to say, well, we are reasonably sure that
13 we are not going to somehow induce different outcomes than
14 would be predicted from the reduction in CO_2 alone, assuming
15 that all the rest is okay.
16 DR. SLUTSKY: I think this is a little bit
17 different than the drug story, because there is always --
18 the same is true with antiarrhythmics -- but I think when
19 you are dealing with drugs, there is a difference.
20 Here, we are dealing with sort of physical
21 mechanisms, and again assuming all the safety issues, the
22 acute safety issues we know about can be handled, it is the
23 sort of very unknown issues of lowering the PCO_2 a little
24 bit, because we can, as Bob said, you can do that with the
25 ventilator, just increase the tidal volume a little bit, so

1 it is not quite the same, although clearly there could be
2 hidden issues we don't know about.
3 The judgment we have to make is sort of to the
4 best of our abilities, and it is very easy to sort of say no
5 to things, but then most of I think the improvements in
6 therapy over the past number of years have been sort of
7 small, incremental therapies, and it appears that mortality
8 from ARDS is dropping.
9 If you stop each one of these incremental
10 advances, you know, in the long term that is not beneficial,
11 so there is obviously no simple answer.
12 Any other comments? We can go back to this
13 because this really is the critical question, it seems to
14 me. The others are dealing with specifics.
15 I would like to open this up for a couple minutes
16 to any short comments from the public.
17 [No response.]
18 DR. SLUTSKY: Let's move on. There is no comments
19 from the public.
20 Next question. This really a corollary, if you
21 like, of the previous question.
22 For evaluation of effectiveness of specific TGI
23 systems as an adjunct of ventilation of adults, is reduction
24 of minute ventilation or PCO_2 without appreciable increase
25 in end expiratory lung volume or pressure a sufficient

1 endpoint? Is this the correct endpoint?

2 Bob.

3 DR. KACMAREK: This is like the first question.

4 It is difficult to separate them. The only thing that TGI

5 has been proposed to do is to alter CO_2 and in doing that,

6 maintain tidal volumes at a smaller level or maintain CO_2

7 and bring tidal volumes down. That is all anybody has

8 proposed that it is to do.

9 Unless we believe there is a need for outcome

10 studies affecting, as you just discussed, to me this is the

11 right question.

12 DR. SLUTSKY: I think is this the correct

13 endpoint, I think it is the correct endpoint. Whether it is

14 sufficient is sort of the issue we were discussing

15 previously, but in terms of the mechanism, what this is

16 supposed to do, it is supposed to decrease CO_2 or decrease

17 tidal volume.

18 DR. ROIZEN: This is a difference of effectiveness

19 and safety, so is this a sufficient endpoint for

20 effectiveness, and I don't think you can get another one for

21 effectiveness in the ARDS situation in a reasonable amount

22 of time. So, I think the two questions are very different,

23 one is safety, one is effectiveness. This is the

24 effectiveness, and this is what I would say is the only

25 effectiveness endpoint we can reasonably expect. As an

1 adjunct, whatever you want to call that form of permissive
2 hypercapnic ventilation is now called, that I still call
3 permissive hypercapnia, but if that is found to be not
4 useful, then, it doesn't matter what endpoint we use here
5 because it won't be used. If it is useful, then, this will
6 be the next thing studied in a larger outcome.
7 So, I think this is, for now, this is a sufficient
8 endpoint for effectiveness.
9 DR. SLUTSKY: Don.
10 DR. PROUGH: I think the answer is yes, but with
11 very, very extensive qualifiers. I think it is critical to
12 recognize that this is an adjunct to theoretically
13 preferable modes of mechanical ventilation, that are
14 themselves at this point of questionable efficacy.
15 I can easily ventilate any patient to produce
16 hypercapnia, and I can easily add tracheal gas insufflation
17 to reduce $PaCO_2$, and I will have proved absolutely nothing
18 other than that tracheal gas insufflation reduces $PaCO_2$, so
19 I think as a minimum, the modality has to be demonstrated to
20 decrease $PaCO_2$ in a population in which that actually
21 represents a serious clinical problem that is not
22 arbitrarily established, that is, a patient who really can't
23 be adequately ventilated to reduce $PaCO_2$, not one who is
24 arbitrarily placed in the hypercarbic category.
25 DR. SLUTSKY: I think that is a good point and, in

1 fact, part of this is, it is much simpler to show a decrease
2 in CO_2 in normal subjects or normal animals, for example,
3 and what you are saying is that just taking normal subjects
4 and showing that there is a decrease in PCO_2 really isn't --
5 it's a no brainer, as they say, and it is not how this is
6 going to be used, so it is in the context of which this is
7 going to be used, and for the moment that looks like it is
8 largely patients with ARDS, but not only patients with ARDS.
9 There are certainly theoretically other ones.
10 DR. PROUGH: I think it might even be critical to
11 define not only that they have ARDS, but that they have ARDS
12 that makes it difficult to generate hypercarbia with some
13 sort of arbitrarily defined safe level of mechanical
14 ventilation.
15 I don't think you can take patients who are
16 arbitrarily assigned to protective lung strategy, effective
17 lung ventilation strategies, and then add TGI and prove very
18 much. I think they have to be patients who, with some sort
19 of rigorously defined criteria, can't be ventilated at a
20 normocarbic level.
21 DR. SLUTSKY: In fact, the Rouby study was sort of
22 a prototype of the kind of thing that might be done, for
23 example, patients who did have a high CO_2 in order to keep
24 them within that window of lung protective, not just for the
25 sake of having their PCO_2 increase.

1 Any other comments about this point?

2 DR. SASSOON: I think another important thing that
3 needs to be brought up is the indication. I think that
4 needs to be spelled out carefully, what level of CO_2, what
5 level of pH, for example, which has not been raised here.

6 DR. SLUTSKY: So, the level at which you apply TGI
7 you mean? I don't know that we can address that
8 specifically here. Actually, another problem related to
9 that, what would the panel think about what is a clinically
10 significant decrease in PCO_2 or increase in pH?

11 You could have a statistically significant
12 decrease in PCO_2 of 1 millimeter of mercury, but that is
13 clearly not clinically significant.

14 DR. KACMAREK: It depends on the patient. It is
15 tough to make that kind of broad generalization. As you
16 well know, minor changes in some patients have a big impact,
17 and big changes in other patients have no impact on their
18 overall status.

19 Clearly, there are patients in which you want to
20 keep the PCO_2 at 40, as you have indicated, head injury
21 patients, in which you might want to decrease the mean
22 airway pressure to maintain that CO_2 of 40 by using this
23 technique.

24 So, I am not sure you can totally define an
25 arbitrary circumstance where if you are above this level

1 only or below that level, I mean there are many clinical
2 settings in which it would be useful to have an adjunct to
3 conventional mechanical ventilation that allowed you to
4 maintain a CO_2 at whatever level, at less pressure, less
5 volume cost.
6 DR. SLUTSKY: Right, but if TGI reduced, let's say
7 somebody developed a system where TGI reduced the PCO_2 by 1,
8 from 41 to 40, and that could be studied in enough patients,
9 that would be statistically significant. We also could say,
10 yeah, big deal.
11 DR. KACMAREK: Right. I mean you wouldn't buy the
12 system.
13 DR. CLARK: The way I would answer that question
14 is again in study design. I think that you select a group
15 of patients that have met a threshold of CO_2, and you have a
16 target CO_2 that you are trying to accomplish, and rather
17 than saying, looking at continuous variables, you would ask
18 treatment success. You would say this patient had a CO_2 --
19 they enrolled patients with CO_2 greater than 60, and our
20 goal was to introduce tracheal gas insufflation at a rate
21 that would bring the CO_2 to 50, that was successful 80
22 percent of the time compared to controls where without
23 adjusting the ventilator or without adding this new therapy,
24 there were no successes.
25 Now, the reality is any randomized control trial,

1 there are going to be some successes just from the time-
2 related course of the thing, and again I think I am not real
3 happy with a physiologic endpoint. I guess it is because
4 everything I have ever studied has been held to a different
5 standard, so that makes me feel uncomfortable, and I guess I
6 am convinced by many of the anecdotes that the FDA has told
7 me over the years, that just changing physiology can have
8 unanticipated long-term consequences.
9 Certainly, we have learned that in the premature
10 infant where we know that we can use high frequency to
11 protect the lung, I think relatively well from clinical
12 trials, but if we don't use high frequency and we change CO_2
13 quickly, we damage the brain, or stronger surfactants
14 showing the same thing.
15 So, I am not so sure that changing CO_2 quickly
16 with tracheal insufflation is necessarily a benign or
17 necessarily a good thing. Normalizing CO_2 slowly might be a
18 good thing, but again you get into a lot of issues.
19 So, I want to just infect, as the neonatologist of
20 the group, the baby doctor, that just looking at physiology
21 as the efficacy endpoint makes me a little anxious.
22 DR. SLUTSKY: I can understand your concerns, but
23 I think always the issue is again what is the relative risk,
24 and with, for example, high frequency ventilation,
25 introduction of high frequency ventilation, clearly, there

1 are lot of potential and real relative risks, as well, so
2 you then have to balance it in that respect.
3 I don't think the issue is so much as lowering the
4 PCO_2 quickly because most of the patients, it is the
5 opposite. You try to use this lung protective strategy,
6 your PCO_2 goes up very quickly, and this is to stop the
7 increase, if you like, PCO_2. So, I am not sure that, in and
8 of itself, is a major concern.
9 DR. KACMAREK: What you are really talking about
10 is how you apply the technique. I mean you could start out
11 slowly. I mean you could do whatever you wanted to
12 theoretically, you know, going low flows to high flows, and
13 over a period of time you can change CO_2 at whatever speed
14 you felt was clinical efficacious.
15 DR. PROUGH: This is a study design issue, but the
16 other potential problem in trying to randomize patients to
17 get TGI or not get TGI, it will be essential to basically
18 define the non-TGI group and define their management in such
19 a way as to keep them hypercarbic or there won't be a
20 difference.
21 DR. SLUTSKY: Or look at tidal volume as your
22 endpoint, how much have you been able to decrease -- sorry?
23 DR. CLARK: Ventilation index of some form or
24 fashion where you used tidal volume and $PaCO_2$ and rate
25 together to come up with some measure of intensity of

1 ventilation to get the outcome you look for.

2 DR. SLUTSKY: Comments? Any comments from the

3 floor? Neil, do you want to come up? Just announce who you

4 are, Neil, and how you got here.

5 DR. MacINTYRE: I am Neil MacIntyre. I am a

6 Professor of Medicine at Duke University. I am here because

7 I do some consulting work for Trudell Medical, which is not

8 in the TGI business, but does other things.

9 I just want to make one quick comment that I think

10 both you and Bob can identify with. We had a consensus

11 conference a couple of years ago on assessing efficacy of

12 innovations, and I find this question fascinating, because

13 it was the very same question we addressed at our

14 conference.

15 I think our conclusions that we agreed to or at

16 least sort of agreed to was that intermediate endpoints,

17 physiologic endpoints were legitimate endpoints providing

18 two things. Number one, that safety was claimed and was

19 very clearly there, and that was the major issue for using a

20 physiologic endpoint. If safety was of concern, then, more

21 in-depth outcome studies were required.

22 The other consideration, of course, was cost,

23 which is not really the issue of the FDA, but similarly,

24 physiologic endpoints for an inexpensive device are fine.

25 If the device costs a substantial amount, then, more

1 impressive outcome studies are required, and we formed that
2 little grid that I still find very, very useful in thinking
3 about whether physiologic endpoints or outcome endpoints are
4 important.
5 Thank you.
6 DR. SLUTSKY: Neil, before you sit down, just one
7 quick question. In terms of the safety issues here, where
8 would you put this on the grid?
9 DR. MacINTYRE: Art and Bob, you may remember we
10 actually put TGI on the grid there, and it ended up being
11 we, as a group, agreed it was what we called a Level 2,
12 which was that the safety issues were of such a concern that
13 we felt physiologic endpoints were legitimate, that an
14 outcome study was not required for TGI.
15 DR. SLUTSKY: Any other quick comments from the
16 audience, from the public?
17 [No response.]
18 DR. SLUTSKY: Let's move on.
19 Question 3. Are there special considerations
20 about the data the FDA should review for TGI submissions in
21 relation to ventilation of children, infants, newborns, or
22 premature infants?
23 DR. CLARK: I think the biggest concern obviously
24 is the ET tube size and the need to monitor distal airway
25 pressures. I mean you are talking about nanoseconds at 10

1 liters per minute before you have blown out the lung, and I
2 unfortunately have seen that happen in a variety of
3 different situations with catheters that are down in the ET
4 tube, and that does happen.
5 I haven't had it happen to me personally, but I
6 have come on call after it has happened to somebody, and
7 that consequence is almost all the time lethal.
8 DR. ROIZEN: Should there be limitations in the
9 flow rates or based on weight or size of child?
10 DR. CLARK: Absolutely, I think that would be
11 important.
12 DR. ROIZEN: Is that the way you would handle the
13 situation?
14 DR. CLARK: I think that the issue of distal
15 pressure monitoring is basically essential. If you think
16 about a jet device, the jet device monitors pressure
17 distally in large part because, again, even at 3 liters per
18 minute, if you were looking at a lung volume that is not
19 more than 20 cc or 30 cc at max in a big kid, I mean not a
20 child, but in a baby, even at 3 liters per minute, if you
21 have a partially obstructed endotracheal tube, and that flow
22 is distal to that obstruction, you are not going to see it
23 proximally until the baby has bilateral tension
24 pneumothoraces.
25 DR. SLUTSKY: Clearly, by the way, 3 liters a

1 minute is way, way too high.

2 DR. CLARK: But even to take that further, there

3 has to be in that setting a mechanism, not just to monitor

4 distal pressure, but based on distal pressure, immediately

5 inactivate the TGI flow. I mean I think it's a double

6 issue. You have got to be able to identify the problem, and

7 if the problem exists, there has to be a mechanism to stop

8 that flow immediately for any of these systems to be safe,

9 whether it's a child or an adult for that matter.

10 DR. MONK: When we deal with drugs in the FDA,

11 often drugs are approved initially for adults and then for

12 children much later on. I would wonder if there is enough

13 data out there on TGI in children and infants that it should

14 even be considered at this time. I haven't seen a lot of

15 information.

16 DR. CLARK: There is actually a study that was a

17 part of the packet, that was a randomized control trial that

18 looked at --

19 DR. MONK: How many patients were in it?

20 DR. CLARK: It was small.

21 DR. MONK: That is not a very big study. There is

22 not much out there. I mean one little study, certainly in a

23 totally different physiologic model, doesn't make me

24 comfortable.

25 DR. ROIZEN: Can we ask Dr. Miro, do they use this

1 at Pittsburgh in the Children's Hospital there?

2 DR. MIRO: My answer is very brief. Yes, they do,

3 but I am not involved in it at all.

4 DR. SLUTSKY: You are going to have to repeat it.

5 DR. MIRO: Yes, they do use it in Children's

6 Hospital from my conversations with some of the pediatric

7 ICU people there, but I have not been involved with it at

8 all.

9 DR. ROIZEN: And you don't know what safety

10 precautions they take.

11 DR. MIRO: No.

12 DR. SLUTSKY: John, do you want to comment?

13 DR. ARNOLD: I am John Arnold from Boston

14 Children's Hospital. I consult for Cook Catheter

15 Corporation occasionally.

16 We have used it in five babies with CDH,

17 congenital diaphragmatic hernia, not the TGI design, but an

18 ITPV reverse thrust design, and we have had no problems

19 other than humidifier problems, no problems with the baby,

20 but as Reese has mentioned, if you don't monitor distal

21 airway pressure, then, you can't undertake to ventilate

22 anybody of any size.

23 I would add to Bob's comment about immediate

24 catheter shutoff, is immediate venting to atmosphere,

25 because you need -- that applies both to ventilator circuit

1 and to the catheter, because if the ventilator circuit is
2 occluded, then, the catheter is the only hope that you are
3 going to decompress the lung.
4 So, we have used it, and we have used it in a
5 homemade system, and I think that as part of your review of
6 systems, maybe not this panel, but the FDA's review, that an
7 integrated system will be essential to address all these
8 safety and monitoring features in one fell swoop.
9 DR. SLUTSKY: John, what flow rate did you use?
10 DR. ARNOLD: Well, we used total ITPV, very high
11 flow rates, where if the endotracheal tube became occluded,
12 we would have an immediate problem, so we used total
13 catheter flow rates up to about 6 or 8 liters per minute in
14 a 3, 3.5 kilogram child.
15 DR. SLUTSKY: Thanks, John.
16 DR. NAHUM: The paper in the packet used 0.5
17 liters per minute, half a liter per minute.
18 DR. SASSOON: But then the ITPV, I think it is as
19 reverse thrust catheter, so that is different.
20 DR. SLUTSKY: Right
21 DR. CLARK: In the babies, the type ET tube that
22 you were talking about, it had multiple ports on it, that
23 was at least the paper I was looking at, so it was not
24 reverse thrust.
25 DR. NAHUM: I think that is the modified

1 Boussignac tube, if I remember correctly.

2 DR. SLUTSKY: So, clearly, there are issues. I

3 mean you have got obviously the smaller endotracheal tube

4 and the ratio of the catheter that goes in there to the

5 actual size is one issue, and then the flow rates are

6 clearly another issue.

7 I think what you need is distal pressure

8 monitoring and action based on that distal pressure, not

9 just monitoring it, because as we have all said, by the time

10 an alarm goes off and someone comes in, that's too late.

11 Clearly, that is doable.

12 Any other points about children, infants,

13 newborns? Again, anything from the public?

14 [No response.]

15 DR. SLUTSKY: Let's move on.

16 Question 4. What are the minimum system functions

17 that include all the functions needed to provide TGI for

18 clinical use as an adjunct to or replacement for

19 conventional ventilation?

20 If I understand this question right, the FDA

21 personnel, this is really what are the safety issues in

22 terms of what you want to monitor from a system point of

23 view?

24 DR. BAZARAL: I guess what we are asking is what

25 should we review as the minimum specifications, and now

1 somebody has a tracheal tube that is a TGI tracheal tube,
2 presumably we would say, well, what does this thing connect
3 to.
4 So, at some point, maybe the first one that gets
5 reviewed, you would have to ask, well, how much do you
6 review. Now, they don't have to necessarily provide the
7 entire system, but they may need to specify components of a
8 system, but they would at least need complete labeling to
9 say how you are going to use this thing and how their device
10 fits in that.
11 So, I guess we are saying not just what does a
12 manufacturer have to make, which may be more than you would
13 ask, but really what does the manufacturer have to specify
14 at one point to say, yes, they have a TGI thing that we can
15 review, we will be able to say this is the effect of this
16 system, this is the expected operations of the system. I
17 don't think personally we can review a catheter. You may,
18 in which case tell us that.
19 DR. ROIZEN: Let me go and give five immediate
20 ones, and then have people add on, but there are probably
21 10, but the five immediate ones, they have got to specify
22 gas source, heat and humidity, how to monitor, how to
23 monitor alveolar ventilation and some way of shutting it
24 off.
25 DR. SLUTSKY: So, it's gas, heat and humidity, and

1 give me the other three again.

2 DR. ROIZEN: Alveolar ventilation, shutoff for

3 increased pressure, and monitoring.

4 DR. SLUTSKY: Monitoring of what?

5 DR. ROIZEN: Monitoring the requirements that you

6 have for the system, whether it's pressure or alveolar

7 volume or some other. I don't want to limit what may be

8 developed in the future, but I think it is pressure now.

9 DR. KACMAREK: I would add I think you need to

10 have the ability to monitor end inspiratory, as well as end

11 expiratory pressure in the system, that you have to have

12 some mechanism, whether it's a continuous or phasic system

13 of momentarily inactivating the system, so you could allow

14 for an evaluation of where you are at, end inspiratory or

15 end expiratory.

16 I realize you can play games with tidal volume and

17 pressure targets, but that doesn't always work in every

18 patient, you know, very easily when you add a secondary

19 system to understand the effect that that system is having

20 on FRC level or end inspiratory volume level.

21 DR. ROIZEN: I guess I want to add one or two more

22 in thinking about it, and I don't know whether you have got

23 to specify how to suction, and also how to determine where

24 the catheter is.

25 DR. KACMAREK: Depending on the design of the

1 system, clearly, both of those would be important.

2 DR. SLUTSKY: Do you want to comment on those?

3 DR. CLARK: I just want to ask a question.

4 Alveolar ventilation, help me. Were you talking about CO_2

5 or were you talking about actual tidal volume changes at the

6 alveolus?

7 DR. ROIZEN: Someday there may be the latter

8 system, I don't know that, so I don't want to limit the

9 FDA's evaluation saying by current technology, but you want

10 one of those. Right now it's obviously pressure, because we

11 aren't going to get that other one now, that I know of.

12 DR. SLUTSKY: Do you mean minute ventilation? I

13 mean alveolar ventilation is PCO_2.

14 DR. ROIZEN: Alveolar volume is what I actually

15 wanted. No, there is no alveolar volume, but someday there

16 may be, but right now you are going to use pressure.

17 Really, what you want, you don't care, I mean what I see you

18 want is alveolar volume, not pressure, but we don't have

19 that now.

20 DR. SLUTSKY: You want regional volume.

21 DR. KACMAREK: End expiratory pressure would be

22 the surrogate for that.

23 DR. ROIZEN: That's as close as we have got. That

24 isn't the ideal, but you don't have the ideal now.

25 DR. KACMAREK: Did we include issues of

1 recommended flow through the tube, through the system, the
2 way it is designed, because depending upon the design of the
3 system, clearly, there is going to be issues about how you
4 would set flow.
5 DR. SLUTSKY: Flow, presumably, you can use these
6 at different flow rates.
7 DR. CLARK: You just want to know exactly what --
8 I mean whatever, gas source or some measure of that flow.
9 DR. CALLAHAN: Just in general, if it is going to
10 be used as conventional ventilation, the conventional
11 ventilator has to work. Its controls, alarms, and monitors
12 all have to work. I think that is a minimum requirement.
13 My argument would be that we haven't really heard
14 anything today that says that this should be considered as a
15 replacement for conventional ventilation. I would think
16 that if it were to be proposed as a replacement for
17 conventional ventilation, that would require really a much
18 more comprehensive assessment of functionality and some sort
19 of outcome study.
20 DR. KACMAREK: I would agree.
21 DR. ROIZEN: Totally agree.
22 DR. SLUTSKY: I think really what is important is
23 how does it affect the ventilator, the ventilator-TGI
24 interaction, and we talked about [teregrene], for example,
25 and that is not listed here, but things like that, all those

1 systems. One of the slides that Avi had one dealt with a
2 lot of the potential problems, and you could almost put the
3 specification besides them or an in issue that each of those
4 has to be addressed.
5 Anything else?
6 DR. BAZARAL: Suppose with respect to the
7 conventional ventilator modification, you are saying, well,
8 fine, the system, whatever is, will be labeled for very
9 limited, specific subset of the ventilator function, in
10 other words, say you use it during pressure, limited
11 ventilation, and nothing else, no triggering, no pressure
12 support ventilation, just those, the plain old controlled
13 pressure-limited ventilation, and the device was labeled for
14 only that subset, so the device-ventilator interaction could
15 be circumscribed and perhaps understood by the therapist?
16 DR. KACMAREK: I think clearly if you have a
17 stand-alone system that doesn't interphase with the
18 mechanical ventilator, it is going to have to be described
19 under those very specific circumstances.
20 DR. BAZARAL: But would that be acceptable?
21 DR. SLUTSKY: Well, I think you have got real
22 problems there potentially.
23 DR. PROUGH: I don't think that would be
24 acceptable at all, because the one thing you can be
25 reasonably sure with a stand-alone system is that the first

1 day that is available, it will be used with the other
2 modalities.
3 DR. ROIZEN: But on the other hand, I mean look at
4 it this way, you are not going to get where you want to get,
5 I mean if you want to get there, you are not going to get
6 that right away, so you are going to have to specify some
7 requirement right away if you are going to have anything
8 that replaces the homemade systems that are currently used.
9 DR. BAZARAL: A colleague of mine, who I recently
10 spoke with, said that given a little money and a couple of
11 weeks, that they could adapt a reasonable ventilator to do
12 all that you want to do in terms of controls, and is
13 wondering why that hasn't been done.
14 I don't know that it has to be done in an
15 incremental way. In other words, with a microprocessor and
16 half a brain of your own, you can go ahead and do that.
17 Somebody is nodding his head over there.
18 DR. KACMAREK: Avi has done it, we have done it.
19 You can do this, you know, you can interphase with the
20 ventilator and do this stuff.
21 DR. SLUTSKY: I have concerns with a stand-alone
22 system. You know, we are talking about the relative safety
23 and efficacy, and we don't know what the answer is yet in
24 terms of the relative efficacy or safety, but in terms of
25 efficacy, it is not going to be a huge impact. If it is

1 going to decrease tidal volume by, as I said, 15 percent
2 sort of on average, that might have some effect, but I
3 wouldn't want to increase the danger of somebody putting it
4 on at 10 liters a minute, on volume control, and not
5 realizing that the tidal volume set on the ventilator is not
6 what the patient is going to get, it is going to be a lot
7 higher, and a lot of issues like that, that I think it is
8 better from sort of an integrated system rather than picking
9 one, let's just say pressure control, and letting it go.
10 Bob, you look like you have some disagreement with
11 that.
12 DR. KACMAREK: I am not disagreeing, but -- I
13 guess I am. Theoretically, I could design a system that
14 would meet all your requirements, that would be a stand-
15 alone system. Are you saying I should be prevented from
16 doing that?
17 DR. SLUTSKY: No, no. If you can attach it to a
18 ventilator, and all those issues are taken care of, no
19 problem.
20 DR. KACMAREK: Interphase it with the ventilator,
21 it could deal with sensitivity issues, it could be used in
22 different modes of ventilation, it would have all the safety
23 features that we have talked about, I don't have a problem
24 with that if it can truly interface with the ventilator and
25 be used no matter how the ventilator is being used.

1 DR. SLUTSKY: I think we are in agreement. I
2 consider that an integrated system whether it happens to be
3 made by a ventilator manufacturer or -- it just got to be
4 able to be integrated with the ventilator, and not screw up
5 with the ventilator does.
6 DR. SASSOON: I think we should limit this minimum
7 system function for use in ARDS, and not weaning, nothing to
8 do with weaning, but an acute respiratory failure.
9 DR. SLUTSKY: I don't think that is up to us
10 necessarily to limit it now. If a manufacturer comes in and
11 shows data that it can aid the weaning process, and, you
12 know, there is no data out there now, but I don't think we
13 should say it should not come in.
14 DR. CLARK: Maybe the question is, is that the
15 efficacy outcome that we are looking for, ARDS, is different
16 than what we would consider for weaning, because there you
17 have a measurable outcome, did the patient come off the
18 ventilator when weaning was initiated more effectively.
19 DR. SLUTSKY: The outcomes would be different,
20 clearly. Good point.
21 Any other comments from the panel? Questions?
22 [No response.]
23 DR. SLUTSKY: How about from the public, any of
24 the manufacturers want to address this issue?
25 MR. FITZGERALD: Peter Fitzgerald, Spirit Medical.

1 I think all of medicine in my 25 years of
2 experience, selling all kinds of products, surgical,
3 dialysis, dialysis had no integration whatsoever in 1975,
4 nothing. It was a machine that just ran some dialysate
5 fluid through, and people monitored aneroid measurements and
6 adjusted pressure on venous resistance.
7 It took about 10 or 12 years before integrated
8 systems came on the market, and I think this not any
9 different than that. Before you get an integrated system
10 into a ventilator company -- I would have thought they would
11 have done this a long time ago, but they haven't because
12 they have demonstrated no market.
13 Until you demonstrate that there is a market,
14 then, I think the integration will happen, but usually it is
15 small, innovative companies that introduce this type of
16 technology, and then the other people get on.
17 If you can't get into the market because you want
18 a totally complete, finished, wonderful, tied-up-in-a-bow
19 package, it probably won't happen because the market hasn't
20 been demonstrated.
21 DR. SLUTSKY: I think that what has changed since
22 1975 is 1976, and the amendments for the FDA, and we have to
23 show safety and efficacy.
24 MR. FITZGERALD: Of course, but what has to happen
25 is, is that you have to not only write the software, which

1 is the easier part, you have to validate it. That is not so
2 easy. That takes a lot more time and money than writing it.
3 So, our perspective is, is provide a safe system
4 to do continuous, and then you can move on to phasic, you
5 can move on to other things, but you can develop the
6 communication system with the other ventilator manufacturers
7 if they choose to do that. They may not, and besides you
8 have to then upgrade your ventilator, the number of
9 ventilators you have, so that you always have one ventilator
10 that can integrate with the system.
11 So, our approach has been to have a system that
12 can stand alone and ultimately can be integrated, to that
13 you are never caught in a situation where you can't use it
14 or you have to switch ventilators or you have to find the
15 one that has the communication system.
16 DR. SLUTSKY: Thank you.
17 Any other comments?
18 [No response.]
19 DR. SLUTSKY: Okay. Let's move on.
20 Question 5. What specific safety provisions are
21 important? Is distal pressure monitoring essential?
22 DR. KACMAREK: Yes.
23 DR. SLUTSKY: Yes, the answer for question 1 or 2?
24 DR. KACMAREK: Question 2. As I said before, I
25 think you have to monitor distal pressure, you have to have

1 a mechanism of inactivating the system, and as John said,
2 you should be able to dump pressure from the total system as
3 soon as it recognizes that we have a distal pressure
4 increase above some threshold.
5 DR. SLUTSKY: So, it is more than monitoring, for
6 Question No. 2, it is more than monitoring obviously.
7 DR. KACMAREK: Yes.
8 DR. SLUTSKY: And we said that a couple times.
9 DR. DEXTER: I think that if it seems that the
10 endpoint of effectiveness is devoted to lower the CO_2, and
11 if it is going to be an adjunct to conventional ventilation
12 part of the safety provisions, is the impact of the device
13 on the other ventilator, and whether it be an integrated or
14 non-integrated component, if, for example, it is going
15 affect the accuracy of the tidal volume on the conventional
16 ventilator, it needs to be addressed as part of the safety
17 provisions, if it's an adjunct.
18 DR. CLARK: I would like to ask a question of -- I
19 am sorry, I misplaced your name in my brain -- that has done
20 most of the clinical data, I am very surprised that you have
21 never had -- are you measuring pressure distally in your
22 group of patients, and you have never seen -- because in the
23 newborn nursery, the ET tube becomes occluded not
24 infrequently. I guess in adults, you just don't see that as
25 a problem?

1 DR. MIRO: Dr. Miro from Pittsburgh.

2 We have never seen complete occlusion of the
3 endotracheal tube during TGI. Distal pressure, I presume
4 you mean something within the thorax, such as certain
5 endotracheal tubes, I know come with lumens that you can
6 measure distal pressure. We don't use any of those
7 specialized endotracheal tubes. We measure proximal airway
8 pressures, and from our experience we have never had any
9 endotracheal tube occlusion problems, neither partial
10 occlusion nor complete occlusions.

11 It is not to say it is not going to happen. I
12 gave you an approximation of how many patients we have done
13 total, approximately 100, perhaps a little bit more. So,
14 maybe it is just a matter of time, but we have not seen it.

15 I am not sure -- again, when we use it clinically
16 for longer term, we do add the heat and humidification,
17 which is I think critical in avoiding desiccation of
18 secretions and obstruction of the tube, so perhaps for those
19 reasons we don't see it.

20 DR. PROUGH: I think there is certainly no
21 question that adults periodically do get obstructed
22 endotracheal tubes, albeit much less frequently than
23 neonates obstruct 2.5 millimeter tubes.

24 The other problem you have occasionally in adults
25 depending on how you manage the airway is sometimes they

1 bite the endotracheal tube, so the possibility of having
2 either transient or prolonged occlusion of endotracheal tube
3 can't be ignored in adults.
4 DR. SLUTSKY: That all gets to point number 2, if
5 you have a distal pressure monitoring and appropriate
6 controls.
7 DR. KACMAREK: Or a patient who is moving around,
8 you can easily occlude the expiratory limb of the system and
9 have the same issues in relationship to a flow where there
10 is no monitoring, you know, a distance from the exhalation
11 valve.
12 DR. SLUTSKY: What about No. 1? I think the
13 second part of this question, we all agree. What about No.
14 1? What specific safety provisions are important? We have
15 dealt with some of these along the way, but it might be
16 worth summarizing them, and some of them actually go in the
17 list we had before.
18 Anything we haven't covered or does somebody want
19 to review them?
20 DR. KACMAREK: The issues of monitoring pressures
21 and inspiratory and expiratory pressures, as has already
22 been indicated, a method of identifying tidal volume
23 delivery in this system in which we are providing a
24 secondary gas flow.
25 We have dealt with the pressure monitoring and the

1 release, issues of humidification, temperature regulation of
2 the insufflated gas. I am running out of issues.
3 DR. SLUTSKY: Avi, anything we haven't covered?
4 DR. NAHUM: Pressure popoff. Did you include
5 that?
6 DR. SLUTSKY: Some sort of pressure release.
7 DR. KACMAREK: Some sort of release system.
8 DR. NAHUM: Do you want my slide?
9 DR. SLUTSKY: Maybe it's worth putting that slide
10 up.
11 I will just read this for the record. The
12 pressure volume monitoring, pressure popoff mechanism,
13 humidification, issues of bronchial injury, issues with
14 suctioning, issues with optimal catheter configuration and
15 flow, and interaction with mechanical ventilator.
16 Those are really a list of problems, but get at
17 some of the issues that would have to be addressed.
18 Anything not covered there? You said you made
19 this slide seven years ago, Avi. You don't have anything
20 since then? [Laughter.]
21 Any other comments?
22 This now gets back to an in essence sort of
23 question. If each one of these can be handled, are we happy
24 with intermediate outcomes? I guess the proof is in the
25 pudding in some sense, how well are each of these handled,

1 and on and on.

2 Bob.

3 DR. KACMAREK: As I said before, if these are

4 handled to the specifications of the FDA, based on these

5 recommendations, I don't see why we cannot accept for this

6 level of technology, you know, intermediate, physiologic

7 outcomes.

8 DR. SLUTSKY: Any other comments?

9 DR. MONK: I agree, but I think that it should be,

10 as Mike said earlier, linked with postmarketing studies to

11 look at incidence of morbidity, so that at least in that

12 way, you can be collecting data on tracheal injury, sepsis,

13 some of the other problems that we have alluded to today.

14 DR. SLUTSKY: I guess that is getting us a few

15 steps in advance, but I can see a difficulty with ARDS

16 patients, monitoring for sepsis, let's say, almost -- I am

17 not sure how you get an answer unless 98 percent had sepsis.

18 DR. KACMAREK: Again, as I said earlier, I think

19 that that is a separate issue, the issue of the catheter

20 design and the potential morbidity associated with the

21 catheter outside of the system, because you can get a gas

22 delivery system that can be used with multiple catheter

23 designs.

24 As I said, I think there may be two different

25 issues to look at, one that is put together, it seems to me

1 that if you put a catheter that is simply being placed
2 through an endotracheal tube, you would have to show that
3 that catheter -- and I would say even before it was approved
4 -- did not create any morbidity when it is used the way it
5 is designed to be used.
6 DR. SLUTSKY: A catheter that is 1 cm at the
7 carina, blowing gas at 10 liters a minute for --
8 DR. KACMAREK: And maybe 3 cm from the tip of the
9 endotracheal tube can be moving pretty good, you know, and
10 if it is sitting there doing that for a lengthy period of
11 time, I don't know.
12 DR. SLUTSKY: I think it depends clearly on the
13 specifics, but just having a catheter a centimeter from the
14 carina, blowing gas at a single point on the carina or on
15 the airway over a prolonged period of time, clearly,
16 intuitively, you know, could potentially cause problems.
17 DR. MONK: We know that from our CVP literature,
18 that having a catheter at the wrong place in the vascular
19 system can cause problems.
20 DR. KACMAREK: We know it from the jet literature
21 as is indicated already.
22 DR. SLUTSKY: Those are much higher flow rates,
23 but yes.
24 DR. KACMAREK: Right.
25 DR. SLUTSKY: I want to get the panel first, and

1 then I will open it up. Any other comments from the panel?

2 [No response.]

3 DR. SLUTSKY: Anything from the public? Come on

4 up again.

5 MR. FITZGERALD: Peter Fitzgerald, Spirit Medical.

6 With regard to catheter whip, Trans-Tracheal

7 Systems have been in business for about 15 years, and they

8 use a 9 French catheter without the endotracheal tube. I

9 think most of you are familiar with it, for the delivery of

10 oxygen.

11 Dr. Christopher has run those as high as 25 liters

12 a minute, 8 hours at a time, without any catheter whip. We

13 have done bench studies, and I think Pete Bliss can verify

14 this, at over 10 liters, 12, 15 liters. There is no whip.

15 It settles. These catheters have enough durometer to them,

16 that they are about 85 Shore, but 92 durometer, they don't

17 move, and neither does the trans-tracheal. It settles in a

18 position and it stays there.

19 So, it doesn't move around back and forth, and it

20 just stays where it is placed, where it finds its position

21 is where it stays. If you put it into, and can anchor it

22 into its position 1.5, 2 cm from the carina, as Avi's study

23 shows, you will get the results that you are looking for,

24 but that catheter is not whipping around.

25 DR. KACMAREK: I think, as I said, it all depends

1 on the design and how narrow that lumen is. You choose a
2 catheter of a smaller lumen to be used in a smaller size
3 endotracheal tube or to minimize the amount of obstruction
4 through that tube, and you try to put through 10, 12 liters
5 per minute flow, that catheter whips. I mean it simply
6 depends on the design, and that is the point I am trying to
7 make, that it would have to be shown that those were not
8 issues, that there was no adverse outcome issues associated
9 with the specific tube design.
10 MR. FITZGERALD: You can show that easily in a
11 bench study.
12 DR. SASSOON: But the problem with the difference
13 with TGI, is that here you are integrated with the
14 mechanical ventilator that delivers certain flow, certain
15 flow rate up to like 60 liters per minute or so, in addition
16 to the gas insufflation itself.
17 MR. FITZGERALD: And you think that is making it
18 move around?
19 DR. SASSOON: Yes, possibly.
20 MR. FITZGERALD: I don't think so. I haven't seen
21 it.
22 DR. SLUTSKY: I think the issue is if you have got
23 a catheter down there, and that is a potential concern, you
24 have to show that it doesn't.
25 MR. FITZGERALD: I am just saying you can do that.

1 DR. SLUTSKY: Right, that is not a problem.

2 MR. FITZGERALD: And I don't think that is a big

3 problem.

4 DR. SLUTSKY: John, you have been waiting for a

5 while.

6 DR. ARNOLD: John Arnold from Boston.

7 Just a few pediatric issues, and these may be

8 assumed, so if I am being redundant, I am sorry, but a

9 couple of things came to mind in our clinical experience.

10 One is a specific catheter-endotracheal tube size

11 combination should be specified, because as you get small,

12 then, the size of the catheter and endotracheal tube becomes

13 very important, as Reese I think mentioned earlier.

14 The other is this distal pressure monitoring idea

15 we have all talked about and agreed it is important, it is

16 actually very hard to keep that device patent if it is air

17 filled. So, our experience is that a continuous low bias

18 flow through the system to continuously flush it is

19 important, and then some fail-safe system, either a display

20 of that output or some way to monitor whether, in fact, you

21 are monitoring what you think you are monitoring.

22 DR. SLUTSKY: Neil.

23 DR. MacINTYRE: Neil MacIntyre. I would just like

24 to make a comment about the distal pressure measurement

25 requirement, listening to Bob's statement. As a separate

1 system, I can certainly understand the need for that, and I
2 would encourage that.
3 I might argue, however, if you have an integrated
4 system with the ventilator, where the ventilator was
5 providing the TGI flow and the ventilator flow, that it is
6 conceivable that the proximal pressure sensor would be
7 adequate to do that.
8 Any occlusion distal to the TGI catheter would be
9 detected as a high peak pressure, and the ventilator and the
10 TGI flow would cycle off. Any obstruction proximal to the
11 TGI catheter would still be detected by the ventilator as a
12 high pressure situation, and both TGI and ventilator flow
13 would be turned off.
14 So, while I certainly appreciate the fact that
15 distal pressure monitoring is critical, I think in the
16 situation of an integrated system, where the ventilator was
17 supplying both TGI and ventilator flow, that it is
18 conceivable that a proximal pressure sensor may do the job
19 for you.
20 DR. KACMAREK: I think it is a matter of proving
21 that you can design a system that would work that way under
22 all possible circumstances. I mean it gets back to the
23 point if it is truly integrated into the ventilator, a lot
24 of things are different from trying to add something to an
25 existing ventilator.

1 DR. MacINTYRE: I agree.

2 DR. SLUTSKY: I think the issue is what are the
3 potential dangers, and then there may be very innovative
4 ways we haven't thought of to overcome those, and one danger
5 is blockage of the endotracheal tube, and if someone has got
6 an innovative way, or a ventilator can handle it, that's
7 fine, but that has to be taken into account sort of in the
8 thinking about what a potential down side of this technique
9 is.

10 DR. BLISS: My name is Peter Bliss. I am with
11 [Valley] Products from Minnesota. We are an engineering
12 company. We have been involved in making tracheal gas
13 insufflation controllers for research, and my plane ticket
14 down here was bought by Mallinkrodt, so let there be no
15 doubt that my intentions are impure.

16 [Laughter.]

17 DR. BLISS: I have got a question that is also
18 relative to the distal pressure monitoring, and this ties
19 into Dr. MacIntyre's comment also, that if I say do you
20 really mean that you need distal pressure monitoring or do
21 we need to protect against tube occlusion or, in a grander
22 sense, do we need to protect against blowing up the
23 patient's lungs, that may seem like an inane question to the
24 physicians, but as an engineer, adding the requirement for
25 distal pressure monitoring is certainly a big concern, and I

1 apologize, the gentleman from Boston had mentioned that it
2 brings up some issues with keeping that conduit patent is an
3 issue, the fact that you have to now have two conduits to
4 the bottom of the endotracheal tube instead of one is an
5 issue from possibly a marketing sense because how am I going
6 to do that possibly without having to reintegrate the
7 patient.
8 So, I would just like to, if possible, a
9 discussion or just to Dr. Kacmarek, do we need that
10 pressure, do we need to know what that pressure is, or do we
11 need to protect against blowing up the lungs?
12 DR. SLUTSKY: I think I suggested in the last
13 comment that really what we want to do is a fail-safe for
14 blowing up the lungs, and distal pressure monitoring is one
15 approach, but whatever technique you use has to be pretty
16 good because that is a real danger.
17 DR. KACMAREK: What Reese said before, you have
18 got a small child who is ventilated with a low rate for
19 whatever reason. It may be breathing spontaneously a little
20 bit at some point in time. You get an obstruction in the
21 endotracheal tube.
22 If we rely purely on the mechanical ventilator,
23 the amount of expiratory time may be so long before it
24 senses that there is an obstruction and inactivates the
25 system, that that two seconds or whatever time may be

1 sufficient with an ex-flow through your catheter to cause
2 significant damage to the patient.
3 So, I am not engineeringwise how you would avoid
4 this, but clearly, those kind of situations in some way
5 have to be prevented by the design of whatever system people
6 come up with.
7 DR. BLISS: Agreed, and I could just say that,
8 well, I am a wizard and I can do it somehow, but I think you
9 are right, you are definitely right, and probably the
10 pediatric -- what I am hearing is that the pediatric
11 situation or the neonatal situation has to be dealt with
12 possibly separately than the adult situation, because they
13 have completely different time constant and volume of the
14 system.
15 DR. SLUTSKY: Any other comments from the panel?
16 From the public?
17 [No response.]
18 DR. SLUTSKY: Let me ask a question to the FDA
19 staff. Have you got the sort of advice and comments that
20 you wanted or is there anything we haven't addressed in
21 sufficient detail that you would like us to address?
22 DR. BAZARAL: You have covered everything on my
23 list.
24 DR. SLUTSKY: Has anybody else got a list out
25 there?

1 Okay. Let me just one final time ask those of
2 you, the public, if you have any comments, suggestions that
3 you want to bring up now? I think we tried to keep this a
4 very open process.
5 [No response.]
6 DR. SLUTSKY: It looks like none. So I would like
7 to officially adjourn the meeting. I would like to thank
8 all the members of the panel and the FDA staff for their
9 presentations, and thank you all very much.
10 [Whereupon, at 3:55 p.m., the meeting was
11 adjourned.]
12 - - -

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO