

UNITED STATES OF AMERICA
 FOOD AND DRUG ADMINISTRATION
 PEDIATRIC ADVISORY COMMITTEE
 MEETING

Wednesday, November 16, 2005

The meeting came to order in the ballroom of the Hilton Washington North, 620 Perring Parkway, Gaithersburg, MD., at 8:00 a.m., Dr. Robert Nelson, Chair, presiding.

PRESENT:

ROBERT M. NELSON, M.D., Ph.D.	CHAIR
ROBERT DAUM, M.D.	MEMBER
ANGELA DIAZ, M.D., M.P.H.	MEMBER
DEBORAH L. DOKKEN, MPA	MEMBER
MICHAEL E. FANT, M.D., Ph.D.	MEMBER
ELIZABETH A. GAROFALO, M.D.	INDUSTRY REPRESENTATIVE
RICHARD L. GORMAN, M.D.	PEDIATRIC HEALTH ORGANIZATION REPRESENTATIVE (NON-VOTING)
MELISSA M. HUDSON, Ph.D.	MEMBER
JOHN W. M. MOORE, M.D., M.P.H.	MEMBER
THOMAS B. NEWMAN, M.D., M.P.H.	MEMBER
JUDITH R. O'FALLON, Ph.D.	MEMBER

CONSULTANTS PRESENT:

SILVA A. ARSLANIAN, M.D.	CONSULTANT
JEFFREY BOTKIN, M.D., M.P.H.	CONSULTANT
PATRICIA S. CHOBAN, M.D.	CONSULTANT
DOUGLAS S. DIEKEMA, M.D., M.P.H.	CONSULTANT
NORMAN FOST, M.D., M.P.H.	CONSULTANT
THOMAS INGE, M.D., M.P.H.	CONSULTANT
WILLIAM KLISH, M.D.	CONSULTANT
PAUL KNUDSEN	CONSULTANT
JOHN KRAL, M.D., Ph.D.	CONSULTANT
ROBERT LUSTIG, M.D.	CONSULTANT
WALTER PORIES, M.D., F.A.C.S.	CONSULTANT
ALBERT ROCCINI, M.D.	CONSULTANT

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ROBERT WARD, M.D.	CONSULTANT
JACK YANOVSKI, M.D., Ph.D.	CONSULTANT
CATHARINE CHAMPAGNE, Ph.D.	CONSULTANT
JACK YANOVSKI, M.D., Ph.D.	CONSULTANT
JAN N. JOHANNESSEN, Ph.D.	EXECUTIVE SECRETARY
SARA GOLDKIND, M.D., M.A.	OFFICE OF PEDIATRIC THERAPEUTICS, FDA
DIANNE MURPHY, M.D.	OFFICE OF PEDIATRIC THERAPEUTICS, DFA
RON YUSTEIN, M.D.	OFFICE OF DEVICE EVALUATION, FDA

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Pediatric Obesity Agenda
Pediatric Advisory Committee Meeting
November 16, 2005

8:00	Welcome	Robert Nelson, M.D., Ph.D. (Chair)	6
	Conflict of Interest Statement	Jan Johannessen, Ph.D.	6
	Opening Comments	Robert Nelson, M.D., Ph.D. (Chair)	12
8:15	Summary of Deliberations from the Pediatric Ethics Subcommittee Meeting of November 15 th	Norman Fost, M.D., Ph.D., Chair, Pediatric Ethics Subcommittee	15
	Discussion and Recommendations from the Committee	Pediatric Advisory Committee	16
9:45	Break		10 8
10:00	Conflict of Interest Statement	Jan Johannessen, Ph.D.	10
	Brief Overview	Dianne Murphy, M.D. Director, Office Pediatric Therapeutics FDA Ron Yustein, M.D. Acting Clinical Deputy Director, CDRH	11 8 12 5
10:30	"Obesity: A National Health Issue" -- Epidemiologic Talk	William Dietz, M.D., Ph.D., National Center for Chronic Disease	

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		Prevention and Health Promotion, CDC	15 4
10:50	Committee Questions of Clarification for Speaker		
11:00	"Obesity: A National Health Issue" -- Scientific Overview	Sandra Hassink, M.D., FAAP, Assistant Professor of Pediatrics, Jefferson Medical Collect	
12:00	Committee Questions of Clarification for Speaker		
12:30	Lunch		
1:30	Open Public Hearing		
2:30	Assent in Pediatric Research	David Wendler, Ph.D. Head, Unit on Vulnerable Populations, NIH	
3:00	Committee Questions of Clarification for Speaker		
3:10	Break		
3:25	Conservative Intervention	Deanna H. Hoelscher, Ph.D., RD, LD, CNS Associate Professor, U of Texas	
4:05	Committee Questions of Clarification for Speaker		
4:15	Surgical Intervention Including Devices	Victor Garcia, M.D. Professor of Surgery, U of Cincinnati	

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5:15	Committee Questions of Clarification for Speaker		
6:00	Adjourn		

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

(8:07 a.m.)

CHAIRMAN NELSON: I guess we'll have to get really close to these microphones.

So if we could begin to get our coffee at tables and start to drink them, so in 15 minutes we're ready to have some great conversation. But to remind the members of the Committee, before we actually get started, this first session, an hour and a half, is to consider a Subcommittee Review of a 5054 45 CFR 46.407 Panel that occurred yesterday. And the rest of the consultants and other individuals for the portion of the meeting that's going to be dealing with obesity will join us after the break, which is why the table looks quite empty.

So, welcome. And I guess I'll turn the initial starting of the meeting to Jan who will deal with the Conflict of Interest Statement.

EXEC. SEC. JOHANNESSEN: Good morning. The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee. The following announcement addresses the issue of Conflict

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1 of Interest with regard to the discussion of a
2 referral by an institutional review board for proposed
3 clinical investigation that involves both an FDA-
4 regulated product and research involving children as
5 subjects that may be supported by their Department of
6 Health and Human Services and is made part of the
7 record to preclude even the appearance of such at this
8 meeting. Based on the submitted agenda for the
9 meeting and all financial interests reported by the
10 committee participants, it has been determined that
11 all interests in firms regulated by the Food and Drug
12 Administration present no potential threat and
13 appearance of conflict of interest at this meeting.

14 In the event that the discussions involve
15 any other products or firms not already on the agenda
16 for which an FDA participant has financial interest,
17 the participants are aware of the need to exclude
18 themselves from such involvement and their exclusions
19 will be noted for the record.

20 We note that Dr. Norman Fost, Dr. Jeffrey
21 Botkin and Dr. Robert Ward are participating in the
22 meeting as voting consultants and that Paula Knudsen

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1 is participating as the acting voting consumer
2 representative. We would also like to note that Dr.
3 Elizabeth Garofalo has been invited to participate as
4 an industry representative, acting on behalf of
5 regulated industry. Dr. Garofalo is employed by
6 Pfizer. Dr. Richard Gorman is participating as a
7 pediatric health organization representative, acting
8 on behalf of the American Academy of Pediatrics.

9 With respect to all other participants, we
10 ask in the interest of fairness that they address any
11 current or previous financial involvement with any
12 firm whose product they may wish to comment on.

13 Thank you.

14 CHAIRMAN NELSON: Now, before we start
15 with the opening comments and overview, since there's
16 a number of fresh faces on the committee and it's a
17 new day, why don't we go around the table and
18 introduce ourselves as a start. Dianne, if you want
19 to begin.

20 DR. MURPHY: I'm Dianne Murphy and I'm the
21 Director of the Office of Pediatric Therapeutics at
22 the FDA.

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1 DR. GOLDKIND: I'm Sara Goldkind. I'm the
2 Bioethicist in the Office of Pediatric Therapeutics.

3 DR. GAROFALO: I'm Elizabeth Garofalo and
4 I'm the industry representative. I work for Pfizer.

5 DR. GORMAN: I'm Richard Gorman, a
6 Pediatrician in a suburban private practice and the
7 Chairperson of the section on Clinical Pharmacology
8 and Therapeutics for the American Academy of
9 Pediatrics.

10 MEMBER HUDSON: I'm Melissa Hudson. I'm a
11 Pediatric Hematologist/Oncologist at St. Jude and a
12 new member of the Pediatric Advisory Committee.

13 DR. BOTKIN: I'm Jeff Botkin, Department
14 of Pediatrics and Medical Ethics at the University of
15 Utah.

16 MEMBER DAUM: I'm Robert Daum. I'm in
17 Pediatric Infectious Diseases at the University of
18 Chicago and a new member of the Advisory Committee.

19 DR. FOST: Norm Fost, Departments of
20 Pediatrics and Bioethics, and Director of the
21 Bioethics Program and Chair of the IRB at the
22 University of Wisconsin.

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1 MEMBER DIAZ: Angela Diaz at the
2 Department of Pediatrics and Community Medicine at Mt.
3 Sinai School of Medicine and Director of Adolescent
4 Medicine.

5 DR. WARD: I'm Bob Ward, a Pediatrician
6 and Pharmacologist at the University of Utah. I'm
7 directing the pharmacology program there.

8 MEMBER FANT: I'm Michael Fant. I'm at
9 the University of Texas Health Science Center in
10 Houston. I'm a Biochemist and a Neonatologist on the
11 faculty there. I'm a member of the Pediatric Advisory
12 Commission.

13 MEMBER NEWMAN: Tom Newman. I'm a General
14 Pediatrician and Professor of Epidemiology and
15 Biostatistics and Pediatrics at UCSF and Head of the
16 Clinical Epidemiology Program there.

17 MEMBER O'FALLON: Judith O'Fallon. Mayo
18 Clinic Emeritus Professor of Biostatistics, a member
19 of the Committee.

20 CHAIRMAN NELSON: I'm Robert Nelson, also
21 known as "Skip." If you hear that name around, I'm
22 the new Chair of the Committee and previous member,

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1 and I'm in Pediatric Critical Care Medicine and
2 Bioethics at Children's Hospital in Philadelphia and
3 the University of Pennsylvania.

4 EXEC. SEC. JOHANNESSEN: I'm Jan
5 Johannessen. I'm the Executive Secretary of the
6 Pediatric Advisory Committee.

7 DR. KNUDSEN: I'm Paula Knudsen from the
8 University of Texas Health Science Center in Houston
9 and I am an IRB Administrator.

10 MEMBER MOORE: John Moore from UCLA,
11 Pediatric Cardiologist.

12 MEMBER DOKKEN: I'm Deborah Dokken. I'm
13 the Patient Family Representative on the Pediatric
14 Advisory Committee.

15 CHAIRMAN NELSON: Thank you. And Dianne
16 or Sara, Opening Comments?

17 DR. MURPHY: Well, comments are welcome,
18 particularly to our new members. I heard you had an
19 excellent training session last night. We're going to
20 start on a slightly different foot and actually, Skip,
21 if you would just say a few things to them about this
22 process this morning, for the new members, I think

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1 that would be appreciated.

2 CHAIRMAN NELSON: Well, before then I turn
3 to Norm about the actual protocol we discussed
4 yesterday, a brief comment. The Subpart D, which is
5 in both the Federal Regulations in two places
6 pertinent to this meeting, both the HHS that oversees
7 NIH-funded research and with the FDA in 21 CFR 50 and
8 56. There's three sections under which a local IRB
9 can approve protocol. One is minimal risk, the other
10 is minor increase over minimal risk with some other
11 conditions set to it, one of which is that the child
12 had a condition. The third is prospect of direct
13 benefit with a balancing of the reasonableness of the
14 risks against the benefits and being rated a minimal
15 risk. And then there's a fourth category that if the
16 local IRB thinks that the research presents a
17 reasonable opportunity to understand a serious problem
18 affecting the health or welfare of children, that they
19 can refer that protocol, but they can't approve it
20 under the other three categories, that they can then
21 refer that protocol for review at the federal level.

22 Up until about, I guess a year and a half

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1 ago now, there was no public process by which that
2 review could take place. And when the Pediatric
3 Advisory Committee was chartered as a part of the
4 Pediatric Research Equity Act, its charter was written
5 to be able to provide such advice and the mechanism
6 through which it was set up to do that is through a
7 Pediatric Ethics Subcommittee, of which the previous
8 two reviews I chaired and now Norm Fost is the Chair
9 of that Ethics Subcommittee.

10 It turns out that, according to the
11 Federal Advisory Committee Act, the only committees
12 that can actually advise the FDA Commissioner and
13 Secretary of HHS is a fully constituted advisory
14 committee. So we need to then discuss, consider, and
15 vote on the recommendations of the Subcommittee in
16 order for it to be passed on to the FDA Commissioner
17 as part of that process. After the FDA Commissioner
18 puts together an assessment of that review and then
19 makes a determination, that then goes to OHRP within
20 HHS, which puts it together for the Assistant
21 Secretary of Health to make a determination on behalf
22 of the Secretary of HHS.

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1 So that's why we're here. Because
2 yesterday, there was a meeting that went for all day
3 to consider a protocol submitted by the University of
4 Chicago that I believe is -- everyone should have
5 received all of the briefing materials for that.
6 There's a few minor changes to the slides and I think
7 one new set of slides from yesterday, which you should
8 have, I think, before you, to be able to refer that.
9 And that's our task, which we will, hopefully,
10 complete by 9:45 a.m.

11 Is that sufficient?

12 DR. MURPHY: Yes. What -- the overview
13 that I was going to provide later, Skip, is for the
14 next topic. So that's why I was asking you to make
15 sure --

16 CHAIRMAN NELSON: Oh.

17 DR. MURPHY: -- the new members --

18 CHAIRMAN NELSON: Okay.

19 DR. MURPHY: It's in the wrong place on
20 the agenda because we didn't realize we were not going
21 to have everybody here.

22 CHAIRMAN NELSON: No problem.

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1 DR. MURPHY: So we wanted to surprise you
2 and change the agenda without telling you.

3 CHAIRMAN NELSON: Okay.

4 DR. MURPHY: Thank you.

5 CHAIRMAN NELSON: So Norm is going to give
6 a summary of the deliberations from the Pediatric
7 Ethics Subcommittee Meeting of yesterday. Norm?

8 DR. FOST: Thank you, Skip.

9 So the protocol that we reviewed yesterday
10 is from the University of Chicago Medical School. Dr.
11 Robert Rosenfield is the principal investigator and
12 this is a study to assess gonadotropin-releasing
13 hormones for their use in disorders of puberty. Next
14 slide, please.

15 The purpose of the study is to establish
16 the diagnostic effectiveness of a stimulation with
17 this agent leuprolide and the norms for it. That is,
18 to get normal data. This will improve the
19 differential diagnosis of the most common disorders of
20 puberty so that we may provide more accurate and
21 earlier treatment for these disorders. Next slide.

22 The basic problem is that there are many

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1 children with disorders in pubertal development,
2 mainly precocious puberty or delayed onset of puberty.

3 The Gold Standard Test has been a sleep study, which
4 requires admitting a child overnight usually to a
5 clinical research unit. This is expensive and not
6 generally covered by insurance and, therefore, really
7 not available to large numbers of children and
8 endocrinologists.

9 An alternative way of assessing these
10 children includes stimulation, inadodropins with
11 injection, inadodropins releasing hormones, but there
12 have been frequent changes of the available product in
13 doing this. That is, there have been several
14 products, some of which are no longer available in the
15 U.S. Some are no longer available at all. And the
16 current product, Leuprolide, which in its long-term
17 form is called Leupron, is what is being used but
18 there is a lack of normal values that is valued for
19 normal children in the age ranges of patients that
20 present. So Dr. Rosenfield is proposing to study
21 patients with various pubertal disorders in a control
22 group with normal, healthy children and the central

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1 problem that the University of Chicago IRB had with
2 this involved the use of the normal children. Next
3 slide.

4 The illness in this study is that
5 everything I'm saying is true of both groups, but the
6 major issue here involved a healthy control, so I'll
7 just be referring to them.

8 The children in the healthy control group
9 would be between seven and I think the upper age is 17
10 or 18 years old. They would be admitted for 36 hours,
11 so for part of two days and one overnight admission to
12 a clinical research center. They would receive one
13 self-contained injection of Leuprolides and micro
14 (*8:19:53 inaudible). This drug is improved for
15 treatment of pubertal disorders in children, but it is
16 not approved as a diagnostic agent.

17 There would be a \$150 payment to the
18 normal children and no payment to the patients or the
19 children who had a disorder. Next slide.

20 So the procedures include a 36-hour
21 admission, one injection of Leuprolide, a physical
22 exam, an in-dwelling venous catheter from which blood

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1 would be obtained -- I'll come back to the amount in a
2 few minutes -- x-rays to determine the bone age, DNA
3 banking for future as yet unspecified genetic tests,
4 if and when they become available, and children would
5 be discharged on iron to help them reconstitute
6 whatever blood they lost. Next slide.

7 There were no public comments at the
8 meeting, that is, no spoken public comments. We
9 received letters, eight letters, and this is a brief
10 summary of those letters. Four of them were from
11 patients, that is from adults, who had received Lupron
12 and these individuals were concerned about serious
13 adverse affects, both long-term and short-term use, in
14 themselves and others. They expressed concern that
15 the chemical itself is hazardous and that double
16 gloving is needed and that this was not identified in
17 the protocol in the Consent Form. There were charges
18 in these letters of misconduct against TAP, a company
19 that had been involved in the distribution of
20 Leuprolide. There was concern about alleged numerous
21 lawsuits against TAP that had been settled under
22 secrecy agreements so that information was not

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1 publicly available. There was concern about the
2 disappearance of a popular web site of Lupron victims,
3 which reportedly had over a million hits a year and
4 then allegedly disappeared, and concerns about
5 inadequate information on the Consent Form about
6 serious adverse affects of Lupron and Leuprolide.

7 Another letter came from a parent whose
8 child had both Cancer and a delayed onset of puberty.

9 That is, so this child had been in clinical trials
10 for Cancer and also in a clinical trial involving
11 Leuprolide for its use as a gonadotropin releasing
12 hormone and this parent commented favorably on the
13 effectiveness of the drug, its safety, the low risk of
14 the trail that her child was in, and on the importance
15 of getting better information so that there could be
16 better tests for precocious puberty. Next slide.

17 There were three letters from professional
18 societies, the Endocrine Society, the Lawson-Wilkins
19 Pediatric Endocrine Society, and the American Society
20 for Reproductive Medicine. These letters had a
21 certain sense of deja vue about them. They all
22 stressed the importance of normal controls in

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1 pediatric research. They expressed concern about the
2 46.407 process, about the cumbersome nature of trying
3 to get studies and normal controls done, concerns
4 about the variation among IRBs and the definition of
5 minimal risk that made it challenging for
6 investigators to do this kind of research, but made no
7 specific comments on the protocol. So they expressed
8 mainly general concerns about the 46.407 process and
9 about the importance of normal control data. Next
10 slide.

11 So as Skip Nelson said, this is a summary
12 of the sections, development sections, of the common
13 rule under which research involving children,
14 particularly normal, healthy controls, were done.
15 Section 46.404, just to refresh your memories,
16 involves research not involving greater than minimal
17 risk. The University of Chicago IRB felt that this
18 study could not be approved for the normal controls.
19 They felt that the risks of the study were greater
20 than minimal and, therefore, could not be approved
21 under Section 46.404.

22 Section 46.405 has to do with research

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1 involving greater than minimal risk, but presenting
2 the cost break of direct benefit to the subjects, the
3 IRB concluded that there was no direct benefit to
4 these normal controls and, therefore, could not be
5 approved under Section 46.405.

6 Section 46.406 involves research that's
7 greater than minimal risk and the prospect -- and no
8 prospect of direct benefit for individual subjects,
9 but likely to yield generalizable knowledge about the
10 subjects' disorder or condition, and since the normal
11 children do not have a disorder or a condition, it
12 could not be approved under Section 46.406.

13 So the Chicago IRB thought the subjects
14 could be approved, but this would require approval by
15 the Secretary, namely research not otherwise
16 approvable, but which presents an opportunity to
17 understand, prevent or alleviate a serious problem
18 affecting the health or welfare of children. They
19 felt it did meet those criteria, but the approval of
20 the Secretary was needed, hence, the process that
21 we're here today to conduct. Next slide.

22 So, the protocol was submitted to the

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1 University of Chicago IRB in November of 2004 and I
2 should add that there was considerable concern
3 expressed by individuals yesterday about the long time
4 for this process. It's now a year later. Much of
5 that time was at the University of Chicago, the study
6 apparently was submitted to FDA sometime around June
7 of 2005.

8 So the Chicago IRB approved the study for
9 patients, that is for children who had disorders in
10 which they considered it a minor increment over
11 minimal risk with the prospect of direct benefit.
12 What would happen to the children with pubertal
13 disorders is not very different from what would have
14 happened to them if there was any study at all.
15 Almost everything that is being proposed in the study
16 would be part of what would be, in the investigator's
17 opinion, the correct work-up for these children. So
18 there was no added risk for them and there was the
19 prospect of direct benefit. So the issue was normal
20 controls, which required the approval for which
21 required the 46.407 process. Next slide.

22 So the options for our Committee

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1 yesterday, for the Pediatrics Ethics Subcommittee,
2 were first, to revisit the issue of 46.404, that is,
3 it is permissible for the Advisory Committee and for
4 this Committee today to decide that the Chicago IRB
5 was mistaken, was unduly conservative, and that if the
6 study is at minimal risk and could be approved under
7 Section 46.404, this Committee today could make that
8 recommendation. So we first considered that
9 possibility, that is, to revisit the question of
10 whether the use of normals could be approved under
11 Section 46.404, namely research not involving greater
12 than minimal risk. Next slide.

13 Minimal risk, to refresh your memories, is
14 defined in the Common Rule as the probability and
15 magnitude of harm or discomfort anticipated in the
16 research that are not greater in and of themselves
17 than those ordinarily encountered in daily life or
18 during the performance of routine physical or
19 psychological examinations or test.

20 One of the recurring problems in applying
21 this definition is, to understate the case, enormous
22 disagreement about what the phrase "routine physical

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1 or psychological examination or test" means. Next
2 slide.

3 Some individuals, some IRBs believe that
4 that phrase refers to the kinds of tests that would be
5 conducted on a routine health supervision visit, a
6 child who comes in for a health supervision visit.
7 But others have interpreted it to refer or to include
8 risks that would occur on a routine visit to a
9 specialist. So, for example, form IRBs have approved
10 non-therapeutic kidney biopsies, small bowel biopsies,
11 based on a statement by the investigator that a -- an
12 nephrologist, that in my clinic, a kidney biopsy is
13 routine. Everybody I see gets a kidney biopsy or a
14 lot of them do, and I haven't had any problems with
15 it, so to do it on a research basis doesn't involve
16 anything more than happens on a routine basis.

17 There was published in JAMA last year a
18 survey of IRB Chairs -- and the next slide, please --
19 I don't know if you can see this. I can't. But the
20 fourth line down, on the left, I believe, is the -- on
21 the left column is a list of various studies that have
22 been where -- this was a questionnaire sent to IRB

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1 Chairs, IRBs that review research involving children,
2 and the left is a list of various interventions, and
3 they were asked whether they thought this was minimal
4 risk, minor incremental over minimal, or more than a
5 minor increment over minimal, and the main point of
6 the slide is there is just enormous scatter in these
7 results. One of the more striking ones is skin
8 testing for allergy -- I think it's about fourth down
9 on the left -- and roughly 40 percent and 25 percent
10 of the respondents selected either minimal risk, more
11 than minimal or minor increment over minimal. That
12 is, it was almost random distribution. If you look at
13 the first line, which I think is a venapuncture, a
14 single draw of a small amount of blood, and look at
15 the far right column, two or so IRB Chairs thought
16 that was more than a minor increment over minimal.

17 So there's inconsistency among IRBs around
18 the country and great frustration by investigators who
19 see some of these studies being approved in some
20 centers and not others. In fact, their institutions
21 with multiple IRBs in which one IRB will approve a
22 certain procedure in children and the other one will

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1 not. So there is some high -- there is a high noise
2 to signal ratio in the interpretation of that phrase.

3 And the bottom line is there is no right answer to it
4 or no universally agreed upon answer, so the Committee
5 yesterday and the Committee today will simply have to
6 deal with it as best you can and see what you think.
7 Next slide.

8 So, we discussed four issues to see where
9 consensus might lie and then had a formal vote, which
10 I'll mention at the end. That is, we divided the
11 questions before us into four issues.

12 The first issue was whether the proposal
13 to study the responsive normal children involved more
14 than minimal risk and we divided those into medical
15 risks and psychological risks. The medical risks
16 seemed to be mainly three: risks of Leuprolide and
17 the asterisk there means that a majority of the
18 committee -- I think, these asterisks were actually
19 unanimous, but unanimous minus one perhaps. So nearly
20 everybody on the Committee thought that the
21 administration of Leuprolide, although a very low
22 risk, and the panel members did not agree with the

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1 public comments that there were serious adverse
2 affects from this. The consensus was that that was
3 more than minimal risk, that the procedures involved
4 the in-dwelling catheter, it was more than minimal
5 risk. There was agreement that the amount of blood
6 volume -- and I would say we spent most of the day
7 yesterday discussing how much the blood volume
8 actually was -- and finally determined that the
9 amount was about three cc's per kilogram and that this
10 was not -- this was at minimal risk, this was not more
11 than minimal risk. And finally that the psychological
12 risks of being hospitalized for 36 hours with the
13 various procedures also constituted more than minimal
14 risk. So, in summary there was unanimity among the
15 Ethics Subcommittee that this study -- the Chicago IRB
16 had this right. We agreed with them that the study
17 could not be approved under the eyes of minimal risk.
18 Next slide.

19 So, the remaining question was whether it
20 could be approved under Section 407 or whether we
21 could recommend such an approval. To do so, several
22 criteria had to be met. The first was whether the

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1 need for improved diagnostic tests for a diagnosis of
2 problems of puberty was a "serious problem" affecting
3 the health of children, one of the criteria for the
4 Secretary to approve such a study.

5 Whether this is a serious problem, we
6 divided into two questions: one, is the diagnosis and
7 problems of puberty -- are problems of puberty a
8 serious problem? Yes. These are medically serious.
9 They are psychologically serious, and it's
10 epidemiologically serious. There are large numbers of
11 children who have precocious puberty or delayed onset
12 of puberty and this is a serious problem. There was
13 no need to discuss that.

14 But the second question was whether the
15 need for improved diagnostic tests, particularly the
16 need for normal data following a Leuprolide
17 stimulation test, whether that was a serious problem,
18 that is whether the existing armamentaria available to
19 endocrinologists was really sufficient to evaluate
20 these children or whether it was a serious problem,
21 that the lack of normative data for a stimulation test
22 was a serious problem. Everybody thought that it was

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1 a serious problem. That is, that was unanimous, but
2 two panel members thought that it wasn't necessary to
3 use normal controls to answer this problem. That is,
4 two of the panel members thought that in the workup,
5 in the study of children with disorders, there would
6 inevitably be some children who turned out not to have
7 a serious -- not to have major medical problems and
8 whose data could, therefore, be used as normative
9 data. And that it wasn't necessary to regroup so-
10 called normal controls to get this data.

11 So, in summary, seven of the nine panel
12 members thought that normal controls were important to
13 establish the normative data that were needed to --
14 and those two are here today, who can comment and say
15 this in more detail during the discussion.

16 So, there was unanimity that improved
17 tests were needed, but two out of nine panel members
18 thought that you didn't need normal controls to do
19 that. Next slide.

20 The next issue was whether the research
21 was designed in a way that "presents a reasonable
22 opportunity to further the understanding, prevention,

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1 or alleviation of a serious problem affecting the
2 health or welfare of children." So, the Committee
3 here was operating on the principle that design is a
4 serious ethical issue. That is, if -- even if the
5 study is addressing an important problem, if the study
6 can't be carried out or if the study is not likely to
7 answer that question, then it's wrong to exposure
8 children to even minimal risks, if nothing is likely
9 to be learned from it. And here, the central issue
10 was whether Dr. Rosenfield was likely to achieve his
11 accrual goals and this discussion was stimulated, in
12 part, by a letter sent to the Chicago IRB from the
13 Clinical Research Center in their independent review
14 of the study. They noted that two prior studies that
15 Dr. Rosenfield had been doing involving similar
16 issues, similar children, one of which had been
17 approved in 1994 and the other in 1998, had only
18 accrued 29 out of a target of 240 children over the
19 ten or eleven-year period. And so they, the
20 statistician on the GCRC Review Committee had
21 expressed concern about whether the present study was
22 really likely to succeed. Dr. Rosenfield replied that

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1 the accrual of the patients, that is, the children in
2 the Children With Disorders Arm of the study, was
3 already quite satisfactory. That is, he was confident
4 that he was going to be able to meet his accrual goals
5 in that category. Whether or not he will be able to
6 achieve normal controls, of course, is unknown because
7 he can't proceed on that part of the study until he
8 gets approval from the Secretary.

9 So, the Committee was -- a majority of the
10 Committee was persuaded by this response that there
11 was sufficient evidence of successful accrual that the
12 study -- that the design of the study and the accrual
13 goals could be met.

14 Next is the -- the next slide is the last
15 issue -- involved payment. The proposal involved
16 payment of \$150 to the children in the control group,
17 but no money to the children with disorders, to the
18 patients. This \$150 payment would be in the form of a
19 check, written out directly to the children, not to
20 their parents. So, we had a brief discussion, trying
21 to figure out whether this payment was compensation
22 for costs. It seemed that the children did not

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1 themselves have cost, so it didn't seem to be
2 compensation, or -- but a suggestion was made that
3 this was an appropriate -- it was comparable to wages
4 that the children might obtain for babysitting, as the
5 amount of money that was being offered to them was
6 less than they might have made from babysitting.
7 There was discussion about whether it was an
8 honorarium and, if so, it should not be disclosed
9 ahead of time, so that it -- lest it be seen as an
10 inducement; that is, if it was an honorarium, the
11 suggestion was made it should be given after the
12 involvement of the children is completed so they
13 wouldn't be induced to join the study just for the
14 money. And the third possible explanation for it was
15 that it might be necessary as an inducement. That is,
16 that enrollment might be difficult and that this
17 payment was an important part of being able to
18 complete the study.

19 As best we could figure out, I think it
20 appeared that the payment was something, some
21 combination of an honorarium and an inducement, so we
22 then discussed briefly whether, if it was an

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1 inducement, is it an undue inducement and nobody on
2 the panel thought so. So, the consensus was that
3 whether it's an honorarium or an inducement, the
4 amount was not undue and the Committee did not have a
5 problem with it. Next slide.

6 There was then some discussion of -- so
7 the conversation, as you can sense, was drifting
8 towards approval, recommendation for approval of the
9 study, and various members of the Committee thought
10 that if it were to be approved, that some
11 modifications would be needed, or at least
12 recommended. And the -- those are listed on this
13 slide.

14 First, there was concern about the
15 disclosure of results to the normals and there was
16 unanimity that results should not be disclosed, that
17 the significance of the results were unknown by
18 definition because previous normative data were not
19 available, that there was great potential for
20 stabilization, possibly even insurability problems,
21 and that while it would be appropriate to give the
22 results of the study as a whole to parents and

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1 children after it was concluded, while it was in
2 process with the results being of uncertain
3 significance, that results should not be disclosed.
4 And so, there was -- I'll come to the vote on this
5 issue in a minute.

6 Second, there was concern that since DNA
7 samples were being collected for unspecified future
8 genetic testing, that children should have the chance
9 to withdraw from the study at any point, and that that
10 right to withdraw should include a right to have the
11 samples destroyed when they reached an age of
12 majority, or before, if they wanted them. So, a
13 second modification that was suggested that to ensure,
14 to take steps to ensure the children could have their
15 samples withdrawn.

16 Third, there were Consent Form changes,
17 which the -- the three central concerns were a concern
18 that the Consent Form had overstated the possibility
19 of benefit to the children -- that's the second line
20 there. The first line that the non-beneficial nature
21 of the study for the control of children was not
22 prominently featured and should be prominently

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1 featured at the beginning of the Consent Forms.

2 And third, there was agreement that the
3 Consent Form should say something about the possible
4 adverse effects of long-term Lupron use, even though
5 there were not thought to be any serious adverse
6 effects of Leuprolide in the way it was being given,
7 that subjects and parents should -- were entitled to
8 know that there were possibly concerns about adverse
9 affects from long-term use.

10 So, the next slide, I think, summarizes
11 the vote -- well, this is just to review the
12 conditions of 407 once more. So, Section 407 says
13 that the Secretary can approve -- such research can be
14 approved, as research of more than minimal risk
15 without a prospect of direct benefit. If approved by
16 the Secretary, following a recommendation that
17 concludes that the research presents a reasonable
18 opportunity to further the understanding, prevention,
19 or alleviation of a serious problem affecting the
20 health or welfare of children. The research will be
21 conducted in accordance with sound ethical principles,
22 adequate provisions are made for soliciting the assent

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1 of children and the permission of their parents or
2 guardians as set forth in Section 408.

3 One member of yesterday's panel thought
4 that there should be SN monitoring in this study.
5 That is, that the acceptability of the protocol hinge
6 on the ability of the children to say no, and to stop
7 at any point, and that there was sufficient concern
8 about this study, that the IRB should consider doing
9 some assent monitoring. That is, a sample of the
10 children in this study, after they participated, to
11 see if they understood what had gone on, if they
12 understood the non-beneficial nature of it and
13 understood that they could withdraw at any time.

14 The next slide is the last, which is the
15 actual votes. So, Question Number 1 was whether the
16 Committee recommended that the Secretary approve this
17 study under Section 404. That is, as minimal risk,
18 and that was a unanimous "No." It was unanimity that
19 this study involved more than minimal risk. Could it
20 be approved as written under 407, and the answer to
21 that was "No."

22 But the question, could it be approved with

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1 modifications, and the answer to that was seven to
2 two. A final option, of course, was they could
3 recommend that it not be approved at all, but the
4 previous bullet shows that the Committee, by a vote of
5 seven to two, recommended approval.

6 Thank you.

7 CHAIRMAN NELSON: Thank you, Norm. Just
8 two brief comments on the slides. I think the lower
9 age limit for the study is eight for girls and nine
10 for boys, if I recall for the controls. It's
11 important to note we're only discussing the controls.

12 And then, I might just add, in the interest of equal
13 time, 21 CFR 50.51, 50.52, 50.53 and 50.54 are the
14 same FDA regulations that you saw as 404, 405, 406,
15 407. So, they are comparable language.

16 So, with that, why don't we just open up
17 the presentation for discussion. Tom, and then Bob.

18 MEMBER NEWMAN: Maybe the two who
19 dissented would like to comment, but I guess I'm
20 inclined to agree, or at least, not to understand the
21 need for the normal controls. It seems to me if all
22 of the children that are in the precocious or possible

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1 precocious puberty are getting the current Gold
2 Standard, which is a sleep study, then the results of
3 the new test could be compared with the Gold Standard
4 and we would be able to calibrate the new tests
5 according to the sleep study, and so I guess I don't
6 see why we need to have the normal controls if they're
7 all getting the votes.

8 CHAIRMAN NELSON: Bob, should we open that
9 question up, or do you want to --

10 MEMBER DAUM: I think we ought to address
11 that question first.

12 CHAIRMAN NELSON: Okay.

13 MEMBER DAUM: Is Dr. Rosenfield going to
14

15 CHAIRMAN NELSON: He will at the point that
16 I invite him to --

17 (LAUGHTER.)

18 CHAIRMAN NELSON: If you -- and you were
19 there, so why don't you see where we can go up to that
20 point.

21 MEMBER DAUM: Well, I mean, he can comment
22 better than I do, or else the three Endocrinologists

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1 on the Committee who all thought it was important to
2 have normal controls -- I think their central argument
3 was that the children in the -- with disorders are not
4 normal children. There is something different about
5 them. And that the issue that a Pediatric
6 Endocrinologist faces when evaluating such children
7 is, is this child normal or not, or is he not. And
8 there are urgent treatment decisions that hinge on it
9 and just watchful waiting is often not acceptable.

10 So, they just thought, from a scientific
11 standpoint, that comparing children with treatable
12 disorders with those who did not require treatment was
13 not the question. The question was, was the child
14 before you a normal child? Now, obviously, there are
15 right-line boundaries between these categories, but
16 that was the argument.

17 MEMBER NEWMAN: But -- I mean, I thought
18 that was the purpose of the sleep study, was to
19 distinguish between -- I mean --

20 CHAIRMAN NELSON: But not everybody will
21 have a sleep study going forward, and so the sleep
22 study is only done as a research-only test.

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1 MEMBER NEWMAN: Right, but I -- but the
2 sleep study, it seems to me, could be used to
3 calibrate the new test because the children who are
4 going to get this test are already going to know that
5 there is some concern about their pubertal
6 development. We will already know that they are not
7 normal. We won't need the test to tell us that they
8 don't have something maybe wrong with them about
9 puberty, so that the group of children in whom this
10 test would be applied in practice are all going to be
11 children to whom there is some concern about pubertal
12 development.

13 So, we already know that. So we don't
14 need a test to tell us that. We know that. What we
15 need to know is are they children with whom there's a
16 concern about pubertal development who have something
17 that we need to treat or not, and it seems to me that
18 that's why we're doing the sleep study, to be able to
19 -- if that's the current Gold Standard to be able to
20 tell.

21 CHAIRMAN NELSON: I think, Tom, you're
22 giving the presentation of the two people that

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1 objected, and they can certainly say that, but the
2 other seven felt that that was, in fact, incorrect.
3 That you want to be able to tell people who present
4 with, say, the late puberty who might appear normal if
5 they were nine, but abnormal if they're 14, that, in
6 fact, they were normal, not that they were untreatably
7 abnormal. So it's -- in the absence of that data,
8 it's a guess. And in terms of being able to say what
9 the individual test might show once you do it, what
10 the sensitivity and specificity is in saying, "Hi, you
11 came to see us, but you were, in fact, normal on this
12 test, which we've now developed." It is difficult to
13 say in the absence of normative data. And having only
14 normative data on people who present with the problem,
15 in fact, doesn't allow you to draw that conclusion.
16 So, that was --

17 MEMBER DAUM: If I could state it another
18 way, I think this is paraphrasing Dr. Rosenfield. If
19 you submitted an article to a rigorous journal that
20 did what you suggested, that a critical reviewer would
21 say, "Where are the controls?" You showed me what the
22 difference is between children who had serious

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1 disorders requiring treatment and those who are, but
2 you haven't showed me what the value -- what the
3 Leuprolide values are for children who are completely
4 healthy. And that that's the standard that
5 practitioners would want to know.

6 DR. FOST: Jeff, and then --

7 DR BOTKIN: I think, Dr. Newman, as one of
8 the minority two -- I think Dr. Newman said nicely,
9 expressed my concerns with the study, and I would just
10 add to that, not that I don't think that there's some
11 scientific validity to collecting data on so-called
12 healthy children. We've had some language
13 difficulties because, just as you had stated, many of
14 the children who present with atypical pubertal
15 development are, in fact, normal children, healthy
16 children. It's just that you don't know that until
17 they've undergone some sort of evaluation. So, I
18 think, it seems to me the primary and most important
19 clinical outcomes of this study can be answered with
20 those children alone, without the so-called healthy
21 controls. It seems to me that there's a secondary set
22 of hypothesis that Norm sort of referred to, which is,

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1 well, are those kids really normal and can we identify
2 some differences between children with atypical
3 puberty who turn out to be fine and kids who show no
4 evidence of atypical puberty. Now, that may be an
5 interesting question from a scientific standpoint,
6 understanding normal pubertal physiology, et cetera,
7 but for me, it was not a compelling enough reason to
8 override the normal standards by which we hold
9 pediatric research to, and therefore, for me, it was
10 not approvable for that reason.

11 CHAIRMAN NELSON: Bob?

12 MEMBER DAUM: From the input either of the
13 Endocrinologists or from the written input from Loss
14 and Wilkins Society, was there agreement that as
15 proposed, that this would set standards for this kind
16 of testing that could be applied all over the country?

17 CHAIRMAN NELSON: Yes.

18 MEMBER DAUM: Could I -- there is another
19 component of the response to the issues that Tom and
20 Jeff and others are raising. Part of the answer has
21 to include a perspective of what the study actually
22 involves. That is, is this a big deal? So, you know,

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1 if we were doing brain biopsies to figure this out, it
2 would be a non-starter. But there was a lot of
3 discussion to the point that there was an overreaction
4 on the part of the Review Committees and this whole
5 process for something that really is really -- well,
6 technically more than minimal risk under the
7 definition, really not very risky. And as the
8 Endocrinologists on the Committee described
9 cumulatively many decades of experience in doing this
10 kind of GCRC admission to children, it's not a big
11 deal. It's fun for most of them. It's an adventure.

12 For the occasional child to whom this is really
13 unwelcome, he or she is easily screened out and
14 there's no desire to include them. So that this is,
15 when all is said and done, it's not much more than it
16 being a puncture or -- and certainly the medical risk
17 was to be quite trivial. So that had something to do
18 with it. That is, it's not a silly question that Dr.
19 Rosenfield's answered. There's a coherent reason for
20 wanting these numbers. If the study involved really
21 much more invasive or risky procedures, then your
22 argument might have carried more weight.

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1 CHAIRMAN NELSON: Rich?

2 MEMBER GORMAN: Before I make my comments,
3 yesterday and in this part of the presentation, I'm
4 speaking as a voting member of the Ethics Subcommittee
5 and not representing the American Academy of
6 Pediatrics, which when we move to the regular Advisory
7 Committee, I'm a non-voting member and speak for the
8 Academy. So, --

9 CHAIRMAN NELSON: So, you're going to give
10 two different opinions, depending on --

11 (LAUGHTER.)

12 MEMBER GORMAN: I hadn't thought about
13 that, but it would suit some other people's needs
14 perhaps.

15 Dr. Newman and Dr. Botkin have summarized,
16 I think, some of the scientific issues that made me or
17 led me to believe that yesterday as a dissenting vote,
18 that constitutional delay of puberty is within the
19 range of normal and those children or young adults can
20 be considered as normal controls for the study, and
21 therefore, was one of the dissenting votes.

22 One of the things that I heard

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1 repetitively from the Endocrinologists yesterday was
2 in considering pubertal issues, one of the issues was
3 tempo. They kept repeating that as to how children
4 develop and how rapidly that progresses. And this may
5 be an unfair analogy, but it is one that I drew in my
6 own mind yesterday, was that this test, in effect,
7 becomes a rapid diagnostic test, as well as a standard
8 norm. And then you have to decide how important that
9 is to the tempo of making the diagnosis. Rapid strep
10 tests do not radically change my practice of pediatric
11 medicine. Lymph node biopsies for people with -- or
12 breast biopsies with people with suspected Cancer
13 would really be a serious issue that would alleviate
14 concern. And I felt that this particular test fell
15 much closer to the rapid strep test in the sense that
16 Endocrinologists would most often take this test and
17 then continue to observe as opposed to individuals who
18 have a breast biopsy would rapidly, if it was
19 Cancerous, would end up being taken to surgery or
20 Chemotherapy or Radiation, depending upon what was
21 appropriate, or if it was not abnormal, would be
22 alleviated of their present concern. I felt in most

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1 cases, this particular test would end up with watchful
2 waiting as the outcome and, therefore, didn't think it
3 met the criteria of a serious health issue that would
4 alleviate an issue of childhood disease.

5 CHAIRMAN NELSON: Rich, let me comment on
6 that later point to amplify Norm's comment, which goes
7 away a little bit from the scientific necessity of the
8 normal controls. And that's to speak, at least to my
9 perspective, on what the serious problem under 407 or
10 5054 really means in the context of this process.

11 If you look at 5052 and 40 -- no, sorry.
12 I'm going to stop saying numbers after a while -- but
13 5053 and 45 Subpart 46.406, has language of vital
14 importance. Okay? So, what -- and the question
15 before us is there's really two levels, and I think
16 this came out in the discussion yesterday of a review
17 at the federal level. There are existing gaps in the
18 Regulations that some would perceive needing to be
19 filled, which precisely, in my mind, would be the use
20 of normal, average, healthy children as controls for
21 minor increase over minimal risk research that results
22 in information that's important, diagnostically, or

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1 therapeutically for a condition. All right, and
2 that's what this question is.

3 If you look at most of the reviews that
4 have forward, except, I think, for two, all of them
5 have been around that issue. The past two were around
6 this issue, and all of them have been around the issue
7 and there's literature that argues that, in fact, it's
8 unethical not to allow us to enroll average, healthy,
9 normal children in minor increase over minimal risk
10 research. All right, but the Regulations, currently
11 as they're written, and I don't anticipate that
12 they'll change anytime soon, don't allow that. That's
13 very different than saying we do federal review for
14 really big problems, whatever those problems might be,
15 pandemics, whatever. And, if, in fact, we hear from
16 the scientific community and from the therapeutic
17 community that they believe the use of normal, healthy
18 average controls is important to the interpretation of
19 a diagnostic test for a serious problem that affects
20 even a small group of people, my fear is if we don't
21 allow that to go forward under the minor increase over
22 minimal risk, but they just don't have the condition.

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1 They say, we'll orphan that same population who's
2 been orphaned by the lack of availability of testing,
3 diagnostic testing or otherwise that precisely put
4 them in the position they're in in the first place, so
5 I think there's a serious problem if we hold it to too
6 high a standard, other than the scientific necessity
7 within the protocol of some sort of social worth or
8 social purpose if that we, in fact, will do a
9 disservice to the population where this diagnostic
10 test would be important. So, that's -- to try and set
11 a context, this is not pandemics, but it's important.
12 Norm?

13 MEMBER DAUM: Right, but Skip, one piece
14 of that is what do you have to do to the normal
15 controls to get to the data. If it's a venapuncture -
16 -

17 CHAIRMAN NELSON: Well, that's why I said
18 it's a minor increase over minimal risk and it just --
19 one final -- if you look at the National Commission's
20 report, the answer to those people, in fact, that
21 category, minor increase over minimal risk, had two
22 dissenters. And if you look at the answer of the

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1 Chair to that, they said, (a) it's a really, really,
2 really low risk, and (b) it's scientifically
3 necessary. So the question is applying that.

4 So, that's the broader picture and I guess
5 I -- the scientific necessity is one question. It's
6 important to get some resolution, but to say it might
7 be scientifically important, but it's not really that
8 big a problem, that's a whole separate set of issues.

9 And I'm hearing both, but I think that we just need
10 to keep them separate.

11 Rich and then Jeff.

12 MEMBER GORMAN: For about 20 years, I've
13 been trying to extend or make available to more
14 children more research on their issues, especially
15 concerning pharmaceuticals. In this particular case,
16 I didn't think the science justified the inclusion of
17 normal controls because I felt children with
18 constitutional delay of puberty could serve that
19 purpose and then the research could be approved under
20 one of the numbers, which I think, is 405.

21 DR. BOTKIN: You know, I think we may have
22 a difference in how we would prefer to look at 407

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1 reviews, but absent clearly articulated standards by
2 which 407 Panels make their decisions, I think it is a
3 matter of individual interpretation by panel members.
4 I personally would prefer to say that the existing
5 Pediatric Regulations have pretty solid ethical
6 justification and, therefore, we ought to have quite
7 compelling reasons not to, what I would perceive,
8 undermining those by using the 407 approach that uses
9 a different articulated ethical standard. Now, you've
10 articulated one, but those are not within the
11 Regulations themselves. In other words, the 407 Panel
12 could decide to use healthy, normal children with a
13 substantially greater than a minor increase over
14 minimal risk if it chose to do so. Now, I don't think
15 that would happen, but those standards aren't within
16 the Regulations. So, I think -- it seems to me that
17 there probably needs to be some ongoing national
18 debate about what level of risk constitutes an
19 appropriate approvable standard within 407, and the
20 Regulations do say, in accordance with ethical
21 principles. And I think somebody needs to think more
22 carefully and articulate what ethical principles we're

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1 talking about in that context, if we're not talking
2 about the ones that underlie the established
3 principles behind the other categories.

4 CHAIRMAN NELSON: Before going to Norm, I
5 agree with that, Jeff. The protocol before us,
6 though, does fit minor increase over minimal risk, so,
7 you know, we need to -- we're doing a casuistic case-
8 by-case basis. It's not a greater risk than that.
9 So, that's the protocol before us.

10 DR. BOTKIN: I think you're right,
11 although I would say that the Ethics Subcommittee
12 never said that this was a minor increase over minimal
13 risk, it said it was more than minimal risk. It might
14 have been an action to perhaps agree on that
15 explicitly.

16 CHAIRMAN NELSON: Norm?

17 DR. FOST: Well, two things. First, I
18 don't think the present Subpart D has a firm ethical
19 basis. I don't agree with Jeff about that. That is,
20 the whole idea of doing any non-therapeutic research
21 on children, I don't think, has ever been adequately
22 justified. The argument is, well, it's good for

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1 children as a whole and children as a whole will
2 suffer if we don't allow non-therapeutic research
3 without consent. But that's true of adults, too.
4 That is, we could advance knowledge of all sorts of
5 adults disorders much more quickly if it weren't for
6 this pesky consent issue, if we just said it's the
7 interest of the class that matters. And that's not
8 considered an adequate reason to do research on adults
9 without consent, and it shouldn't be on children.

10 So, the whole infrastructure from the
11 beginning was a compromise without any real moral
12 justification, in my view. I don't think it's a
13 horrendous compromise, but I don't think it has a firm
14 ethical basis, point one. Point two, that compromise
15 that was made, "Well, let's just keep it to stuff
16 that's really minimal risk," is not being followed. I
17 was at those discussions and I know what was intended
18 was things that happen on a routine visit to a General
19 Pediatrician and there are now non -- there's one IRB
20 in the U.S. that has approved non-therapeutic
21 Bronchoscopies for years on children on the ground
22 that it's minimal risk because the investigator says,

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1 "I've been doing them for 20 years and I've never had
2 a serious complication. And also kidney biopsies,
3 small valve biopsies and everything else you see on
4 that list. So I think there's been enormous slippage.

5 It needs to be revisited and I think making it a big
6 deal through the 407 process, even for an admission,
7 the 36-hour admission to the GCRC, is a good idea. I
8 think that sends a signal to IRBs, we take the non-
9 therapeutic intrusions very seriously. So, I'm not
10 sympathetic to the concern that this system needs to
11 be greased or oiled. I think it's already too greasy.

12 CHAIRMAN NELSON: Now, let me, for the
13 moment, put in abeyance this conversation and then ask
14 Bob, is there an issue you wanted to get on the table
15 that when you originally said, "I'd like to talk?"
16 Other issues? Go ahead, Melissa -- right?

17 MEMBER HUDSON: Well, for those who
18 attended the meeting, could they provide some insight
19 about recruitment and how the recruitment cannot be
20 coerced by the parent? Because I don't think it would
21 be on a child's radar to look at postings to
22 volunteer. And if they were young, the money would

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1 have to go to the parent. So can they provide some
2 information about how the child is protected? I
3 assume that if they were difficult venapuncture or
4 they appeared frightened, they would not be recruited?

5 Just how is that process evaluated when the patient
6 is -- the volunteer appears and it's the parent with
7 the child.

8 CHAIRMAN NELSON: A couple of comments on
9 that. There was a fair amount of discussion about it.

10 I think the Subcommittee was reassured that the
11 process was reasonable. Personally, I disagree with
12 your observation if they're nine years old, it goes to
13 the parent. I mean the parent has an obligation to be
14 the steward, if you will, of the child's use of that
15 money, but most RBs often try to direct it in
16 different ways to the child or make it clear that
17 that's the intent of the -- of the compensation or
18 honorarium or inducement. Based on the amount, people
19 didn't feel that that was inappropriate and if, in
20 fact, most children who are eight or nine, if they
21 don't want to do it, \$150 is not going to make them do
22 it. So that was part of the discussion, I think, that

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1 Norm alluded to about the assent monitoring and the
2 capability to say, "Stop." And there was -- and
3 there's been some children that have said, "Stop."
4 And we had a discussion of that and people were
5 reassured that that could be handled appropriately
6 within sort of Pediatric Standards by people who've
7 been doing this for a number of years within their
8 GCRC.

9 Norm, do you want to elaborate?

10 DR. FOST: Well, one other issue just
11 along these lines was whether -- there was
12 considerable discussion about whether this is a single
13 location GCRC or scatter bits. The Committee thought
14 it was relevant that it was a single location with
15 experienced Pediatric nurses. There are scatter beds
16 in which ordinary floor nurses might not be as tuned
17 in to these things. So, we thought there was a
18 physical setting in place that was accustomed to
19 treating children well in this regard.

20 CHAIRMAN NELSON: The analogy was to a
21 "sleep-over." You know, you could set it up in a way
22 that that would be the nature of the experience for a

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1 child, a sleepover.

2 Judith?

3 MEMBER O'FALLON: So this now brings up
4 the issue of the sample size. There was a lot of
5 evidence throughout the whole packet that there were
6 concerns about whether they could get enough patients
7 to do this study and I understand that Dr. Rosenfield
8 addressed that. But the other part is then how many
9 controls do we need here. And if they have to go
10 outside, as there were suggestions in the packet that
11 we got, they were going to make it a multi-
12 institutional study, well then, do these -- these
13 other places have this nice, friendly sleep-over
14 environment for the kids to have this test? So, I
15 mean, it does -- this is all kind of interrelated.

16 DR. FOST: Yeah, I mean, as Dr. Rosenfield
17 said, it's a catch-22. He can't assess his ability to
18 get control until he has approval. And he's
19 optimistic. There are other, certainly other studies
20 of this sort in which parents have -- and their
21 children have volunteered. So he's optimistic about
22 it, but he can't test the hypothesis until an IRB lets

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1 him try.

2 MEMBER O'FALLON: But seriously, how many
3 controls are they looking for? I don't remember
4 seeing it. I may have missed it.

5 DR. FOST: I don't have the numbers at my
6 fingertips.

7 CHAIRMAN NELSON: I think it's 20, 20, 20.
8 I think it's the same number, the same groups that
9 they had within the patient population.

10 MEMBER O'FALLON: Okay.

11 CHAIRMAN NELSON: And, as I recall, a
12 large portion, not quite the majority, of the diseased
13 children have already been recruited in the year that
14 this has, in fact, been open. And I think it's fair
15 to say that it's hard to call up another investigator
16 and say, "You know, I'm going before a Federal panel.
17 Do you want to join me?"

18 (LAUGHTER.)

19 CHAIRMAN NELSON: Which, as opposed to,
20 "I'm already through the Federal panel and these are
21 the issues." And it would be certainly appropriate to
22 -- I mean, there will be ongoing oversight. I think

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1 one of the themes from the past two reviews is that
2 this has ongoing oversight, both at the local and
3 Federal level and, in fact, I can't imagine, with this
4 discussion, hopefully, that someone would have it done
5 in a scatter bed GCRC that has no pediatric
6 experience. And I don't think, knowing the
7 Endocrinology world, that that's what would happen.
8 It would be within Pediatric GCRCs that could
9 accomplish the same sort of approach and
10 appropriateness to do that. So that was, I think, the
11 discussion. The Committee was reassured by that.

12 DR. MURPHY: Skip, this is Dianne.

13 CHAIRMAN NELSON: Dianne?

14 DR. MURPHY: I think yesterday that Dr.
15 Rosenfield did mention he had already identified a
16 number of units that he thought would be applicable
17 and have --

18 CHAIRMAN NELSON: Yes, there are
19 collaborators, right.

20 DR. MURPHY: -- and have accommodations in
21 the -- to the degree which you were describing. It
22 would be, you know, child-friendly, et cetera. So I'm

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1 just trying to -- for those who weren't there
2 yesterday to weigh the information, that they have
3 thought about this. They have identified units. They
4 know the type of areas that they would like to proceed
5 to utilize.

6 CHAIRMAN NELSON: Right. Norm?

7 DR. FOST: I should have mentioned in my
8 presentation also that Dr. Rosenfield was very pleased
9 with the suggestions for modifications of the protocol
10 on the Consent Form. He didn't see those as
11 intrusive. So, he was -- reflected a willingness to
12 try to make sure it gets done in the right way.

13 CHAIRMAN NELSON: Are there other issues
14 that the Committee feels are important to discuss?

15 DR. DIEKEMA: So as the new person, new kid
16 on the block, I should probably follow the rules that
17 rookies should keep their mouths shut for a while, but
18 I'm just inquiring a little bit about the process
19 here, I guess. This protocol was submitted first to
20 the U of C IRB in November of 2004 and it's now
21 November of 2005. Let's assume for a moment that this
22 is a compelling research question, which I presume

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1 someone feels it is, to have gone to all this trouble
2 to get it considered. And let's assume that -- I can
3 tell you that this is fairly prompt for the U of C
4 IRB, to get a review done in two months. Here we are,
5 a year later, still considering this. Let's just cut
6 to supposing that this research was about the need for
7 controls to assess a cure for Leukemia with one dose
8 of one drug or something like that. Is this really an
9 acceptable timeframe and process for this kind of
10 review, and what about the investigator's willingness
11 to put up with this kind of length of process to get
12 this done? Are we concerned about the need for
13 research to go forward in the face of a year to get it
14 to this point?

15 CHAIRMAN NELSON: I can just comment on
16 that. I'm sure Norm can then elaborate further. In
17 this particular protocol, it did not arrive for even
18 consideration at the Federal level until June. For
19 those previous members -- I wouldn't say "old"
20 members, but previous members of the Committee, June
21 was our last meeting. So, it arrived around the time
22 of that last meeting. Now there's a certain time it

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1 takes to put a meeting like this together, so you can
2 imagine that. But most of the process of the past
3 year, at least half of it, was within the University
4 of Chicago.

5 Now, should there be -- you know, are
6 there ways to speed it up and other options? Yes.
7 This is a year and a half into a process that didn't
8 exist, even though the National Commission recommended
9 the process exist in 1977. So -- and could there be
10 ways of trying to optimize it? Perhaps. I mean, we
11 can have that kind of broader discussion, but within
12 the timeframe, this is actually fairly spry. I mean,
13 we're responding reasonably quickly, compared to
14 what's happened in the past, which has been a long
15 time.

16 DR. DIEKEMA: In no way should my comment
17 have been to impugn this Committee or the FDA's part
18 of the process. I'm just looking at the whole
19 process, from soup to nuts, and so if the fault is at
20 the U of C IRB, I can assure you that wouldn't be the
21 first time. It's still a long, long process, and I'm
22 looking at it as the need to do the research versus

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1 the length of time it takes to get to this point.

2 CHAIRMAN NELSON: Right. My suggestion
3 would be -- I mean if we have time, we can spend time
4 talking about that process and suggestions and things
5 and we can do that with our time. It is what it is
6 for this particular protocol. I mean, I guess my
7 preference is we could decide to take action on at
8 least this protocol and then whatever time we have
9 before the break, and talk further about the process
10 and ideas people may have for trying to improve it,
11 which I'm sure would be worthwhile.

12 Norm?

13 DR. FOST: I had three comments. First,
14 seven of those twelve months were at the U of C. And
15 with regard to that, notwithstanding what I've said
16 before about this system being too slippery, I also
17 think the system is wildly over regulated and dis-
18 regulated. That is, I think doing the really simple
19 things that should take five minutes does take three
20 months and that's beyond the purview of this
21 Committee, but I think both things are true. That it's
22 just way too difficult to do the simplest things. We

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1 published a study showing a dramatic reduction in
2 medical records research at our institution following
3 the Institution of HIPPA. There have been three
4 similar studies published now elsewhere, one in Europe
5 that database medical records research is in a
6 nosedive because of what, I think, are just wildly
7 difficult regulations. They're just stopping good
8 people from doing important studies.

9 DR. DIEKEMA: That's my point really.

10 DR. FOST: So, I'm in agreement with you
11 on that. The last point I wanted to make about the
12 scientific merit of this and the questions of the
13 normal control that I forgot to mention, because Dr.
14 Rosenfield mentioned it several times. This has been
15 approved -- some rigorous -- this has been invented by
16 NIH Study Section, that is, some people with a lot of
17 scientific credibility in this field, have approved
18 this. And in light of what I just said, how difficult
19 it is to do research, how difficult it is to get NIH
20 funded, to survive that filter, I think, is a pretty
21 good, at least, procedural screening test for the
22 importance of doing it in this way.

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1 CHAIRMAN NELSON: Thanks, Norm. Let me
2 ask a question of the Committee. We've heard Dr.
3 Rosenfield's name mentioned a number of times. Is
4 there any desire on the part of members of the
5 Committee to hear him respond to some of these issues
6 or ask him, at least, if he feels we've adequately
7 represented those issues? Norm?

8 DR. FOST: Yes. I mean, I think -- I
9 don't know how -- I have no sense yet of where the
10 Committee is leaning on this, and some objections have
11 been raised by a series of people, so I think Dr.
12 Rosenfield should have a chance to respond to them.

13 CHAIRMAN NELSON: Tom?

14 MEMBER NEWMAN: Can I respond to what
15 Norman just said?

16 CHAIRMAN NELSON: Feel free, Tom, while Dr.
17 Rosenfield formulates his thinking.

18 MEMBER NEWMAN: I mean, I guess, yes, I
19 guess the Study Section approved this and thought --
20 and liked the design and I will definitely acknowledge
21 that there will be some journals who would prefer to
22 have normal controls. I just -- I agree with the

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1 other two Committee members that scientifically that
2 is not necessary. And I think what it really comes
3 down to is your other argument that this isn't a big
4 deal because if you're studying the accuracy of the CT
5 Scan, for example, to diagnose Appendicitis, you don't
6 need to do it on children who don't have abdominal
7 pain. The group of children with whom we want to
8 study that test are children who have abdominal pain
9 and might have Appendicitis and then you compare the
10 CT Scan with the Gold Standard of Surgeons and find
11 out how accurate it is. I just -- I think --

12 CHAIRMAN NELSON: Tom, the --

13 MEMBER NEWMAN: -- in this case, you're
14 saying that the test is not a big deal and may be even
15 less of a big deal with a CT Scan.

16 CHAIRMAN NELSON: Let me just -- with all
17 due respect, I don't think that I suspect -- if I
18 thought anyone was going to be convinced differently
19 by your argument or that you'll be convinced
20 differently by their arguments, I would continue to
21 have us discuss it. It's not clear to me that we'll
22 do other than -- is just get back into the same

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1 discussion and do it twice. So --

2 MEMBER NEWMAN: So if someone thinks that
3 they have something new to say on that point that
4 might change people's minds, I'm happy to hear it, but
5 I suspect it's going to be just back again for the
6 next twenty minutes to what we just discussed for the
7 last twenty. So, Norm?

8 DR. FOST: I don't know if it's new or
9 not, but I think your example is a good one, Tom.
10 That is, children with abdominal pain may have
11 abnormal CTs for reasons that I don't -- maybe their
12 Appendix lights up a little bit, too, from
13 Gastroenteritis or something. Who knows? The assay
14 sensitivity of a CT Scan, it seems to me, requires
15 knowing the children who had nothing going on in their
16 abdomens. So it seems to me a metaphor or an example
17 that, at least, supports the other point of view also.

18 CHAIRMAN NELSON: So, let me -- speak
19 closer. No, I'm planning to ask him now if I get a
20 chance. Dr. Rosenfield's, whose topic it was, the
21 adequacy of the controls with people who have
22 constitutional delay, is that an adequate control

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1 group?

2 So, you've heard the discussions and the
3 key issue to address is the importance of average,
4 normal, healthy children who don't present with some
5 phenomenological condition for the establishment of
6 the controls.

7 DR. ROSENFELD: Well, in a short time, I
8 don't think I can review the whole subject and outline
9 the rationale as well as it's outlined in the written
10 research protocol. And I think that Dr. Fost and Dr.
11 Nelson represented the overview of the Committee, and
12 I would like to just point out that the Committee as a
13 whole was convinced by a vote of seven to two. And at
14 that time, there was an Endocrinologist present who
15 vouched for the importance of this. It -- it's just
16 that I can't answer everything in moments, but I'd say
17 I know that Pediatricians have been brought up with
18 the concept that constitutional delay of puberty, for
19 example, is a variation of normal. Most of these
20 children go on to have normal puberty. But to use --
21 but you have to realize these are outliers of the
22 population. In other words, this group of children

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1 are -- the 2.5 percent at the extreme end of normal,
2 and to use those children, our priorities is as
3 normals, gets into circular reasoning. And I agree
4 very much with Dr. Fost that you don't know what
5 "normal" is until you test it. I didn't make a big
6 point about it in my slides yesterday, but the few
7 normals that we accumulated in a precursor protocol
8 with a different agent had a very -- had a narrower
9 range of normal that, in response to the precursor of
10 (*9:21:20 inaudible) than it was the late puberty.
11 It's not clear whether these are really normal and
12 there's reason to believe that there's some population
13 within the constitutionally delayed children that has
14 some sort of abnormality now. And a similar argument
15 holds true for children in early puberty. There's
16 quite an argument about whether puberty that occurs at
17 seven years of age and is, therefore, early, there is
18 some concern about whether those children are just a
19 normal thing happening early or whether this is an
20 abnormality of some sort, or a pre-stages of
21 predisposition to that normality.

22 So, it's just that those children tend to

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1 go through puberty at a slower tempo than normal. So
2 it's not clear that they're really normal. So to use
3 them as normal gets into circular reasoning and will
4 obscure science for a long period of time. Your
5 question about why not just use the sleep test, you
6 know, you're comparing each person to himself. And
7 the -- one of the issues that wasn't mentioned in Dr.
8 Fost's summary is that all of the historical data on
9 normals -- the great majority of it was with National
10 GRH, which has a very different profile and does not
11 give quite the same results as Leuprolide does.
12 Leuprolide gives a more prolonged and somewhat
13 different stimulants to the Pituitary Gland and to the
14 gonads as well.

15 And furthermore, the historical data is
16 based on an over generation of assays that are no
17 longer necessarily available and of an equal quality.

18 And although they are -- there are a variety of
19 Gonadotropin (*9:23:36 phonetic) assays around the
20 country. CAP approves them as long as there are other
21 people doing them and there are, you know, as many
22 companies as many kids have their own assay with

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1 different results. Some of those assays aren't as
2 good as others or as specific. It's very important
3 for proper Pediatric research to have very sensitive
4 assays to make these distinctions about very early
5 puberty. When does early puberty begin? What are the
6 first markers? What's normal? And we now have
7 sensitive assays that are very specific that are
8 commercially available. And this wasn't true of any
9 historical data. There's no historical data that
10 actually is available at this moment to allow us to
11 discern when early puberty begins and whether it's
12 beginning normally.

13 So, if there were other -- if the
14 Endocrinologists on the panel were here, they would
15 say the same thing. So, I think that briefly
16 summarizes maybe some additional points. If you'd
17 like, I'll answer some -- any questions you have, but
18 I'm not sure I can -- I think it's fairly well
19 summarized.

20 CHAIRMAN NELSON: Thank you.

21 DR. MURPHY: Skip, can we ask Dr.
22 Rosenfield questions?

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1 CHAIRMAN NELSON: Excuse me, Dianne?

2 DR. MURPHY: I want to ask him a question.

3 CHAIRMAN NELSON: Go ahead.

4 DR. MURPHY: One of the things that came
5 up yesterday was the timing also, and if you had this
6 group of referred patients versus normals, is there
7 any knowledge that we could try as to potentially not
8 being able to differentiate the timing of the
9 response? That was one of the things that, I think,
10 was discussed yesterday.

11 DR. ROSENFELD: Are you talking about the
12 timing of the response to tests or --

13 DR. MURPHY: Yes.

14 DR. ROSENFELD: -- the timing of puberty?
15 Well, the four-hour time period is something that the
16 previous tests with natural Gonadotropins (*9:25:25
17 phonetic) and hormonal factorial (*9:25:30 phonetic)
18 does not test at all, nor does factorial allow you to
19 look at the overall gonadal response.

20 Another issue that was mentioned is that
21 the -- Dr. Gorman mentioned the -- why do you need a
22 test when the tempo of puberty will tell you what you

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1 need to know? But the tempo of puberty can take years
2 and for a boy in high school, starting high school,
3 who is delayed or -- this delay can be terribly
4 distressing psychologically, not for all boys, but for
5 many of them. And so it's important to make a prompt
6 diagnosis to optimally manage these children.

7 And as I pointed out yesterday to the
8 panel, there is constitutional delay and then there's
9 constitutional delay. Constitutionally delayed
10 children are late bloomers in a common parlance, so
11 it's sort of an ordinary common variation. But the
12 ordinary ones are screened out. Our protocol doesn't
13 study constitutional delay until they're 14 years old
14 and in high school. By that time, they are clear
15 outliers and in our experience of the patients that we
16 study, about a third of them are Gonaditropic (*927:02
17 inaudible) deficient rather than simply being delayed.

18 And it's not a determination that can be made by in
19 clinic. If it's made in clinic, we don't even study
20 it.

21 CHAIRMAN NELSON: Do you want to ask him
22 again?

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1 MEMBER NEWMAN: Skip, could I --

2 CHAIRMAN NELSON: Go ahead.

3 MEMBER NEWMAN: With this variation in the
4 assays around the country, if someone chooses to apply
5 the same testing protocol at a distant site, will they
6 be able to interpret their results based on your
7 testing?

8 DR. ROSENFELD: As I say, the assay that
9 we're using is now commercially available and I think
10 the design of -- once we have approval, hopefully, and
11 then the decision has to be made whether to do it on
12 the central site or just use the same assay at each of
13 the sites, would probably be really the best way to
14 know what the noise in the system is and to have a
15 more generally valid set of results.

16 CHAIRMAN NELSON: Judith?

17 MEMBER O'FALLON: I'm a Statistician, so I
18 want to ask that question again, about the numbers.
19 How many of the -- how many normals do you plan to
20 accrue under the, you know, modified protocol?

21 DR. ROSENFELD: 20, 40 60, 80. Twenty
22 pre-pubertal boys, 20 pre-pubertal girls, 20 early

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1 pubertal boys, 20 early pubertal girls. And the
2 issues about accrual, for your information, as I
3 mentioned yesterday in your absence, was that that was
4 a pre-review by the GCRC and the final protocol
5 address. For the principal outcome variables, we have
6 sufficient power. That has to do with constitutional
7 delay of puberty and idiopathic central proposal
8 (*9:28:52 phonetic) puberty. We have sufficient power
9 to carry out that study.

10 MEMBER O'FALLON: But that's the normals
11 you're planning on getting?

12 DR. ROSENFELD: Well they -- yes.

13 MEMBER O'FALLON: I thought the normals
14 were -- you're going to take them between eight and
15 something --

16 DR. ROSENFELD: Eight and fifteen.

17 MEMBER O'FALLON: And they're just
18 supposed to be normal and they're supposed to -- and
19 you're going to get 80, right?

20 DR. ROSENFELD: Yes.

21 MEMBER O'FALLON: Okay. Forty boys and
22 forth girls?

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1 DR. ROSENFELD: Yes.

2 CHAIRMAN NELSON: At this point, to give a
3 feel for the tempo of the meeting, ideally we will
4 have, in the next 15 minutes, completed our
5 discussion. To give you an idea of how I want to
6 carry the tempo, there are 13 voting members around
7 the table, and if we started voting one-by-one, it
8 would give you a full minute to sort of expound on the
9 reasons for your vote and the like. So, before doing
10 that, I'd like to ask if there's any informational or
11 further discussion or issues people want to raise that
12 you think might change your mind, as opposed to just
13 express your mind --

14 MEMBER MOORE: I'd like to make one more -
15 -

16 CHAIRMAN NELSON: -- because you'll have
17 an opportunity to do that. John?

18 MEMBER MOORE: Part of how I spend my time
19 involves starting an IV on patients who are about to
20 be catharized. And I have to say that on an eight- or
21 a nine-year-old, sometimes these patients prefer to be
22 sedated before they have an IV started. And just the

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1 thought of that procedure is sometimes a fairly
2 traumatic experience for a child. And I just find it
3 difficult to imagine that an eight- or a nine-year-old
4 would actually freely assent to having that done, and
5 once they understand what's being done, when they're a
6 perfectly normal child, they really have been given no
7 reason why they have to undergo this procedure. So, I
8 mean, I'm -- to me, this is the main issue here, is
9 submitting them to this. I think it's a combination
10 of financial incentive really that's to the parent
11 and, you know, the parents have more or less persuaded
12 the child to participate in this kind of a protocol.
13 So I have a hard time with that whole issue of this is
14 just more than minimal risk because there are a number
15 of risks, and, too, the medical risk is probably not
16 more than minimal, but the emotional and psychological
17 risks, just based upon my own practice, I think, is
18 probably, you know, fairly substantial, at least for
19 some children. And that obviates the whole issue of
20 is the IV easy or hard to start, which I think most
21 Pediatricians in the group here understand the issues
22 there.

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1 The other question, in my mind, that I'm
2 sort of weighing this against as I sit here, is the
3 adequacy of control data that could be obtained from
4 patients who are -- children who have constitutional
5 delay. And I can see how that may not be very
6 adequate and may leave this whole issue very blurry,
7 but I'm just concerned about the risk of this protocol
8 to the normal children and the fact that there are 80
9 of them makes me uncomfortable.

10 CHAIRMAN NELSON: Well, let me ask you,
11 would you be reassured to hear evidence or experience
12 to the contrary? I mean, I think your concerns were
13 discussed and raised, but I in both GCRCs and actually
14 in my own work interviewing normal, healthy, average
15 children about being in research, there are children
16 who, if you approach them with emracream (*9:32:52)
17 and appropriate -- in an appropriate context and
18 without giving the money to the parent and, in fact,
19 soliciting the child's assent independent of the
20 parent, are capable of doing this and doing it without
21 great psychological harm. So --

22 MEMBER MOORE: No, I certainly believe

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1 that, that there are children who could undergo this
2 protocol, these controls, who would not be troubled by
3 it, but I also think that -- I mean, the process of
4 sorting them out from those who would be troubled by
5 it is the critical issue. And I know from my own
6 practice that there are many children who would be
7 troubled by this. And I'm not exactly sure, you know,
8 by just asking them, especially when you're giving
9 money to them and it's all getting very confusing,
10 what the incentives are here.

11 CHAIRMAN NELSON: Well, I guess all I can
12 say is that the Committee talked -- the Subcommittee
13 talked about that yesterday and felt reassured that
14 the investigators, under the guidance of their local
15 IRB, were capable of doing that. Beyond that, you
16 know -- that, in fact, was the discussion.

17 So, I guess -- let me ask again. Does
18 anybody think they are going to change their mind
19 based on further discussion? I'm happy for people
20 saying why they vote the way they vote, but, you know,
21 we can go on -- you know. Norm?

22 DR. FOST: Well, I hope to change Dr.

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1 Moore's mind. The -- I agree with you that the heart
2 of it is the assent of the child, whether he or she
3 really wants to do this, understanding he doesn't have
4 to. Point one, I agree with Skip there. There's
5 empiric evidence from Skip's studies that there are
6 children who do want to do this for altruistic reasons
7 even. Number two, if the assent is taken seriously,
8 it'll weed out those who really don't want to. And I
9 agree with you, probably most do not want to, and it's
10 going to be a struggle to do it. That's why I said
11 that the asset monitoring, to me, is at the heart of
12 this. If we ensure that the only kids that are doing
13 it are kids who really want to do it, and understand
14 they don't have to -- and by the way, they might be
15 siblings, so they may have some desire to help their
16 brother or their sister and so on. So I agree with
17 you that the real willingness of the kids to do it is
18 at the heart of it and that's why I voted to approve
19 it, only on the condition that there was assent
20 monitoring and there was not disagreement with that
21 from the -- we had a Vice Chair of the IRB here
22 yesterday and they -- he seemed user-friendly to that

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1 suggestion. So that could be a condition of the
2 approval.

3 CHAIRMAN NELSON: Now, I might just point
4 out, procedurally, we can make further modifications
5 if, in fact, you want to strengthen what Norm just
6 said, from this Committee, is a condition of your vote
7 one way or the other. This Committee can add further
8 modifications to the Subcommittee. So, it's really,
9 in terms of what we're -- there are really three ways
10 you can go. One is the Subcommittee's decision is
11 fine. Approval is -- it's approval, but you want to
12 add further modifications, strengthening something, et
13 cetera, as you see it, which is -- certainly, that's
14 happened actually on one other decision of the
15 previous two. The third is to say that this just
16 shouldn't go forward. So there is that opportunity to
17 do that. If you have further concerns that you'd want
18 to make a stipulation based on this discussion.

19 MEMBER MOORE: I'm a little confused as to
20 how you monitor the assent process. I mean, I agree -
21 - I mean I'm generally in favor of giving control
22 data, don't get me wrong. But I think that if I was

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1 really comfortable with the fact that children who
2 would likely be distressed by this could truly just
3 opt out, or would truly just opt out, I would be more
4 comfortable.

5 One of the things that actually makes me
6 uncomfortable about this is the money. And I'm afraid
7 that there are some parents, you know, who would see
8 this as a little incentive and pressure their child.
9 And I don't know if there's a way to do this without
10 that incentive to the parent. Maybe there is, maybe
11 there isn't. Maybe some kind of financial inducement
12 is needed to get anybody to show up for this. But I
13 think that it is important to have some type of
14 independent, independent of the protocol apparatus
15 assent monitoring for this, so that somebody, social
16 worker or psychologist, somebody in the hospital is
17 actually reviewing these candidates that has nothing
18 to do -- no interest in the protocol.

19 CHAIRMAN NELSON: And this, I just point
20 out, will be done in a GCRC, which by NIH support, has
21 a research subject advocate as part of that process.
22 So we certainly could make a stronger statement about

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1 the need for that.

2 Judith?

3 MEMBER O'FALLON: Okay, here's my concern.

4 There are going to be -- we're looking for 40, let's
5 say, girls between the ages of eight and 15 or 14.
6 That's roughly six per year. I'm wondering -- you
7 know, I'm not a medical doctor. I'm wondering about a
8 Pediatrician who's seeing normal kids, taking care of
9 regular, old kids, not -- you know, not -- what do you
10 call it? -- not an expert in some area here. How much
11 variability are we going to be able to get at with
12 only 40? I'm concerned about -- I hate to say this,
13 but I'm really worried about whether 40 kids between
14 the ages of eight and 14 will give us a very good idea
15 about how the normal process is evolving in that very
16 volatile age range. You know, in terms of measuring
17 the -- well, whatever -- whatever it is that you're
18 going to be measuring. I know there are hormone
19 levels, but --

20 MEMBER MOORE: Ruth, until you start doing
21 that, you can establish a confidence interval around
22 the variability of that, there's no way you can answer

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1 that question. So, I mean, you can't say it's a
2 question that can't be answered without starting to
3 try and answer it.

4 MEMBER O'FALLON: No, I'm -- I'm in favor
5 of getting the -- actually, I'm in favor of looking at
6 the normals, but I am concerned about how much you're
7 going to get in that volatile period, how much
8 information, and whether it's going to be so much all
9 over the map that it's -- on any one of the hormone
10 measurements that you take, that it's going to not
11 really help a lot and you're going to find out you
12 need to have a lot more kids, in which case, they'd be
13 coming back for more normals.

14 MEMBER MOORE: The devil's in the details,
15 and that's why there's continued oversight of the
16 research. But it really comes down to preliminary
17 data that could give you a confidence interval and you
18 have no preliminary data on which to do that.

19 MEMBER O'FALLON: It's not a confidence
20 interval, people, exactly because we're looking at a
21 process. We're going --

22 MEMBER MOORE: It's about distribution

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1 over time, but you don't know how that's going to be -
2 -

3 MEMBER O'FALLON: Yeah, I mean, it's going
4 to be like over a regression line, is what we'd be
5 dealing with.

6 CHAIRMAN NELSON: So what I'd like to do,
7 and I'm going to say this slowing to give Melissa a
8 chance to gather her thoughts because I'd like to
9 start at that end of the table and, Rich, and
10 Elizabeth are non-voting members, so you would be
11 first up. So, what I'd like each person to do is
12 basically -- you know, we have a Subcommittee Report,
13 we have a recommendation from the Subcommittee, seven
14 to two to approve -- I should say, to recommend that
15 this Committee send forward to the Commissioner a
16 recommendation for approval under 407 and 5054 with
17 the stipulations that Norm mentioned in terms of the
18 protocol. I don't know if those stipulations can be
19 put back up on the slide just so people see those, if
20 you want to look at them. Now, if -- if you would
21 approve, but you think you would do that only with an
22 additional stipulation, what I would suggest is just

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1 add that and then at the end of the voting, I'll take
2 those stipulations and basically see if there is,
3 among the people that voted in favor and those, in
4 fact, that vote against, if there's a consensus or not
5 around those stipulations, rather than go one-by-one
6 to each one of those. So if, for example, on the
7 assent strengthening that's something that you want to
8 strengthen, if you haven't heard it before, say it,
9 and then after the process is done, we'll go through
10 and clean up those additional modifications just to
11 sort of move us along. So, it's really either
12 "approve" or "disapprove" or "approve with
13 modifications." If you say you'd approve it with
14 modifications, just what is the nature of that
15 modification and then we'll go around and then clean
16 up those modifications at the end, assuming that the
17 vote is for approval or approval with modifications at
18 that point. Does that make sense?

19 Okay. So I'd like to start with Melissa.

20 MEMBER HUDSON: Well, I think the
21 objectives outlined in the study are important and
22 will help us gain important knowledge in diagnostics

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1 for these children, and I believe that it's important
2 to have control of the situation because of the
3 variability in children with constitutional delay. I
4 would approve, with the understanding that there be
5 very strict assent monitoring. And I've been
6 reassured, at least what I've heard so far, that this
7 is an institution that would have that as a priority
8 and that they're used to implementing these studies in
9 children who had a fear or clearly were not -- were
10 being coerced by their parents, and the situation
11 would be eliminated.

12 CHAIRMAN NELSON: Okay. Jeff?

13 DR. BOTKIN: Do I get --

14 CHAIRMAN NELSON: You are a voting
15 consultant to the Committee, I was informed. If you
16 need time to think, I'd be happy to pass you, but
17 usually you're pretty quick on your feet.

18 DR. BOTKIN: Well, a nice surprise to get
19 to say something additional. I would maintain my
20 assessment from yesterday, which would be not to
21 approve the inclusion of healthy children in the
22 protocol. I think it's otherwise approvable and would

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1 provide valuable scientific evidence for the
2 evaluation of kids with either delayed or precocious
3 puberty, in the absence of healthy children in the
4 protocol. I also would strongly support the assent
5 monitoring if the protocol goes forward.

6 CHAIRMAN NELSON: Okay. Bob?

7 MEMBER DAUM: I have a bit of a problem
8 and request some help from the Chairman. I didn't
9 realize until this discussion started that Dr.
10 Rosenfield is, of course, at my institution, and not
11 only that, is in my department. So, I feel like -- I
12 think I would consider that a conflict. I do consider
13 it a conflict, and I would prefer not to vote, or to
14 abstain.

15 CHAIRMAN NELSON: Well, then, we'll
16 consider that a non-vote. You wouldn't be allowed to
17 review a grant on NIH, nor would you be on the IRB
18 protocol, so I think we should hold that same
19 decision.

20 MEMBER DAUM: No, I was actually going to
21 jump up and ask you if you wanted me to leave the
22 room.

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1 CHAIRMAN NELSON: No, that's all right.

2 MEMBER DAUM: I just didn't know this was
3 going to happen.

4 CHAIRMAN NELSON: That's fine. I think it
5 would be appropriate for you not to vote.

6 MEMBER DAUM: Okay. Having said that, you
7 can determine whether you'd like to have my opinion or
8 not.

9 CHAIRMAN NELSON: No.

10 (LAUGHTER.)

11 CHAIRMAN NELSON: Norm?

12 DR. FOST: I would vote to approve, with
13 all the -- with conditions that are on the screen,
14 plus the additional requirement for consent or assent
15 monitoring by someone not connected with the study.

16 CHAIRMAN NELSON: Okay. Angela?

17 MEMBER DIAZ: I also vote to approve, with
18 the three modifications and closely monitoring of the
19 assent.

20 CHAIRMAN NELSON: Okay. Bob?

21 DR. WARD: I would vote to approve, and I
22 actually think it's essential to have the normal

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1 controls because of our lack of understanding of
2 variability with this test in children who wouldn't be
3 presenting to an Endocrinologist. I think Norm's
4 concern about having assent monitoring is essential
5 because of the magnitude of the monetary rewards, in
6 particular. And I think Judith's point about power
7 analysis is important and I would wonder if there
8 shouldn't be a mid-way analysis of variability to
9 decide whether we properly powered this so that at the
10 end of the day, we have a definitive test.

11 CHAIRMAN NELSON: I would hope that that's
12 routine on IRB oversight, but we can make that much
13 more --

14 DR. WARD: I didn't see it specified.

15 CHAIRMAN NELSON: No, it's not specified,
16 right. Michael?

17 MEMBER FANT: Yeah, I vote to approve,
18 with the previously stated modifications. Just one
19 comment with the discussion that centered around the
20 inclusion of controls. Based on the discussions that
21 I've heard, I really think those discussions sway me
22 more toward the necessity to include normal controls.

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1 I don't think we can assume that kids that end up
2 having constitutional delay and are otherwise
3 considered "normal" can be considered as normal for
4 the purposes of this study. And I think the kids who
5 you are trying to get a better understanding of, a
6 diagnostic tool, they may be short-changed if we're
7 not allowed to include normal controls in this
8 process. So, only with those comments, I vote to
9 approve with the previously stated modifications.

10 CHAIRMAN NELSON: Okay. Tom?

11 MEMBER NEWMAN: Well, my concerns about
12 the scientific value including the normal controls, I
13 think, were addressed, to some extent, by Dr.
14 Rosenfield when he said that actually the sleep study
15 is not a very good Gold Standard and hasn't been well
16 standardized, so having some children about whom there
17 is no concern might actually be helpful in making this
18 test more interpretable. So, I'm reassured about
19 that. I share the concern about the incentive, and
20 actually got a little bit more worried when somebody
21 mentioned maybe siblings of patients who have this
22 might, you know, want to do it because then, you know

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1 -- whatever we say about your participation is
2 voluntary, you don't have to do it, this child is
3 going to go home with a parent who may have wanted
4 them to do it. So, I do have a little bit of concern
5 there about this incentive. I'm going to give a weak
6 "yes" and defer to the Ethics colleagues who have
7 actually researched this, and certainly compared to a
8 Bronchoscopy, this is not too bad.

9 (LAUGHTER.)

10 CHAIRMAN NELSON: We can come back to the
11 sibling issue. Judith?

12 MEMBER O'FALLON: Yes, I would like to --
13 I vote yes. I do have the concerns about whether
14 we've got enough normals, but I think they're needed.
15 And I do agree with all of the above-mentioned
16 modifications.

17 CHAIRMAN NELSON: Okay. I'll just skip
18 me. I'd like to go last. And I'll go to Paula.

19 (LAUGHTER.)

20 CHAIRMAN NELSON: That's not why, but --
21 Paula?

22 DR. KNUDSEN: I vote yes, with the

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1 modifications and the added stricture that for
2 certain, the Pediatric assent monitor must be distinct
3 from the research team.

4 CHAIRMAN NELSON: John?

5 MEMBER MOORE: Yeah, I vote to approve,
6 with the same caveat. I think that it's important, at
7 least for the control group patients -- for the study
8 patients, it's probably not as critical -- that there
9 be an independent monitor that is not related to the
10 protocol or the research team.

11 CHAIRMAN NELSON: Deborah?

12 MEMBER DOKKEN: I vote to -- is this on?
13 I vote to approve, but also to underscore the
14 independent assent monitoring.

15 CHAIRMAN NELSON: Thank you, and what I'll
16 do is give you my vote, but then as I go through the
17 modifications, I'll do those in the context of re-
18 stating what I've heard and then seeing if there is
19 consensus around requiring those modifications as
20 additional stipulations. So, I would vote to approve
21 as well, and what I've heard on the concerns are
22 three. The first is a consensus around the importance

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1 of assent monitoring. Now how that's done, I think,
2 is open to debate. I mean, there's not been a lot of
3 experience with assent monitoring, but at least, in
4 the GCRC environment, there is an independent research
5 subject advocate and there is a mechanism by which
6 they can monitor assent. How that's done, how you
7 pull a child separate from the parent, I mean, it is a
8 complicated question, John, and in many ways, they'll
9 be breaking new ground. But I think that is an
10 important stipulation, to say there should be a
11 process in place. I've also heard, not from everyone,
12 but from enough -- and I'll see if this is a consensus
13 or not -- is the importance of whether to mid-point
14 review or review at some point about the variability
15 of the data coming from normals and what does that
16 mean in terms of sample size, and if it's going to
17 turn out to be a thousand kids, I mean that's an
18 extreme because there's such variability in the data
19 to reassess, but not to just run through the 80
20 without some assessment of that issue. So a mid-point
21 analysis of the variability -- and this is not a
22 clinical trail, so this is not as if you take a look

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1 at the data, you have to then do another 50. It's
2 just an assessment of the actual data itself. So, I
3 think that can be an important -- even though I think
4 they should do that as part of the continuing review,
5 we'll make it an explicit request. Is that fair?

6 (NODDING OF HEADS AFFIRMATIVELY.)

7 CHAIRMAN NELSON: And then the third thing
8 I heard, I think, the comment of siblings. I don't
9 recall if that was discussed in the protocol. It may
10 just be an aside. I agree with Tom's issue. It's
11 unclear, the balance between a sibling who wants to
12 act altruistically and the risk of undue influence
13 within the family environment. And it's also unclear
14 if you need siblings and that's a controversial issue.

15 So, it's not clear to me if (a) it's necessary. It's
16 also not clear to me if we need to make it a
17 stipulation. But we could certainly add it as part of
18 the mix of concern. I don't know, Norm, if you have
19 further thoughts on that?

20 DR. FOST: Yeah, I mean, Will Gaylon wrote
21 a great article about 20 years ago saying that parents
22 had a right to raise their kids not to be selfish

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1 little bastards.

2 (LAUGHTER.)

3 DR. FOST: That is, some parents want to
4 teach their kids community service, and sometimes it
5 means some sort of mild and modest physical sacrifice.

6 And again, we're not talking about brain biopsies and
7 we have assent monitoring. I think that's within the
8 realm of what parents can legitimately ask their kids
9 to do. I think it's sufficiently undeveloped an area
10 that we shouldn't make it a condition here. I think
11 we can add it as a comment. But I would be concerned
12 if we excluded siblings.

13 CHAIRMAN NELSON: Hopefully, if there's a
14 robust assent monitoring that you'd pick up those
15 siblings who are being coerced by those who are in the
16 tradition of Will Gaylon's approach on that. I guess
17 -- you know, I think that would be fine with me and if
18 that's fine with the rest of the people, we can assume
19 that that could be an issue within the assent
20 monitoring.

21 Rich?

22 MEMBER GORMAN: In the search for normal

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1 controls, I would suggest that siblings of people with
2 constitutional growth delay may not be the ideal group
3 to select.

4 CHAIRMAN NELSON: Important point.
5 Important point. Okay. So, we can add that as a
6 comment without any particular direction in terms of
7 stipulations.

8 So, let me summarize, then, what I've
9 heard and then see if there's anything else. The vote
10 is, by my count, eleven to one, in favor of approval
11 of recommendation to the Commissioner, which will then
12 go through the process to approve under 45 CFR 46.407
13 and 21 CFR 5054, with the stipulations by the
14 Subcommittee, but then in addition to that, two
15 further stipulations with commentary around siblings,
16 but the further stipulations is a robust assent
17 monitoring process within the framework of the GCRC
18 and the research subject aggregate system, and then
19 the second is the importance of a mid-point assessment
20 of the variability of the normal data and a re-
21 affirmation of the appropriateness of the sample size
22 and re-assessment of the utility of that data against

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1 the abnormal data that has already been collected and
2 with appropriate decision-making by the IRB under
3 those circumstances.

4 Are there any other comments?

5 DR. BOTKIN: This might be a little late
6 in the process to raise this question, but perhaps
7 others have a better recollection of the protocol than
8 I do. I think there's a certain element of confusion
9 in my mind about whether the sleep study was going to
10 be the Gold Standard or whether the clinical outcome
11 of the kids was going to be the Gold Standard. In
12 some circumstances, you seem to be saying that he was
13 going to compare the Leuprolide assessment with the
14 sleep study in order to demonstrate equivalence. In
15 another section of the protocol, he said these kids
16 would be followed longitudinally so that the
17 sensitivity and specificity of both the sleep test and
18 Leuprolide test could be independently assessed. I
19 think part of the question Rich just addressed is
20 you're using the healthy controls -- in fact, some of
21 those kids may well turn out to have delayed puberty
22 and unless you follow that whole set of kids

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1 longitudinally, I guess the question is how are you
2 going to independently assess the sensitivity and
3 specificity of both tests independently as well as the
4 clinical status of the healthy controls? So, maybe
5 you adequately addressed this in the protocol, but I'm
6 not certain.

7 CHAIRMAN NELSON: As I recall, the
8 discussion of that was the primary objective is the
9 comparison with the sleep study. The secondary
10 objective is the longitudinal analysis and sensitivity
11 and specificity. I mean, it's -- so, you're right.
12 It's both in the protocol, but one's the primary and
13 one's the secondary objective.

14 DR. BOTKIN: And so did he adequately
15 describe the fact that they will be clinically
16 following all of these children over a period of time
17 to assess their pubertal development?

18 CHAIRMAN NELSON: He certainly said it in
19 the comments that I heard him say yesterday. Now,
20 whether we can find chapter and verse in the protocol,
21 I don't recall. But that is both -- those are both
22 objectives of the study, one being primary and one

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1 being secondary. I'm confident that that's how it's
2 going to happen. But you're right, you're a little
3 late.

4 (LAUGHTER.)

5 DR. MURPHY: So, Skip, pursuant to this
6 conversation, is Dr. Botkin suggesting that that is
7 one of his recommendations, that we make it clearer?

8 CHAIRMAN NELSON: I mean, I think it is
9 clear. I mean, I guess we could certainly go back and
10 look at the protocol and decide is it clearly enough
11 described. But in Dr. Rosenfield's comments from
12 yesterday, it was pretty clear what, in his mind, was
13 the primary objective as opposed to the secondary
14 objective; one being, obviously, a more short-term
15 analysis based on the testing, and the other,
16 obviously, more long-term because you've got to wait
17 and see what an eight- and nine-year-old does when
18 they get to 16. So I'm comfortable with deferring to
19 your office and to OHRP to make sure that that's
20 adequately described in the protocol. But I think Dr.
21 Rosenfeld described it in verbal comments yesterday.

22 DR. MURPHY: Thank you.

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1 CHAIRMAN NELSON: Angela?

2 MEMBER DIAZ: In the protocol, healthy
3 controls are being compensated and were not patients
4 and yesterday I learned that that's the norm of, I
5 guess, the industry. And it's something that I -- I
6 usually either compensate everyone or not. Even if
7 it's not part of this protocol, I'm just interested in
8 hearing if that's really the norm.

9 CHAIRMAN NELSON: I think the difference
10 is, here, the individuals are coming in that this
11 protocol is direct benefit and offers diagnostic
12 testing. And it is the norm if, in fact, you're going
13 to benefit with respect to your own health care to not
14 provide whether you call it compensation or
15 inducement, money for that exchange, as opposed to --
16 so, if this was a basic science protocol where this
17 testing, even for the diseased group, did not offer
18 benefit, then it would have been to compensate as
19 well. So that's the important difference, not that
20 they happen to be patients.

21 MEMBER DIAZ: No, no, I know.

22 CHAIRMAN NELSON: That is -- that is the

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1 standard. That is the standard.

2 What I'd like to do, if I hear no
3 objection, is to basically close this portion of the
4 meeting, have our break, and then we're on to a
5 different subject.

6 (NO RESPONSE.)

7 CHAIRMAN NELSON: Hearing no objections --
8 we're running a few minutes late. Maybe if we try to
9 start at ten after ten, which gives us about 12
10 minutes by my watch.

11 (Whereupon, the above-entitled matter went
12 off the record at 9:58 a.m. and resumed at 10:16 a.m.)

13 CHAIRMAN NELSON: Good morning and
14 welcome. We'll eventually go around the table for
15 introductions, but from the start, I guess, -- do you
16 want to start with that?

17 We're going to start with comments that
18 Jan has to make and we'll proceed from there.

19 EXEC. SEC. JOHANNESSEN: I'd just like to
20 note the mistake that is entirely mine on the roster.

21 I omitted to include on the roster Dr. Catharine
22 Champagne, who is the Chief of Dietary Assessment and

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1 Counseling at Louisiana State University at the
2 Pennington Biomedical Research Center. So I apologize
3 for that omission. We will have an updated Agenda for
4 you tomorrow.

5 I think, at this time, I can also read the
6 meeting statement. "The Food and Drug Administration
7 is convening today's meeting of the Pediatric Advisory
8 Committee under the authority of the Federal Advisory
9 Committee Act of 1972. The Advisory Panel Meeting
10 provides transparency to the agencies deliberative
11 process. With the exception of the industry
12 representative and the Pediatric Health Organization
13 representative, all members and consultants of the
14 Committee are special government employees or regular
15 Federal employees from other agencies subject to
16 Federal Conflict of Interest Laws and Regulations.
17 FDA has determined that members and consultants of
18 this Committee are in compliance with Federal Conflict
19 of Interest laws, including but not limited to 18 USC
20 208 and 21 USC 355(N)(4). Under 18 USC Section 208,
21 applicable to all Government agencies and 21 USC
22 255(N)(4), applicable to FDA, Congress has authorized

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1 FDA to grant waivers to special government employees
2 who have financial conflicts when it is determined
3 that the Agency's need for a particular individual's
4 services outweighs his or her potential conflict of
5 interest. Members and consultants who are special
6 government employees at today's meeting have been
7 screened for potential financial conflicts of interest
8 of their own, as well as those imputed to them,
9 including those of their employer, spouse or minor
10 child related to the discussion of today's meeting.
11 These interests may include investments, consulting,
12 expert witness testimony, contracts, grants, gratis,
13 teaching, speaking, writing, patents, royalties and
14 primary employment."

15 Today's Agenda involves a discussion on
16 pediatric obesity and clinical trial designs for the
17 evaluation of devices intended to treat pediatric
18 obesity for future development of a guidance document.

19 In accordance with U.S. -- 18 USC Section
20 208(B)(3), waivers have been granted to Doctors
21 Patricia Joban (*10:18:17 phonetic) and Thomas Inge.
22 A copy of the written Conflict of Interest with waiver

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1 statements may be obtained by submitting a written
2 request to the Freedom of -- Agency's Freedom of
3 Information Office, Room 12A-30 of the Parklawn
4 Building.

5 In addition, Dr. Elizabeth Garofalo is
6 participating as the Industry Representative, acting
7 on behalf of all regulated industry, and is employed
8 by Pfizer Global Research and Development, and Dr.
9 Richard Gorman is participating at the Pediatric
10 Health Organization Representative, and is
11 representing the American Academy of Pediatrics.

12 Finally, in the interest of public
13 transparency, with respect to all other participants,
14 we ask that they publicly disclose, prior to making
15 any remarks, any current or previous financial
16 involvement with any firm whose products they may wish
17 to comment on.

18 This statement will be available for
19 review at the registration table during this meeting,
20 and will be included as part of the official meeting
21 transcript. Thank you.

22 CHAIRMAN NELSON: Thank you, Jan. In

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1 looking at the Agenda, I note both Dianne and Ron are
2 listed as having opening comments. Is there a
3 particular direction, or who would like to go first or
4 second?

5 DR. MURPHY: Mine are shorter.

6 CHAIRMAN NELSON: Okay. Should we do
7 introductions --

8 DR. MURPHY: Yes. I'm --

9 CHAIRMAN NELSON: Dianna, should we do
10 introductions before or after your introduction, of
11 the people around the table?

12 DR. MURPHY: Why don't you do
13 introductions before?

14 CHAIRMAN NELSON: Okay. So, let's go
15 around the table and introduce. We have new people
16 and new people who don't know the old people. So, if
17 we could start down on my left, at the end, and just
18 go around the table introducing ourselves?

19 DR. INGE: Hi, I'm Tom Inge, Pediatric
20 Surgeon from the University of Cincinnati at
21 Cincinnati Children's Hospital.

22 DR. YANOVSKI: Jack Yanovski, National

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1 Institute of Child Health and Human Development. I'm
2 an intramural investigator. I work on pediatric
3 obesity in clinical trials.

4 DR. KLISH: Bill Klish. I'm a Professor
5 of Pediatrics, Pediatric Gastroenterologist from
6 Baylor College of Medicine.

7 DR. CHOAN: Pat Choban. I'm a General
8 Surgeon in private practice in Columbus and an adjunct
9 Professor of Human Nutrition at Ohio State.

10 DR. KRAL: I'm John Kral, a Professor of
11 Surgery and Medicine and my interests are obesity,
12 appetite regulation, and developmental aspects.

13 DR. CHAMPAGNE: Catharine Champagne. I'm
14 a Nutritionist, a Ph.D. at Pennington Biomedical
15 Research Center. My focus is dietary assessment and
16 counseling and we focus on obesity and nutrition at
17 our center.

18 DR. LUSTIG: I'm Robert Lustig. I'm a
19 Pediatric Neuroendocrinologist at UCSF and the
20 Director of our Weight Assessment for Teen and Child
21 Health Clinic.

22 DR. ROCCHINI: Al Rocchini. I'm a

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1 Pediatric Cardiologist at the University of Michigan
2 and I have done -- I have interest in pediatric
3 obesity and hypertension.

4 DR. ARSLANIAN: Silva Arslanian.
5 Pediatric Endocrinologist, Children's Hospital of
6 Pittsburgh. I'm the Director of Pediatric CCRC and
7 for the last year, the new Director of the Weight
8 Management and Wellness Center. And my area of
9 research is insulin resistance during childhood
10 growing levels.

11 DR. PORIES: I'm Walter Pories. I'm a
12 Professor of Surgery of Biochemistry at East Carolina
13 University and Chief of the Metabolic Institute. I'm
14 also a Chairman of the Surgical Review Corporation,
15 which is a non-profit organization for the quality
16 improvement of pediatric surgery.

17 MEMBER DOKKEN: I'm Deborah Dokken. I'm
18 the Patient Family Representative on the Pediatric
19 Advisory Committee.

20 MEMBER MOORE: I'm John Moore, Pediatric
21 Cardiologist at UCLA. I'm a member of the Pediatric
22 Advisory Committee.

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1 DR. KNUDSEN: I'm Paula Knudsen and I'm an
2 IRB Administrator at the University of Texas Health
3 Science Center in Houston and the Consumer
4 Representative to this Panel.

5 EXEC. SEC. JOHANNESSEN: I'm Jan
6 Johannessen. I'm the Executive Secretary of the
7 Pediatric Advisory Committee.

8 CHAIRMAN NELSON: Robert Nelson, also know
9 as "Skip" on the Pediatric Critical Care Physician and
10 Biologist at the Children's Hospital of Philadelphia
11 and University of Pennsylvania.

12 MEMBER O'FALLON: Judith O'Fallon.
13 Biostatistics, Emeritus Professor of Statistics for
14 Mayo Clinic.

15 MEMBER NEWMAN: Thomas Newman, Professor
16 of Epidemiology and Biostatistics and General
17 Pediatrician at the University of California in San
18 Francisco.

19 MEMBER FANT: Michael Fant. I'm a
20 Neonatologist and Biochemist at the University of
21 Texas Health Science Center in Houston. And I'm a
22 member of the Pediatric Advisory Committee.

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1 DR. WARD: I'm Bob Ward, a Neonatologist
2 and Pediatric Pharmacologist at the University of
3 Utah. I'm a consultant to the Advisory Committee.

4 MEMBER DIAZ: Angela Diaz, Professor of
5 Pediatrics and Community Medicine at Mount Sinai
6 School of Medicine. I'm a member of the Pediatric
7 Advisory Committee.

8 DR. FOST: Norm Fost. Professor of
9 Pediatrics and Bioethics. Director of the Bioethics
10 Program and shared IRB at the University of Wisconsin.

11 DR. DIEKEMA: Doug Diekema, Associate
12 Professor of Pediatrics at the University of
13 Washington and Interim Director of the Center for
14 Pediatric Bioethics at Children's Hospital in Seattle.

15 MEMBER DAUM: I'm Robert Daum. I'm a
16 Professor of Pediatrics at the University of Chicago
17 and Head of the Section of Pediatric Infectious
18 Diseases.

19 DR. BOTKIN: I'm Jeff Botkin, Professor of
20 Pediatrics and Medical Ethics at the University of
21 Utah and Associate Vice President for Research at the
22 University.

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1 MEMBER HUDSON: I'm Melissa Hudson. I'm a
2 Pediatric Hematologist/Oncologist at St. Jude
3 Children's Research Hospital and a new member of the
4 Pediatric Advisory Committee.

5 MEMBER GORMAN: I'm Richard Gorman, a
6 Pediatrician in a suburban private practice. I'm the
7 Chair of the Section of Clinical Pharmacology and
8 Therapeutics for the American Academy of Pediatrics and
9 am a non-voting member of the Pediatric Advisory
10 Committee, representing the American Academy of
11 Pediatrics.

12 MEMBER GAROFALO: I'm Elizabeth Garofalo.
13 I'm a Pediatric Neurologist by training, and I am the
14 Industry Representative, non-voting member, for the
15 Pediatric Advisory Committee. I work for Pfizer.

16 DR. GOLDKIND: I'm Sara Goldkind. I'm the
17 Bioethicist in the Office of Pediatric Therapeutics
18 within the Commissioner's Office of the FDA.

19 DR. MURPHY: I'm Dianne Murphy. I'm a
20 Pediatrician and the Director of the Office of
21 Pediatric Therapeutics at the FDA.

22 DR. YUSTEIN: Ron Yustein. I'm a Deputy

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1 Director for the Office of Device Evaluation in the
2 Center for Devices and Radiological Health

3 CHAIRMAN NELSON: Thank you. Dianne?

4 DR. MURPHY: First of all, I want to
5 welcome members of the Committee and guests and
6 consultants. We do recognize your commitment of time
7 and expertise and we deeply appreciate it because we
8 know from trying to obtain people who have a level of
9 expertise that we need who can participate in some of
10 these often difficult because of busy schedules and
11 with the many commitments you have. We want to make
12 sure that you realize how grateful we are. We really
13 do need your input into this important issue and we're
14 glad to see you here today.

15 I want to make a few comments about
16 today's meeting because it is actually a very positive
17 activity. This is a meeting we are having because the
18 Center for Devices anticipated an issue. They wanted
19 to develop -- they could see that there was going to
20 be a need to develop options for the pediatric
21 population in the area of intervention for therapeutic
22 intervention for the treatment of obesity.

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1 They wanted to develop the trials with
2 good science and sound ethical principles. They
3 approached Dr. Goldkind in our office because they
4 realized that the pediatrics scientific trial issues
5 are frequently compounded by the ethical issues. And
6 you will see that in the four pages of questions that
7 we have provided you. This is not an easy subject.
8 This requires even in the planning a cross-center,
9 cross-FDA multi center approach. And the planning, we
10 hope, is reflected in the selection of your expertise
11 in that we had individual representatives from the
12 Center for Foods, the Center for Drugs, the Center for
13 Devices was the lead on all this and it was their
14 initiative to brig this forward.

15 So, you will be advising all of us, is
16 what I'm trying to tell you, in your discussion today.

17 You have before you, as I noted, an extensive series
18 of questions. I can tell you in the decade that I've
19 worked for FDA, I've never seen such an extensive
20 series of questions. A lot of thought and time has
21 gone into them and we really know that you have quite
22 a task before you.

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1 Today we are going to attempt to provide
2 you additional background information to set the stage
3 for your discussion. And I'm just going to walk
4 through the Agenda very quickly with you. You are
5 going to have next, Dr. Houston, who is going to
6 present to you background information on the
7 development of devices in this area for this
8 indication, an outline for you of the issues that have
9 been identified that we are going to be dealing with
10 today.

11 We then are going to have Dr. Dietz from
12 CBC provide for us the context of the epidemic in
13 which we are addressing, which is that of obesity in
14 this country.

15 And then the science -- a different talk -
16 - we call it the scientific overview, not that
17 Epidemiology isn't scientific, Dr. Newman, but that --
18 trying to get at the clinical medical issues, if you
19 will, the comorbidities that are associated with this
20 epidemic.

21 And then we will have Dr. Wendler address
22 some of the assent issues, which per earlier

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1 discussions that some of the individuals weren't here
2 for, you will see are very important in developing
3 these trials.

4 Then Dr. Hoelscher -- and I'm probably
5 mispronouncing that name, I apologize -- will provide
6 us some insight and background information on
7 conservative interventions that are frequently
8 utilized in the population that would be considered
9 for enrollment or potential enrollment in these
10 trials.

11 Then the presentation by Dr. Garcia will
12 include some of the surgical interventions and device
13 application interventions that are presently utilized.

14 Then we are going to be at the end of the
15 day and you'll have an opportunity to cogitate upon
16 all this information and think about it and apply it
17 to your discussion for tomorrow. If we get through
18 this earlier -- I guess we could begin the discussion
19 earlier today, Skip. I leave that up to you, but our
20 plan right now is that it's going to take us pretty
21 much to the end of the day.

22 And with that, I will turn this over to

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1 Ron.

2 CHAIRMAN NELSON: Thank you, Dianne.

3 DR. YUSTEIN: Good morning again. My name
4 is Ron Yustein and I'm coming before you today wearing
5 actually two hats. I am the Clinical Deputy Director
6 for the Office of Device Evaluation, CDRH, but also
7 for the past five years, since I've been at the FDA,
8 I've also been the Lead Clinical Reviewer for all
9 devices for the treatment of obesity. I am an adult
10 Gastroenterologist and I don't claim to be a
11 Pediatrician, but I have been the Lead Reviewer for
12 all obesity devices for the past five years.

13 I did want to second Dianne's points and
14 thank the Panel for attending and participating today.

15 These are issues that we are struggling with in CDRH
16 and certainly appreciate all your input and help. I'd
17 also like to thank the Office of Pediatric
18 Therapeutics, Dr. Murphy and Dr. Goldkind, Jan and
19 also our own Nancy Pluhowski for setting up this
20 meeting. It's quite challenging for the logistics. I
21 think this is definitely one of the larger panels I've
22 seen in my five years at the FDA and I'll bet you it's

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1 up there.

2 I would also like to thank the public for
3 participating. I think we have several people
4 scheduled on the public agenda.

5 Before I go into my presentation, I wanted
6 to address one issue that arose last night at our
7 training session. Dr. Tillman and myself were asked a
8 question regarding MedSun and Children's Hospitals. I
9 can't remember who asked that question. But I did
10 talk to our Office of Post-Market Surveillance today
11 and out of the 300 MedSun Hospitals that are in the
12 active surveillance, post-market surveillance program,
13 22 are children's hospitals and that includes
14 hospitals in Los Angeles, San Diego, Phoenix, Miami,
15 Minneapolis-St. Paul, all across the U.S. I do have
16 that list with me if anybody is interested at the end.

17 Okay. So, my outline for the 25 or 30
18 minutes I have to talk to you, I'm just going to go
19 over some of the goals for this meeting as we see it
20 in the Center for Devices, what we hope to get out of
21 this panel; number two, just briefly touch on the
22 epidemic, why we're here; number three, just give you

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1 a little bit of brief background on CDRH and ODE, what
2 we do -- "ODE" is the Office of Device Evaluation;
3 fourth, give you a little background on the devices we
4 have approved for obesity, and then talk about some of
5 the typical features of adult trials for adult trials
6 for obesity, and I won't be mentioning any specific
7 products -- I'm not allowed to due to confidentiality
8 rules -- talk about any specific applications, but
9 I'll give you general ideas of some of the issues we
10 face. And then I'll kind of sum up and end by giving
11 you a preview of the questions in a summarized form so
12 that you can kind of keep those in the back of your
13 mind while you hear all the rest of the presentations
14 today.

15 Okay, so what are our meeting goals?
16 First and foremost is to provide an open forum for
17 discussion between the Agency, academia, the clinical
18 community, the public and even industry on what we
19 consider a vital public health issue, to discuss the
20 epidemiology of obesity in the U.S. pediatric
21 population as well as the current treatment options,
22 and that's what you'll be hearing about during the

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1 course of today. And then finally, what we'll be
2 focusing on tomorrow is to discuss issues related
3 specifically to designing and performing clinical
4 trials for devices to treat obesity in the pediatric
5 population with, hopefully, obtaining good
6 recommendations from the panel for possible use in a
7 guidance document.

8 A couple of points I'd just like to remind
9 you of. The first one is a key point. Although
10 prevention of obesity is certainly an important topic
11 and a key issue when discussing this epidemic, that's
12 probably for a different forum and a different time,
13 and what we would like to focus on is the present
14 situation, the treatment of obesity for patients who
15 already have the disease or disorder. So, we'd like
16 you to kind of try to avoid the temptation to go into
17 prevention of obesity. We recognize that that's very
18 important, but here in the Center for Devices, we are
19 usually dealing with people that already have the
20 condition.

21 And number two, as emphasized last night
22 by Dr. Tillman in our training, we'd like you to keep

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1 in mind the differences between drugs and devices, not
2 only in the entities themselves, but the differences
3 in how we regulate the devices, and just remember that
4 devices are their own unique entity.

5 A picture is worth a thousand words, and
6 I'm sure Dr. Dietz will go into this in much more
7 detail, so I'm not going to spend any time, but
8 essentially the pink bars are why we're here today.
9 This is from 2002 and this is in the pediatric
10 population, but in the adult population, we're seeing
11 a very similar trend as well.

12 Current treatment options. This is
13 basically from the adult world. Currently you have --
14 what I have here is a graph where on the left-hand
15 side are the things that I consider less invasive, but
16 probably less effective as well, and on the right side
17 are the more invasive and more effective. I think
18 what you'll probably find today, as we talk, is that
19 diet and exercise and medications, although effective
20 in some patients, are probably not as effective as our
21 current surgical and bariatric techniques.

22 Yet, there is probably a void here in the

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1 middle where there is the opportunity for other
2 products or therapies that are more effective than
3 these, but also safer for less morbidity than this.
4 Certainly, these two items may go back and forth and
5 maybe over the next several years, they'll even creep
6 up into this part of the spectrum as more drug
7 companies get involved in obesity, but the way we see
8 things at the Center for Devices is that at the
9 current time, this gap will probably be filled by
10 devices, endoscopically or surgically implanted
11 devices to treat obesity.

12 I just wanted to mention -- you've heard a
13 lot about CDRH last night and the way we regulate
14 devices. I just wanted to kind of go over some things
15 again. Our mission at the Center for Devices and
16 Radiological Health is to promote and protect the
17 public health by ensuring the safety and effectiveness
18 of medical devices. And these are the ways we do
19 that. We assess pre-clinical and clinical data. We
20 have regulation and oversight over investigative
21 trials for significant risk devices. We approve
22 devices or clear devices for marketing, which are

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1 reasonably safe and effective. We keep or remove
2 unsafe or ineffective devices from the market and we
3 monitor devices after marketing.

4 Just as Dr. Tommin (*10:37:24 phonetic)
5 mentioned yesterday, another point that I want you to
6 remember is that we do not regulate medical procedures
7 or surgeries. We do not regulate Tonsillelectomies, we
8 do not regulate Appendectomies, and likewise, we do
9 not regulate bariatric procedures such as Rulenwhy
10 gastric bypass (*10:37:36 phonetic).

11 Again, Dr. Tillman showed a similar slide
12 last night. I wanted to just remind you as we go
13 through the day that we do have different regulatory
14 requirements for valid scientific evidence. The
15 randomized -- multiple randomized control of studies
16 are not necessarily required. Valid scientific --
17 sorry -- valid scientific evidence, according to our
18 regulations, can include other entities besides well
19 controlled studies, including partially controlled
20 studies, case histories and even significant human
21 experience.

22 I wanted to give you some background on

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1 devices and obesity and where we have been to this
2 point, but before I get into some specifics, I wanted
3 to give a couple of definitions. I'm sure most of you
4 know these, but for those who aren't familiar. The
5 first one is that we -- in CDRH, we tend to use "BMI,"
6 "body mass index" as a parameter to assess obesity.
7 That is, the ratio of somebody's height -- sorry, it's
8 weight in kilograms over height squared, meters
9 squared. We tend to use the middle column, which
10 defines various stages of being obese, but for
11 children, perhaps this is different. In the
12 literature, it's been reported that percentile use
13 instead of absolute numbers such as BMIs.

14 The second definition, I wanted to just
15 bring to your attention, for those that aren't
16 familiar with the surgical literature because this is
17 something we tend to use in the Center for Devices, is
18 an end point assessment called the "Percent Excess
19 Weight Loss" or "percent EWL." And that basically is
20 the amount of weight loss as a fraction or a percent
21 of the amount by which the person was over their ideal
22 weight at baseline. So, for example, if you have a

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1 patient that's 300 pounds at baseline and their ideal
2 body weight by life tables for frame, for height and
3 frame, is supposed to be 180, that person's excess
4 weight is 120 pounds. If they lose over the course of
5 12 months by some method, 40 pounds, they've lost 33
6 -- their excess weight loss, percent excess weight
7 loss is 33 percent. And that's just a concept.
8 You're going to see some of these numbers coming up in
9 a couple of slides and I just wanted to explain that.

10
11 In our history of devices -- we've been
12 around since 1976, CDRH. We have only approved two
13 devices for the treatment -- specifically for the
14 treatment of obesity. Both of these are for the
15 treatment of obesity in adults. One is the Garren-
16 Edwards Bubble and the second is the Inamed LAP-BAND,
17 which I'll discuss here in a second.

18 But I just wanted also for you to keep in
19 mind that, certainly, this may just represent the tip
20 of the iceberg. That these two types of devices I'm
21 going to show you may not be the only types of devices
22 people may be thinking of developing.

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1 The Garren-Edwards Bubble was approved by
2 PMA back in 1985. This was brought in front of an
3 Advisory Panel which did recommend approval. It is a
4 cylindrical polyurethane balloon, which is inserted
5 into the stomach and then inflated. The indications
6 for us were a temporary aid to diet and behavior
7 modification in people who were at least 20 percent
8 over their ideal body weight.

9 I wanted to give you a little bit of
10 background on what data was presented to FDA and the
11 Advisory Panel in support of this submission. The
12 data was from a 78-patient, adult patient study
13 conducted at three sites on the East Coast. And to
14 sum up the data that was presented, the effectiveness
15 data, the medium plant time for the balloons was 7.5
16 months. And you can see the numbers here. I'm not
17 going to read each one, but you can see that as time
18 went on, people lost a little bit more weight, but you
19 can also notice that the number of patients followed-
20 up each time was lower. But this was the data
21 presented to the Advisory Panel, which recommended
22 approval.

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1 The safety adverse events which were seen
2 during the clinical trial was one spontaneous
3 deflation of the balloon, with subsequent pyloric
4 obstruction, one spontaneous deflation of the balloon
5 with a subsequent small bowel obstruction, and one
6 gastric ulcer.

7 So what happened after marketing? Well,
8 in the next two years after the device was allowed on
9 the market, there were 100 MDRs and "MDRs" are our
10 Medical Device Reports, that's our post-market
11 surveillance with companies to let us know about the
12 adverse events that occurred for significant --
13 serious patient injuries, malfunction or death. There
14 were over 100 that were presented to the FDA over the
15 next two years, including 79 that required surgery to
16 remove a deflated balloon from the small bowel, that
17 had caused small bowel obstruction. The company
18 voluntarily discontinued marketing in 1988, and then
19 voluntarily withdrew their PMA in 1992. So this
20 device is no longer available in the United States.

21 The second device approved by the FDA for
22 the treatment of obesity is Inamed LAP-BAND. It's an

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1 adjustable gastric band and many of our surgeons on
2 the panel can probably give you more details about
3 this, and I believe the sponsor will be making an open
4 public session presentation today as well. Basically,
5 this is an inflatable band that is surgically placed -
6 - oops, sorry -- surgically placed around the stomach.

7 It has a port -- a tubing that connects to a port
8 underneath the skin and fluid can be inserted into it,
9 and depending on how much fluid you put in, the band
10 gets tighter, or if you remove fluid, the band becomes
11 looser and it changes the diameter of this narrowing.

12 The indications for use are for weight reduction for
13 severely obese patients 18 years and older, with a BMI
14 of greater than or equal to 40, or a BMI greater than
15 equal to 35 with one severe comorbidity. One of those
16 were about 100 pounds overweight. This clinical
17 study, I believe, had a couple of patients that were
18 17 or 16 years old, but not many.

19 This is front our summary of safety and
20 effectiveness that is on the public web site,
21 basically showing you the level of evidence that was
22 used to support approval. The sponsor did

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1 approximately a 300-patient study, which -- the data
2 submitted was three years pre-market. Patients were
3 used as their own control, baseline versus follow-up
4 weights. And the chart on the left-hand side, the
5 table on the left-hand side, basically shows you some
6 of the results that were obtained, and you see about a
7 35 percent excess weight loss over three years. You
8 see the mean change in weight was about 50 to 60
9 pounds over those three years. And the BMI dropped
10 from 8 to 10 points during those three years.

11 The right-hand side of the slide shows
12 some of the safety issues which were reported during
13 the clinical trial. The most common ones being nausea
14 and vomiting, which occurred in 51 percent. Reflux
15 symptoms, which occurred in 34 percent. And so forth.

16 Post-marketing experience. Since that
17 time -- like I said, that was approved in June of 2001
18 -- there was an issue with some leaking from the port
19 and the tubing that this sponsor became aware of and
20 reported to the FDA. They worked to redesign the port
21 and submitted a PMA Supplement. Dr. Tillman mentioned
22 to you PMA Supplements last night. That's the way the

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1 sponsor made a correction to the original device.
2 They did bench testing to show that the new device
3 would work better than the other one as far as
4 leaking. And they also put out an advisory, you know,
5 that stressed the new device as well as the new
6 technique in 2002.

7 As far as U.S. clinical experience since
8 that time, from what I could tell, it appears -- and
9 maybe our surgeon can comment later -- that it may be
10 replacing vertical banded gastroplasty as the
11 restricted procedures choice, which is the second
12 procedure choice behind a gastric bypass. Also, the
13 results, if you look in the literature over the past
14 couple of years, the results as far as excess weight
15 loss are approaching what our European colleagues, who
16 have been using this device much longer, have been
17 obtaining and that is, that the excess weight loss is
18 approaching 50 to 60 percent in the one- to two-year
19 range, which is significantly better than we've seen
20 in the clinical trial, as might be supported by the
21 fact that our surgeons are getting better at
22 implanting them and uses and experience is increasing.

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1 If you look in the literature, there are
2 some other products that are out there, including
3 newer balloons that are being studied in Europe.
4 There is also some literature on gastric stimulators
5 where leads are placed on the gastric wall and
6 electrical impulses are imparted to the stomach wall.

7 I'm not at liberty to discuss any of those
8 applications here, but those are things that you can
9 look in the literature for and read about. Just to
10 show you that there are other possible potential
11 things coming down the pike.

12 So what are some of the issues? When we
13 study obesity in adults, which is where most of our
14 experience is in CDRH, what are some of the issues
15 that we struggle with? Number one is patient
16 eligibility, and these are -- I'm just going to point
17 out some of the things that we tend to see in our
18 submissions and our protocol applications. Of course,
19 our sponsors tend to limit their studies to the age of
20 18 and over. We tend to use a BMI as an eligibility
21 criteria. And for a reason, I'm not necessarily sure
22 why, but we've tended to stick with the original

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1 surgical recommendations for obesity, which is the BMI
2 greater than 40, or the BMI of 35 or greater with at
3 least one comorbidity.

4 There are occasions where a device may be
5 less risky, where a surgical implantation may not be
6 required, and therefore, we have also entertained the
7 idea that those requirements may not be needed and,
8 perhaps a BMI as low as 30 may be acceptable if the
9 device is low risk.

10 We tend to require that the patients have
11 a duration of disease for three to five years prior to
12 undergoing a procedure for a device implantation, and
13 that's been documented, and that they also have failed
14 to respond to more conservative therapy.

15 Some of the other issues that we've seen,
16 and this isn't necessarily across-the-board, but
17 sometimes sponsors choose to exclude patients with
18 poorly controlled diabetes, either because they don't
19 heal as well, or there may be some other issues
20 related to diabetic gastropathy in eating and diet.
21 Some sponsors choose to exclude patients with bulimia
22 or other eating disorders because after these

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1 procedures, patients often need to follow specific
2 dietary recommendations. Certain sponsors may, from
3 experience abroad, or in other places, may come up
4 with other characteristics of patients that they see
5 as predictors of who may be more successful with their
6 device, and so they may limit the exclusion -- the
7 eligibility criteria to those patient populations.
8 And then a lot of our devices are anatomical devices
9 that alter or affect the structure or anatomy, and so
10 making sure that somebody has normal swallowing and GI
11 motility is often part of our eligibility.

12 Before I talk about pivotal study designs,
13 I just wanted to mention a point that probably -- that
14 didn't come up last night in our training session, but
15 I wanted to emphasize, and that is that you all are
16 probably used to CDER or drug trials where there's
17 Phase 1, 2, 3, and 4 trials. In CDRH and the Office
18 of Device Evaluation, we have basically two trial
19 types. We have pivotal -- pilot studies, also called
20 "feasibility studies," and then we have our pivotal
21 study. And then, of course, there's the post-
22 marketing study. But our pre-market studies are

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1 usually pilot studies and pivotal. Our pilots are
2 usually very small, usually 10, 15, 20 patients. Some
3 are in that range. It may be one, two or three sites.

4 Often times, if a company has studied their device in
5 Europe and has some preliminary data from that, we may
6 accept that as their pilot study. We usually use
7 pilot studies to make sure that the device can be
8 implanted safely, used safely, and that there are no
9 major safety concerns to move forward to the pivotal
10 study.

11 For obesity studies, our pivotal study
12 designs, we have been encouraging, when possible, for
13 sponsors to conduct randomized, controlled studies and
14 possibly, when available, SHAM controlled studies. Of
15 course, SHAM controlled studies are easier when the
16 surgically implanted device has an active or an
17 inactive mode where the patient may not know that the
18 device is in active or inactive mode -- is in active
19 or an inactive mode, or for perhaps endoscopically
20 placed devices that a Gastroenterologist or Surgeon
21 might put in with an upper Endoscope where you can
22 SHAM procedure where the patient undergoes an upper

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1 Endoscopy, but just doesn't have the device put in,
2 maybe has 50 cc's of water or saline put into the
3 Endoscope and a SHAM procedure is done.

4 So, in summary, we try to have an active
5 group where the device is active and then any
6 concurrent diet, behavior and exercise that the
7 sponsor believes is necessary and the control group
8 has either the sham procedure or an inactive device
9 placed, plus the same diet, behavior and exercise
10 regime. Usually, if this takes place, we then offer -
11 - if it's an implantable device that was inactive, we
12 offer the patient, after "X" amount of time, to be
13 switched over to the active mode. If it was a sham
14 procedure, often times the patient will be offered the
15 opportunity after that primary assessment time to be
16 given the active device.

17 The problem with that situation is the
18 following. On the right-hand side, we have the fact
19 that a device may not be effective or may not reach
20 its maximum effectiveness for several months or even a
21 year after implantation. And you have to balance that
22 with the ethical fact and consideration of the fact

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1 that you're withdrawing -- you're withholding
2 potentially -- potential therapeutic options from a
3 patient in the sham or control group. And that's been
4 an issue we've often struggled with, not only
5 internally, but with manufacturers.

6 There are other possible designs that,
7 certainly, we would entertain. Like I mentioned
8 before, our level of evidence allows sponsors to
9 propose all different kinds of study designs. Some of
10 the other possible ones might be a control using the
11 approved products. At this point, the only one is the
12 LAP-BAND. And, of course, that might be a superiority
13 trial or non-superior trial with a pre-specified
14 delta. Sponsors may wish to do a randomized control
15 study with the control being a surgery. I think most
16 manufacturers would stay away from this because of the
17 high bar set with the RYGB and the good results
18 obtained with that. They may elect to do a control
19 group using optimal medical care, diet, behavior,
20 exercise, pharmacological agents, et cetera. Or, like
21 the LAP-BAND study, they may elect to do a study where
22 the patient is used as their own control and a single

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1 arm study.

2 Another issue we deal with is when is the
3 right time to assess the primary end point. Drug
4 studies tend to be shorter. They tend to be four
5 weeks or six weeks or three months or four months.
6 Well, for an implantable device that's a permanent
7 implant, you want to know that the device is safe and
8 effective for a longer period of time.

9 We've -- right now, you know, we expect at
10 least one year of pre-market data, if it's a permanent
11 implant. There may be some devices coming down the
12 pike where the intended use isn't to be a permanent
13 implant, where its intended to be used for three to
14 six months for somebody who needs cardiac surgery to
15 lose a few -- 30 or 40 pounds so they can get on the
16 operating room table, et cetera. So that has to be
17 taken into account as well.

18 However, for the permanent implants, we do
19 anticipate that we would be asking for, as a center,
20 long-term studies follow-up in the post-market realm
21 to assure safety and effectiveness. And by that, I
22 mean, at least follow-up for another two to five years

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1 post-marketing to assess that long-term safety and
2 effectiveness.

3 End points. Another issue that we deal
4 with and we'll be asking you to deal with. In our
5 adult studies, we tend to use the ones that the
6 surgeons tend to use, which is the percent excess
7 weight loss, which I explained in the earlier slide.
8 However, there are other end points that people can
9 come forward with. Absolute changes in weight.
10 Changes in BMI on an absolute or percentage scale.
11 Also you can look at people that obtain normal BMI.
12 Quality of life assessments. Change in medical
13 comorbidity, such as Hypertension, Dislipodemia, Sleep
14 Apnea, et cetera. And although not used anymore,
15 change in HIPPA waist circumference.

16 We also tend to look at safety and STAR's
17 procedure or surgery-related adverse events because
18 many of these devices is not just taking a pill. It
19 either requires, most of the time, a procedure to be
20 placed, or a surgical procedure to be placed. It is
21 often adverse events that are just from the procedure
22 itself. And then you have the separate category of

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1 adverse events that might be related to the device
2 itself.

3 Concurrent treatments. You know, one of
4 the issues with obesity is that there are other ways
5 for people to lose weight besides whatever we do to
6 them. Diet is often an important part of the
7 protocol. Some sponsors may wish to have patients on
8 an ad-lib diet after the procedure or device is
9 placed. Some may elect to use the device as a adjunct
10 to diet and have a specific calorie restriction, such
11 as a daily 500-calorie-a-day deficit diet. Some
12 groups elect to have patients also enrolled in
13 behavioral or group therapy, behavioral modification
14 groups. Some may have built into the protocol
15 specific exercise or physical activity plans that are
16 supervised during the trail. But either way, we try
17 to avoid allowing subjects to use weight loss
18 medications or even herbal medications that may affect
19 weight loss.

20 So, what are we going to ask you tomorrow?

21 And I'd like you to keep this in mind as you go
22 through the rest of today when you're going to be

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1 hearing presentations from other national experts, to
2 keep these questions in the back of your mind because,
3 hopefully, they may help you answer or spark some
4 discussion about these issues.

5 But before I get to the four questions, I
6 wanted to just have this slide up here because I think
7 it's important and this goes back to differentiating
8 devices from drugs. And I want you to keep in mind
9 that devices come in lots of different shapes and
10 forms. They can be permanent, unremovable -- if
11 that's a word -- implants that are in for life, such
12 as Coronary Stents, which once you place them, you
13 cannot take them out unless you take out that artery
14 with surgery. They can be what we call "permanent,"
15 but they're removable. In other words, they're
16 permanent in the sense that they're long-term.
17 They're meant to stay in for a long time, but they can
18 be taken out. An example of that is the LAP-BAND.
19 It's meant to stay in for a long time, but it can be
20 surgically removed. The device can be a temporary,
21 removable implant. The Garren Bubble I showed you is
22 actually -- was meant to be a temporary implant and

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1 can be punctured and removed endoscopically. They can
2 be external devices. Not all devices have to be
3 implanted or placed into the stomach or abdomen.
4 Perhaps there can be devices that are external
5 compression devices that reduce the size of your
6 stomach. I don't know.

7 Devices can be anatomy-altering devices.
8 They can actually change the anatomy in a way that
9 wasn't originally there. They can alter what parts of
10 the Intestine are hooked to other parts of the
11 Intestine or they can be anatomy preserving where they
12 don't necessary -- when the device is removed or taken
13 out, the anatomy reverts back to its normal original
14 anatomy. And they can be any combination of the
15 above. So I just want you to kind of keep those
16 points in mind because you may have different answers
17 to some of these questions based on those types of
18 devices. Unfortunately, since we're trying to be
19 proactive here at this meeting, I can't come to you
20 and tell you every type of device that's going to be
21 coming down the pike. So we're going to be asking for
22 general recommendations.

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1 So let me summarize the four questions
2 that we're going to ask you tomorrow. These are, as
3 you know, the questions are several pages on your
4 sheet, but I just wanted to summarize them here.

5 Our first question deals with the patient
6 population. Who do you think are the right people to
7 study in these trials and to allow these kinds of
8 devices to be implanted to be studied? Are there
9 criteria based on age, weight, BMI status? Should
10 they have reached certain developmental milestones?
11 Should there be a requirement for certain medical
12 comorbidities? If so, how many? Should there be a
13 requirement for a failure of prior conservative
14 medical and/or pharmacological therapy? And if so,
15 how many? What kind of psychological assessments
16 should be done for these patients prior to considering
17 enrollment? Are there other specific exclusion
18 criteria or diseases which you think might be
19 important to exclude from these trials? The assent
20 and consent issues. How do we address that? And then
21 something I didn't have on here that I thought about
22 based on a question that got asked last night is, what

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1 is the role of outside U.S. data? Do you, you know --
2 sponsors will probably tell you that it's cheaper to
3 go abroad to do clinical studies than here in the
4 United States. Is that acceptable? Is the pediatric
5 and obesity practice of medicine abroad, in Europe or
6 Asia, et cetera, equivalent to the United States, such
7 that you would allow that or you would recommend that,
8 or that you would say, "No, we think that the majority
9 or all of the patients should be U.S. patients."

10 Question Number Two. What do you believe
11 are the appropriate end points for studying the
12 devices to treat obesity in the pediatric population?

13 I told you that we tend to use excess weight, percent
14 excess weight loss as the primary end point in our
15 adult studies. Is that appropriate for kids? What at
16 the appropriate primary and secondary effective end
17 points? I told you what we tend to look at for
18 safety. Do you think those are appropriate? Are they
19 adequate? Are they enough? What is the appropriate
20 duration for assessment of the primary end point? Is
21 one year pre-clinical data sufficient? You know, or
22 is six months sufficient? That is another thing we'd

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1 like you to address.

2 Question Number Three, and this is
3 probably going to be the big one tomorrow. What are
4 the appropriate study designs for these trials? I
5 told you that we try to recommend, we try to encourage
6 that sponsors do randomized controlled studies. We
7 don't design the studies, the sponsor does. We have
8 feedback on those studies, but like I said, there's
9 many different routes to approval or clearance and
10 they don't all have to come through a randomized
11 controlled study. And if the sponsor believes there
12 is another least burdensome way to do that, it's their
13 option to. But we try to encourage the best study
14 that we think is going to give us the data that's
15 appropriate. Are randomized control trials
16 appropriate in this population? If so, is a sham
17 control appropriate for this population? If not, what
18 are the appropriate controls if a controlled study is
19 appropriate? How would you go about minimizing some
20 of the other confounding factors? I mentioned diet,
21 exercise, behavioral therapy, medication use, et
22 cetera. Do you agree with what we've been doing for

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1 adults? The appropriate duration of the pre-market
2 study. Dr. Tillman stressed to you yesterday that
3 we're trying to learn the appropriate balance between
4 pre-market and post-market. How much do we need to
5 know pre-market versus how much can we leverage post-
6 market? What's the appropriate duration for that pre-
7 market study? What are the roles of the Data
8 Monitoring Commission, Committee or Data Safety
9 Monitoring Board during those studies?

10 Question Number Four. What are the long-
11 term safety and effectiveness issues that can be
12 addressed, and how should we address them? As I
13 mentioned, several of these devices are meant -- maybe
14 meant to be in place for years, and how does that
15 affect how you would evaluate it? Is it important to
16 look at the effect on future growth and development
17 parameters, effect on future comorbidities? Is
18 maintenance of weight loss -- if the weight loss is
19 assessed out at one year, do you want to see what it's
20 out at three years, five years? And what is the role
21 of a post-approval study to collect that information?
22 Can some of that information be collected post-market

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1 instead of pre-market? And can we use possibly
2 registries? Can any of the organizations or academies
3 help us out with registries that might be able to
4 lower the burden on some of our smaller manufacturers
5 that might be looking for that?

6 So with that, I'm going to go ahead and
7 end my talk. Hopefully, I stayed on time, or about on
8 time, and I will be at the table to answer any
9 questions as the day goes on.

10 Thank you for your attention and, again,
11 thank you for participating.

12 CHAIRMAN NELSON: Thank you, Ron. I would
13 ask any members of the Panel, if you have questions to
14 write them down. We're not going to take them at the
15 moment, since we're running a bit late and I'm sure
16 there'll be time this afternoon and tomorrow for
17 further discussion.

18 So I'd like to turn now to the
19 presentation by Dr. Dietz on the Epidemiology of
20 Obesity.

21 DR. DIETZ: Thank you, Dr. Nelson. It's a
22 great pleasure to be here with you today to talk to

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1 the Pediatric Advisory Committee on such a critical
2 topic. My task is to present you with the
3 Epidemiology by way of background for this problem.

4 I should begin by saying that my opinions,
5 as we're now asked to declare, are my opinions and not
6 those necessarily of the CDC or of HHS.

7 I think that you're probably familiar with
8 these maps showing the obesity trends in the United
9 States in young adults. I would remind you that
10 obesity in adults is defined as a body mass index
11 greater than or equal to 30, and that approximately 30
12 percent of all adults in the United States have a BMI
13 greater than or equal to 30. These are self-reported
14 data so they underestimate the problems of obesity.

15 But NHANES, the current NHANES suggests that about 30
16 percent of adults are obese and there are no
17 significant disparities among men, although very
18 significant disparities among women. Thirty 30 of
19 Caucasian women, 40 percent of Mexican American women,
20 50 percent of African American women meet these
21 criteria.

22 The prevalence of severe obesity, defined

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1 as a BMI greater than or equal to 40, or morbid
2 obesity, has increased even more rapidly than obesity
3 per se. About five percent of all U.S. adults are now
4 in this category, more women than men, and about 15
5 percent of African American women. And a BMI of 40 is
6 one of the cut points for Bariatric surgery in the
7 adult population.

8 Now when we talk about pediatric obesity,
9 we use percentiles to reflect the growth of youth.
10 And one of the questions that has arisen is how valid
11 is the BMI as an index of fatness in the pediatric
12 population. These are data that Data Freedman
13 published this year which were derived from Dexis
14 studies of about a thousand kids in York, a
15 convenience sample. And I'm showing you here the
16 correlation coefficients adjusted for race and age
17 between BMI and fat mass index. Fat mass index is fat
18 divided by height and meter squared. And obviously,
19 fat mass index and fat-free mass index equal body mass
20 index. And I'm showing you here just two groups. The
21 same results hold for younger children and older
22 adolescents. But notice that at the lower percentiles

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1 of BMI, there really is not -- there is a very, a
2 reasonable correlation, but a fairly low level,
3 whereas, above the 85th percentile, there's a very high
4 correlation of BMI with fat mass index. And that
5 becomes even greater at a BMI greater than the 95th
6 percentile, suggesting that at this high level, above
7 the 95th percentile, the BMI is a reasonable index of
8 increased body fat.

9 I should also point out that in
10 adolescence, a BMI at the 95th percentile corresponds
11 to the BMI of 30. And although you'll hear different
12 terminology, and historically we've used the term
13 "overweight" to describe children greater than the 95th
14 percentile. I think that the fact that there's no
15 ICD-9 code for overweight means that we're going to
16 have to start in the pediatric population using the
17 term "obesity" to describe children greater than the
18 95th percentile, which is concordant with the adult
19 definition.

20 Interestingly enough, the 85th percentile
21 corresponds roughly to a BMI of 25, so that the
22 overweight group in the pediatric population is

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1 probably reasonably referred to between the 85th and
2 95th percentiles.

3 It's clear that there have been rapid
4 increases, as Ron has shown you, between 1980 and the
5 time that NHANES became continuous. There was a
6 twofold increase in the prevalence of overweight 6 to
7 11-year-olds and a threefold increase in the
8 prevalence of overweight adolescents. And most
9 recently, we have begun to see the occurrence of
10 disparities not just similar to adults in the female
11 population, as I'll show you in a minute, but
12 increasing disparities among adolescent males. These
13 are 12 to 19-year-olds. You can see that there was a
14 relatively modest increase among the Caucasian
15 population between NHANES 3 and the concurrent NHANES.

16 But more dramatic increases in African American and
17 Mexican American boys. The highest prevalence is in
18 Mexican American boys, about 25 percent, suggesting
19 that the absence of the disparities which currently
20 exists in the adult population, are soon going to
21 change as these adolescents go on to adulthood.

22 And our next slide, please. This doesn't

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1 seem to be working again. Among adolescent girls, you
2 see the same pattern of prevalence that you do in the
3 adult population. The highest prevalence is in
4 African American girls, followed by Mexican American
5 girls, followed by Caucasian girls. Again, the rates
6 of increase in the Caucasian population seem to be
7 lower than those in the other groups.

8 We've also been interested recently in
9 what constitutes "morbid" obesity for adolescents and
10 have done some preliminary runs. These are from a
11 manuscript that's in preparation -- next slide, please
12 -- in which it appears to us that a reasonable
13 definition of "morbid obesity" is a BMI at the 99th
14 percentile. This shows the BMI at the 99th percentile
15 for males roughly at a BMI of 35. Among girls, it's -
16 - and these are adolescents, obviously -- it's about a
17 BMI of 40. Notice that about two percent of the
18 adolescent population has a BMI greater than or equal
19 to 40, and this cut point at the 99th percentile
20 identifies a reasonable number of adolescents. Next
21 slide, please.

22 In addition, using the Bogalusa data,

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1 which is one of the few data sets that track children
2 into adulthood and also has existing, by chemical,
3 comorbidities. It does seem to be a reasonable
4 pathologic diagnosis in terms of the frequency of risk
5 factors, and in this case, these are elevated insulin
6 or glucose levels, elevated lipid levels, or elevated
7 blood pressure. These actually seem to increase at
8 the 98th percentile for two or more risk factors and
9 about the 99th for three or more risk factors,
10 suggesting that this diagnosis of the 99th percentile
11 for the diagnosis of "morbid obesity" meets several
12 important criteria. One, it identifies a reasonable
13 number of adolescents. Secondly, it has some
14 pathologic corollaries. Thirdly, it has some face
15 validity based on the BMI identified by that
16 percentile. Next slide, please.

17 You're very familiar, I'm sure, with the
18 consequences of a childhood and adolescent obesity. I
19 won't dwell on all of these, but clearly, the
20 psychosocial are among the most frequent, and although
21 they're not great published data to this effect, I
22 think the experience, my experience in treating

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1 overweight children and adolescents, as well as those
2 of others in the field, would suggest that the more
3 severe obesity is, the more likely you are to have
4 very severe family dysfunction and psychosocial
5 complications, particularly at a BMI greater than or
6 equal to 40.

7 There is this apputative metabolic
8 syndrome consisting of cardiovascular disease risk
9 factors. These are also increased -- next slide --
10 among the obese children and adolescents. There are
11 data from NHANES 3 and although the metabolic
12 syndrome, this cluster of findings, high
13 triglycerides, low HDL, high fasting glucose, high
14 blood pressure, adapted from the adult criteria for
15 the pediatric population occur in four percent of all
16 children. They're rare in the normal population, but
17 among overweight children, this cluster exists in 25
18 percent of all individuals. And you can see, there is
19 a graded response to these among overweight children
20 and adolescents. There's a higher prevalence in the
21 at-risk group, but the highest prevalence exists among
22 overweight children. Next slide, please.

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1 The next problem, I think, is this
2 question of persistence into adulthood. And -- well,
3 actually, before I do that, I just want to point out
4 that hepatic steatosis is one of the more recently
5 recognized complications of obesity. The estimates
6 are high variable, but probably about 20 percent of
7 pediatric patients have hepatic steatosis. It does
8 seem to increase with severity, although the dose
9 response of some of these -- the obesity to some of
10 these complications is quite variable across groups.
11 And in -- there is an anecdotal experience that
12 hepatic steatosis does occasionally progress to
13 psoriasis and, in even more limited experience that
14 suggests that certainly weight loss resolves elevated
15 liver enzymes and may improve the psoriatic changes
16 that are found in the livers of these severely
17 affected individuals.

18 The concern about persistence into
19 adulthood, I think, is emphasized by the next slide,
20 which are also data from Bogalusa, Louisiana. These
21 data suggests that onset of overweight prior to eight
22 years of age is associated with a much more sever

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1 course if that obesity persists into adulthood. Only
2 25 percent of obese adults were overweight children,
3 but among that severely overweight group, with a BMI
4 greater than 40, the -- about 50 percent of all, of
5 that group, of people with a BMI in adulthood over 40,
6 had onset of their overweight prior to eight years of
7 age. And the mean BMI in this group is 41.7. So even
8 though childhood onset obesity contributes a minority
9 of adult obesity, it may have a disproportionate
10 effect on the morbidity and costs of adult obesity.
11 Next slide, please.

12 I know that you're familiar with the
13 increase in prevalence of Type II Diabetes in
14 populations and some urban centers, this accounts for
15 almost half of all new cases of Type II Diabetes --
16 next slide -- and the course of Type II, I think, is
17 poorly described. There's just one study that I'm
18 aware of which has looked at the natural history of
19 Type II Diabetes in adolescents. These are data from
20 Pima Indians and what we've done here is to
21 superimpose the curves of the cumulative incidents in
22 nephropathy for individuals with onset at 15 to 24

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1 years of age, 25 to 34 years of age, and 35 to 44
2 years of age. And I think you can see that these
3 curves are super imposable.

4 It appears, in this same article, that the
5 frequency of retinopathy associated with Type II
6 Diabetes, with onset in adolescents is slower, the
7 progression to retinopathy is slower in adolescents
8 than it is in later onset disease. But these data,
9 are, of course, a concern because they suggest that in
10 early adulthood, individuals who are obese and have
11 been diagnosed as having Type II Diabetes in
12 adolescents are going to progress rapidly or are going
13 to require Dialysis and treatment for the other
14 complications of Type II Diabetes, such as retinopathy
15 and micro vascular complications.

16 Next slide. There has also been a lot of
17 recent controversy that I'm sure you are aware of with
18 respect to mortality, and I'm not going to address
19 that now, although we can talk about that, if you
20 like, in the discussion. But I wanted to point out to
21 you that this study, which was a very large Norwegian
22 study in which adolescents were screened for

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1 Tuberculosis and their weights and heights were
2 obtained at the time of that screening and then
3 followed up. This study, like other studies of its
4 type, show about a twofold increase in mortality
5 associated with a BMI above the 95th percentile and
6 that relative risk is about the same for both genders.

7 But the implications, in terms of U.S. epidemic, are
8 on the following slide. In this study, in Norway,
9 only about one percent of the population in 1963 to
10 1975 had a BMI greater than or equal to 30. In the
11 United States, that -- the prevalence of a BMI greater
12 than or equal to 30 is about 14 percent, suggesting
13 that although the mortality rates may -- are double,
14 the total risk group, the group at risk for this early
15 mortality is substantially greater than it was in
16 Norway from 1963 to 1975. And the recent JAMA,
17 articles which were the controversial articles, did
18 not dispute the fact that there was an increased
19 mortality above -- of BMI at the 95th percentile --
20 sorry, a BMI of 30 in the adult population.

21 Next slide. I'm just going to deal
22 briefly with costs because the cost in the pediatric

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1 population really paled beside the costs in the adult
2 population. But there's a very substantial emerging
3 literature that is focusing on the costs of obesity in
4 the adult population. Most of this literature is
5 focused on the cost of illness, which are
6 substantially greater for the obese individuals than
7 non-obese individuals, and I'll show you some clear
8 data in a minute about that.

9 But these other costs are probably at
10 least equal to the cost of illness and those include
11 the costs of absence from work, the costs of reduced
12 productivity, the costs of injuries and the costs of
13 disabilities. Next slide. These costs seem to
14 increase in proportion to the severity of obesity.
15 This slide shows some data that Roland Sturm has
16 subsequently published, showing the distribution of
17 costs among people at different BMI levels. And you
18 can see that these costs are relatively equally
19 distributed across these three BMI groups, but the
20 proportion of people in each of these groups declines.

21 That is, there are fewer people in -- at a BMI of 40
22 than there are in a BMI of 35 to 40, than there are in

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1 a BMI of 30 to 35, suggesting that the per capita
2 costs are going to be greatest among the very severely
3 obese individuals, and those groups are likely to be
4 disproportionately represented among children who had
5 onset of their weight at less than eight years of age.

6 Next slide.

7 This is another perspective. These are
8 data from General Motors that have looked at the cost
9 of weight plus additional risk factors in adulthood
10 and stratified this by BMI category and by the
11 frequency of complications. And I think you can see
12 that the highest costs here are among those with a BMI
13 greater than or equal to 35 and multiple
14 complications.

15 In some respects, this type of analysis
16 can be used to examine the potential cost
17 effectiveness of interventions, that the cost of the
18 intervention can be balanced against the cost savings
19 achieved by either reducing someone's weight or
20 reducing the frequency of complications.

21 Now, on the issue of costs, it is not
22 clear to what extent the pediatric onset overweight is

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1 contributing to these costs. That has not been
2 established, but clearly, the contribution of
3 pediatric obesity to severe adult obesity and multiple
4 complications of severe obesity would suggest that
5 there is, likewise, a disproportionate increase in
6 those costs. Next slide and then the next slide.

7 I know that you're going to spend time on a
8 lot of these other therapeutic approaches, most
9 importantly the surgical approaches or device
10 approaches. But I do think, and I think it's
11 appropriate that as you begin to think about this,
12 that you begin to think in a stratified fashion.
13 Certainly, I think we need more evidence with respect
14 to the cost effectiveness of interventions in the
15 pediatric age group because early behavioral
16 interventions -- and I noticed, by the way, in your
17 background work, that behavior modification is somehow
18 separated from diet and physical activity when, in
19 fact, behavior modification is the strategy to
20 implement diet and physical activity. But these are
21 certainly conservative approaches that should be
22 applied to all patients before moving on to the more

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1 invasive therapies like aggressive dietary therapy and
2 pharmacological and surgical therapy.

3 But in the interest of time, I think I'll
4 stop there and take your questions. I hope this
5 information has been helpful.

6 CHAIRMAN NELSON: That's great. Thank
7 you, Dr. Dietz. A brief comment before we go to some
8 questions, given the addition of a new slide and my
9 assumption that we may be referring back to the some
10 of the same data in our discussions later today and
11 tomorrow, I've asked that we get a copy made of the
12 new slides and -- two per page instead of three per
13 page so we can actually look at the data more closely.

14 DR. DIETZ: That's fine. I assumed that
15 this was a young group with good eyes.

16 (LAUGHTER.)

17 CHAIRMAN NELSON: Whatever. So we do have
18 time for a few questions of clarification about the
19 data. I don't know how long you can be with us during
20 the course of the day.

21 DR. DIETZ: I have to leave in about ten
22 minutes.

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1 CHAIRMAN NELSON: Okay, so we have a few
2 minutes for clarifying questions. Dr. Gorman?

3 MEMBER GORMAN: Thank you, Dr. Dietz.

4 One of the statements you made was that
5 when we look retrospectively at adults, that only 25
6 percent, or a quarter roughly, of overweight adults
7 were overweight children. When you turn the telescope
8 around the other way, do we have any data of how many
9 obese children become obese adults and stay obese as
10 they track forward?

11 DR. DIETZ: Those data are harder to come
12 by because of the lack of longitudinal studies and the
13 estimates vary. In adolescents, it looks like 70 to
14 80 percent of those obese adolescents stay obese as
15 adults.

16 And although there haven't been contra
17 studies, my view is that the later obesity studies in
18 childhood and adolescents, the more likely it is to
19 track in adults. And severity at any age seems to
20 increase the likelihood to track to adulthood. But
21 those are poorly supported statements.

22 DR. LUSTIG: Dr. Dietz?

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1 CHAIRMAN NELSON: Dr. Lustig?

2 DR. LUSTIG: Sir, Rob Lustig.

3 Two questions, actually. The first
4 question, you made a very convincing case for a BMI at
5 the 99th percentile as being morbid obesity for
6 children. I was wondering how that stacked up against
7 the BMIZ score and where that was the --

8 DR. DIETZ: That's three standard
9 deviation.

10 DR. LUSTIG: And does that make any more
11 sense than --

12 DR. DIETZ: Well, we debated that. You
13 know, I think pediatricians have enough trouble
14 measuring BMIs and putting them in percentile fashion.
15 And to ask them to go to these sources beyond the --

16 DR. LUSTIG: We don't want to sacrifice
17 them either.

18 DR. DIETZ: Well, the 99th percentile
19 could easily be added to the growth charts. And when
20 we publish this, we're going to publish those cut
21 points. So, you know --

22 DR. LUSTIG: The second question was,

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1 since Whitaker's data demonstrated that, in fact,
2 there is a fair amount of tracking, even at age four
3 months, going up to overweight at seven years -- and
4 you have shown us convincingly that overweight at
5 eight years is a risk factor -- should we be targeting
6 kids even lower in terms of what's on the -- because
7 the target population is actually the one that's
8 showing the increased incidence of obesity.

9 DR. DIETZ: It's an important question.
10 And I would refer you to the paper we published in
11 Pediatrics which looked at the frequency with which
12 young children shifted percentiles, both upward and
13 downward. And there's still a fair amount of shifting
14 going on at age four.

15 If you look categorically, you can see a
16 relationship, but I'm not sure that that is going to
17 help us very much with an individual patient. The
18 other thing I think we have is that how much shifting
19 for whom constitutes a risk. I don't think we know
20 the answer to that question, although I think this
21 early childhood, the data on early childhood, do
22 suggest the risk in that group increased.

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1 CHAIRMAN NELSON: Okay. I've got four
2 people on the list. First is Dr. Kral.

3 DR. KRAL: Dr. Yustein in his introduction
4 mentioned that the Office of Devices here usually only
5 deals with manifest disease and is not interested in
6 preventive disease. Do you have an opinion on that in
7 this context of what we're dealing with today?

8 DR. YUSTEIN: I didn't say we weren't
9 interested. For the purpose of the meeting today, we
10 would like to focus on how devices tend to be devices
11 that treat the disease and don't prevent diseases. So
12 we're kind of being selfish in asking for your
13 assistance on our devices.

14 I didn't want to give the impression that
15 we weren't interested in the prevention of the
16 disease, but for our devices, I don't think there are
17 any devices coming down the pike that are meant to
18 prevent obesity.

19 DR. KRAL: But we're discussing pediatric
20 obesity.

21 DR. DIETZ: Well, I'm hesitant to make a
22 comment on FDA policy.

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1 (Laughter.)

2 DR. DIETZ: But I think that the criteria
3 developed by the expert committee for the
4 recommendations of pediatric surgery is still with a
5 therapeutic intent. And you will recall that that is
6 BMI supporting with a major comorbidity, like pseudo
7 tumor or like type II diabetes or like sleep apnea,
8 and BMI greater than or equal to 50, with additional
9 or with more modest complications.

10 Now, I agree with you that we can get into
11 a discussion of whether surgery in that group is
12 preventing more severe developed disease or treating
13 an existing disease in the pediatric population.

14 My own view is that obesity by itself is a
15 disease. I am hesitant to say, well, we should just
16 open the doors across the border for this, but I think
17 that it's clear given the complications that we have
18 that it is.

19 CHAIRMAN NELSON: Dr. Botkin?

20 DR. BOTKIN: Two quick questions. You had
21 mentioned the psychosocial consequences of obesity.
22 I'm wondering to what extent children who are obese

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1 have comorbid psychiatric or psychological conditions
2 or dysfunctional families. Is there any data on those
3 sorts of issues?

4 Then, secondly, what do we know about
5 socioeconomic status of children with obesity?

6 DR. DIETZ: Well, with respect to the
7 first, it appears that depression predisposes to
8 obesity, not the reverse, although, again, that's not
9 been a well-studied problem.

10 The data that I cited with respect to
11 dysfunctional families and disparity of obesity come
12 out of my own clinical experience. That has not been
13 well-described, although there is a pretty robust
14 literature on the adult side of the psychosocial
15 complications of severe obesity in adulthood in both
16 the cause and consequential fashion.

17 The socioeconomic effects have changed.
18 We kind of have analyzed the more recent data. But
19 yours show there was a direct relationship between
20 obesity and socioeconomic class in children.

21 The data in adults have recently become
22 very muddled. And the only group in the 1999 to 2003

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1 are Mhanes, from which there is an inverse
2 relationship of obesity and socioeconomic class is in
3 Caucasian women. Although there used to be a
4 relationship in African American and Mexican American
5 women, that no longer holds. There doesn't seem to be
6 any relationship between SES and obesity in men.

7 CHAIRMAN NELSON: Let me go to Dr. Daum,
8 then Diaz, and then Klish. And then we'll go to the
9 next presentation. So Dr. Daum?

10 MEMBER DAUM: Thanks.

11 You showed a slide with a list of the
12 costs of obesity that I presume mostly was generated
13 from thinking about this in grown-ups. I guess are
14 there any comparable data or ideas about the cost of
15 obesity in children, school performance, for example,
16 socialization that supports?

17 DR. DIETZ: No, unfortunately not. Those
18 are important questions. The only data on costs are
19 from a paper that we published from the National
20 Hospital Discharge Survey, which showed a threefold
21 increase in costs of obesity and obesity-associated
22 diseases in pediatric population over about a 20-year

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1 period.

2 But those are still pretty modest, I think
3 about -- I can't remember. I think the last year we
4 looked at was 1999 or 2000. I think it's about \$175
5 million, as opposed to the billions of these costs in
6 the adult population.

7 So I think it's fair to think about costs
8 in terms of the projected impact of obesity on medical
9 costs, rather than the direct cost of obesity per se.

10 MEMBER DAUM: And, again, I guess my
11 question goes beyond dollar costs.

12 DR. DIETZ: Yes. No, there have been no
13 -- there are some quality of life analyses, but it's
14 hard to put a cost figure on those other costly
15 activities. I think it's a very important question,
16 but those are not analyses.

17 CHAIRMAN NELSON: Dr. Diaz?

18 MEMBER DIAZ: In addition to looking at
19 Mexican Americans, did you look at other groups of
20 Hispanics, like Cubans, Puerto Ricans, South
21 Americans? And if so, do you see any differences?

22 DR. DIETZ: Unfortunately, the MHANES only

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1 classifies as Mexican Americans. And the other
2 Hispanics have not been analyzed separately.

3 CHAIRMAN NELSON: Dr. Klish?

4 DR. KLISH: Did I hear you say that you
5 now think that the word "obesity" should be used to
6 describe children? I think nomenclature is going to
7 become an issue as we discuss these devices in
8 children. And, you know, as you know, that's been
9 kind of a difficult problem nationally trying to use
10 the nomenclature of adults and apply it to children or
11 vice versa.

12 I might also point out that Dr. Yustein's
13 graph or little table is wrong, too, because the
14 children need to be ratcheted down one space in that
15 table.

16 DR. DIETZ: What I said was that I think
17 what is going to change the medical use of the
18 nomenclature is the need to align the diagnostic
19 criteria with billable diagnoses. I think in terms of
20 conversations with patients the term "overweight"
21 still --

22 DR. KLISH: That's an individual

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1 doctor-patient relationship. I mean, the scientific
2 world is where the confusion lies. And it would be
3 nice to take a stand on nomenclature at some point.

4 DR. DIETZ: The IOM did so. The IOM
5 report on prevention of childhood obesity said we're
6 going to call this "obesity" and referred to kids
7 above the 95th percentile.

8 I am less compelled to rush into this
9 because I am not sure what the public understands by
10 the term "obesity." We can agree. I am sure we can
11 agree in this room. But that agreement to me is what
12 is critical to what patients' and the public's
13 understanding is of this problem.

14 CHAIRMAN NELSON: Actually, we do not have
15 a lot of time because you may not know this, but the
16 public session needs to stay at 1:30. If you guys can
17 eat lunch in less than an hour, we've only got an hour
18 for 107 slides in the next presentation, which we
19 won't have any ability to have a conversation about
20 the next presentation the more we take here. So if
21 it's burning or not?

22 DR. INGE: One quick question follow-up on

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1 Dr. Kral's is -- and I understand the reason for not
2 wanting to focus in this session on prevention of
3 obesity, the disease obesity, but I think it is
4 critical to get an opinion, your opinion, that is, on
5 the notion of preventing comorbidities of a child that
6 meets whatever definition of obesity with a device.
7 Is there any role for considering prevention of
8 comorbidity?

9 DR. DIETZ: Yes. You know, we're only
10 beginning to understand the role of physical activity
11 in reduction of comorbidities in the pediatric
12 population, let alone devices. I really believe that,
13 like the adult population, what we're going to see is
14 that physical activity reduces many of the biochemical
15 comorbidities and possibly disease comorbidities as it
16 does.

17 So I would be personally very reluctant to
18 think about the use of devices as reducing
19 comorbidities without a more robust literature on
20 whether there are other lessened basis rates to
21 accomplish that.

22 CHAIRMAN NELSON: Thank you.

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1 I would like to move to the next
2 presentation. I already tipped my hand on tempo.
3 We're scheduled for lunch at 12:30. It's now 11:30.
4 There are 107 slides in the next one as I counted
5 them, which violates my rule of one minute per slide,
6 but maybe you'll be very quick.

7 So I'm assuming if you get through, we'll
8 have time for questions before lunch. If not, we may
9 have to defer those until this afternoon since the
10 public session scheduled at 1:30 means we really do
11 need to break at 12:30 because I can't imagine all of
12 you would eat lunch in less than an hour. In fact,
13 you're not supposed to given the topic of the meeting.

14 DR. HASSINK: Well, thank you, Dr. Nelson.

15 "OBESITY: A NATIONAL HEALTH ISSUE" --

16 SCIENTIFIC OVERVIEW

17 DR. HASSINK: It is always a challenge to
18 talk about the pathology of obesity and limit it to
19 what should I leave out. So we will try to move
20 quickly, but my attempt here to give you an overview
21 of some of the pathophysiology and pathology of
22 obesity and drill this down into what the individuals

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1 present with, the children that come to clinic come
2 with.

3 We have been running our weight management
4 clinic at A. I. DuPont for the past 17 years. We
5 watched the obesity epidemic explode and the morbidity
6 increase. And we see patients, just so you know, from
7 infancy to age 21 in a multidisciplinary
8 hospital-based setting.

9 Just to make a point that the adipose
10 tissue has its own growth trajectory, this is a graph
11 of a patient at the 50th percentile for weight. And
12 you see that adipose tissue and body composition
13 change during childhood.

14 This is just to remind you that this is a
15 very dynamic process in childhood with a lean body
16 mass index in mid-adolescence for boys, ramping-up of
17 adipose tissue in girls. And this is in normal
18 children. Clearly obesity alters this trajectory very
19 much.

20 You can also see by having a tight growth
21 trajectory that this tissue system is under a lot of
22 metabolic and control, which we'll talk about in a

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1 minute.

2 Obesity is excess adiposity. You see the
3 research methodologies that have been used to measure
4 adiposity, densitometry, underwater weighing very
5 difficult in children, DEXA CT/MRI.

6 Clinical measurements revolve around
7 anthropometry. People have used bioelectrical
8 impedance. Right now, as you heard Dr. Dietz talk,
9 BMI is the clinical methodology for measuring obesity.

10 This is just one of the CDC obesity growth
11 charts. If you're measuring under age two, you need
12 to use weight per length charts, which are also
13 available from the CDC.

14 The adipose tissue we're talking about
15 here is white adipose tissue. There is brown adipose
16 tissue present in the newborn and in situations of
17 cold, stress, and starvation. But white adipose
18 tissue, just to make the point, is a multicellular
19 tissue composed of adipocytes.

20 There are stem cells in this tissue
21 capable of differentiating into muscle, cartilage,
22 adipose tissue, and bone. There are also endothelial

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1 and vascular elements in the tissue.

2 Interestingly enough, there are also
3 macrophages that infiltrate the adipose tissue and are
4 correlated with the degree of adiposity. And this may
5 be one of the pathophysiologic links between obesity
6 and inflammation when you're talking about
7 cardiovascular disease and diabetes.

8 This is just a high-powered micrograph of
9 what that tissue looks like. You see that the cell is
10 taken up with fat storage. The nuclei are in the
11 periphery. There are vascular and stroma elements as
12 well. And this is just a higher-power view.

13 Adipose tissue is a very metabolically
14 active tissue and organ system. In contrast to the
15 older view of the cells were there basically just to
16 store fat for fuel, we now know, thanks to the
17 discovery of leptin in 1994 by Friedman's group,
18 kicked off the age of viewing adipose tissue as a
19 cytokine-producing, hormonal regulating tissue
20 important in growth and glucose homeostasis. It is
21 also involved with energy regulation at the level of
22 the CNS and the periphery.

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1 This is a sampling of the cytokine
2 production from the adipose tissue. You are all
3 familiar with many of these. Leptin has probably
4 received the most notoriety, adiponectin, inflammatory
5 cytokines as well.

6 Leptin is produced by the ob gene. It's
7 produced in white adipose tissue. It was thought
8 originally just to be made in fat, but it has been
9 discovered to be made in stomach, the placenta, and
10 mammary gland. That raises some interesting questions
11 about fetal growth and programming, ovarian follicles,
12 and multiple fetal organs.

13 Leptin receptors are found in most tissues
14 of the body, but the hypothalamic nuclei that are
15 involved in energy regulation are a major target of
16 leptin.

17 You can see here a cartoon showing the
18 adipocyte with impact on the hypothalamus via
19 neuropeptide Y. This would downregulate hunger in
20 animals, increases activity and increases
21 thermogenesis. And when this was discovered in the
22 ob-ob mouse and they were given leptin, they lost

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1 their obesity. However, most humans are
2 leptin-resistant. And so leptin administration is not
3 very effective in the human setting for reducing
4 obesity.

5 This is another drawing just to illustrate
6 a very important point about the complexity of
7 obesity. These are the four hypothalamic nuclei. You
8 can see that the ARC 08 nucleus gets input from
9 peripheral energy stores and also is involved in
10 autonomic regulation of leptin secretion from fat.

11 The paraventricular nuclei also get input
12 about energy stores and help regulate feeding
13 behavior. The dorsal medial nuclei get input from the
14 lateral hypothalamus about hunger. And the ventral
15 medial nuclei are involved in sympathetic regulation
16 and vagal regulation of insulin secretion.

17 All these nuclei communicate with each
18 other, with the cerebral cortex, which communicates
19 with the outside world and with the periphery. This
20 is a highly complex system due to the fact that when
21 you talk about obesity, you are talking about energy
22 regulation, which is linked to our survival.

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1 Other cytokines of note that the adipose
2 tissue produces: TNF alpha alters insulin signaling
3 and increases insulin resistance. IL6 is involved
4 with acute phase reactants, such as CRP. Adiponectin
5 in adults has been linked to a risk of cardiovascular
6 disease. It actually goes down as obesity increases
7 and modulates endothelial adhesion and inhibits
8 inflammatory responses.

9 Worthwhile just thinking about for a
10 moment is the connection between obesity and
11 inflammation. As I said, macrophages migrate into the
12 adipose tissue. And this is because the
13 adipocyte-secreted TNF alpha stimulates the
14 preadipocytes in endothelial cells to produce monocyte
15 chemotactic protein.

16 Also, increased leptin and decreased
17 adiponectin stimulate transport of macrophages in
18 adipose tissue. So you have the scenario here of a
19 huge inflammatory mass with the onset of obesity.

20 The interaction between the environment
21 and the gene is complex in obesity. We know that
22 there is a higher risk of a child being obese with

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1 parental obesity. There is probably a genetic
2 modification of the risks for comorbidity.

3 There are also environmental interactions,
4 which point to possibly critical times in growth, such
5 as the intrauterine environment, that predispose
6 children to obesity and diabetes. And maternal
7 diabetes is one of these. There may also be periods
8 of critical growth that impact later obesity. Early
9 infancy or puberty may be some of those.

10 The field of nutritional genomics attempts
11 to study the impact of what we eat on our genetic
12 regulation. So this is a highly complex system.

13 Obviously you heard from Dr. Dietz, and we
14 will be talking a lot about this. It is a
15 multi-system disease with effects on all major organ
16 systems. It can result in earlier onset of adult
17 disease, as we're seeing in the type II diabetes in
18 our adolescents; end stage disease in the children
19 that progress to fibrosis and cirrhosis from their
20 nonalcoholic hepatitis; and provides some new insights
21 into old diseases, such as the link between insulin
22 resistance and the sleep apnea syndrome.

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1 I think most important to this discussion
2 is to recognize that obesity is a very individual
3 process. Obese children and adolescents have their
4 unique weight gain trajectories, genetic
5 predispositions, and comorbidities. They also have
6 unique family situations, psychological needs, and
7 community settings. So although we talk about
8 population data, this really boils down to patient by
9 patient.

10 You can see these are three weight
11 trajectories of three charts I had in my office last
12 week. I didn't put them on the BMI charts because the
13 BMI charts don't go up as high as we needed, but this
14 little girl had a morbidly obese parent who died in
15 his 50s of diabetes. She had early dysregulation of
16 feeding and eating. She had sneaking behavior and
17 lack of appreciation of satiety, has developed upper
18 airway obstruction, requiring BiPAP, and ankle
19 pathology and bone marrow edema and destruction of her
20 ankles.

21 Patient C is a little girl with two
22 parents with type II diabetes and at age 12 developed

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1 type II diabetes and nonalcoholic statahepatitis.

2 Patient B here was a little girl crossing
3 percentiles early in childhood, developed some peer
4 difficulties in school, had mild hypercholesterolemia,
5 so very different trajectories, all in the obese
6 population.

7 I want to spend some time now on the
8 pathology of obesity. This is the ground-level view
9 of what pediatricians are seeing or are going to see.

10 The first is to talk about some obesity-related
11 emergencies, a slide I didn't have in the talk several
12 years ago, but we're seeing it now. Just to point
13 out, we have seen every single one of these
14 complications in our patient population.

15 The first I'll talk about is a paper that
16 was written by Morales in 2004 entitled "Death Caused
17 by Hyperglycemic Hyperosmolar State at the Onset of
18 Type II Diabetes." He described seven obese African
19 American youth who are considered to have died from
20 DKA, despite meeting the criteria for hyperosmolar
21 state.

22 Morales said -- and this is Morales'

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1 statement from the paper -- "All had previously
2 unrecognized type II diabetes. And death may have
3 been prevented with earlier diagnosis of treatment."

4 This is kind of the nightmare for the
5 pediatricians. Patients presented to medical care
6 with symptoms which were not at that time linked to
7 presentation of type II prior to their death of
8 vomiting, abdominal pain, dizziness, weakness,
9 polyuria, polydipsia, weight loss, and diarrhea.

10 They were found comatose at home or died
11 in the emergency room. The diagnostic criteria for
12 this state is a markedly elevated plasma glucose of
13 over 600, serum CO2 over 15, small ketonuria
14 ketonemia, high osmolality, and stupor or coma. And
15 this is rare, but it certainly has appeared on the
16 radar screen of emergencies related to the obese
17 adolescent.

18 DKA is not uncommon in type II. In some
19 studies, up to 25 percent of children have diabetic
20 ketoacidosis. If basal insulin sensitivity is low,
21 there is an increase in susceptibility to relative
22 insulin deficiency. And this may be more common in

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1 the African American and Hispanic patients in type II
2 who present with a higher baseline insulin resistance.

3 This is just to illustrate the point that
4 obesity is linked with insulin resistance.
5 Hyperglycemia can cause some beta cell toxicity,
6 decreasing insulin secretion, and creating a state of
7 relative insulin deficiency, lipolysis, and DKA.

8 Pulmonary embolism has been seen in
9 children. The symptoms are as they are in adults:
10 dyspnea, chest pain, hypoxia, hemoptysis. It has been
11 seen with surgery and trauma. We have seen it in our
12 population are pinning a femoral fracture. We have
13 seen it present in the ER with a child with a family
14 history of a coag disorder. The risk factors are
15 obesity here, maybe some enhanced risk from the
16 obesity hyperventilation syndrome and children who
17 have coagulation problems.

18 We have also seen, surprisingly,
19 cardiomyopathy of obesity. We had a 17-year-old boy
20 come into clinic morbidly obese. He weighed 600
21 pounds, walk-in, dyspneic, on evaluation had
22 biventricular cardiac failure and cardiomyopathy.

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1 This results from high metabolic activity of excess
2 fat, which increases the total blood volume in cardiac
3 output, resulting in left ventricular dysfunction,
4 dilatation, and can be enhanced by right ventricular
5 dysfunction due to pulmonary hypertension secondary to
6 upper airway obstruction. This is his X-ray just
7 showing an enlarged heart and heart failure.

8 These complications, although rare, are
9 severe and life-threatening and I think have to be
10 placed in the armamentarium of the pediatrician about
11 what to look for.

12 There is another level of comorbidities
13 which require immediate attention. I say to the
14 pediatricians these are the ones you don't want to
15 leave your office without making these diagnoses. And
16 I will start in with pseudo tumor cerebri.

17 This is a state of raised intracranial
18 pressure with papilledema and normal cerebrospinal
19 fluid in the absence of ventricular enlargement. This
20 would be what you would see on fundoscopic exam. You
21 can't see the dismargin. It's swollen. And the
22 vessels are sort of bulging out over that.

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1 The diagnosis, these kids can present with
2 headaches, vomiting, blurred vision, or diplopia.
3 Sometimes neck, shoulder, and back pain have also been
4 reported. Papilloedema is part of the pathology, but
5 the headaches may occur prior to you being able to
6 visualize that.

7 The morbidity here is the loss of the
8 peripheral visual fields and reduction of visual
9 acuity. You might see this at diagnosis, and we
10 certainly have. We have seen it, incidentally, at
11 diagnosis with children coming in for other
12 complaints, obese children. They have papilloedema.
13 And then when you look at them, they have visual field
14 cuts, but they haven't reported them. If this is
15 untreated, it leads to visual impairment or blindness.

16 It is hard to get incidence and prevalence
17 data on some of these conditions, but obesity occurs
18 in about 30 to 80 percent of affected children with
19 this. And in a series of case-controlled studies in
20 adolescents and adults, obesity and recent weight gain
21 were the only factors found more often in the pseudo
22 tumor patients. We still don't know why exactly this

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1 happens, and we don't know how to predict in whom it
2 will happen.

3 There are drugs associated with pseudo
4 tumor, just for a quick review, growth hormone
5 therapy, nalidixic acid, ciprofloxacin, tetracycline,
6 with no dose-response relationship, vitamin A. One
7 wonders certainly. If they have had pseudo tumor, you
8 wouldn't want to give them these drugs. And you don't
9 know what to say prophylactically since we don't know
10 how to predict who is going to get it.

11 The treatment is with acetazolamide. In a
12 severe case, a lumboperitoneal shunt may have to be
13 placed to reduce the pressure while you are attempting
14 weight loss. Clearly, fundoscopic exam should be part
15 of the child care. Visual field cuts need to be
16 looked for. And pseudo tumor is a diagnosis
17 exclusion. You have to rule out other causes of
18 increased intracranial pressure.

19 This next one is a particularly pediatric
20 complication because the growth plates are open in
21 pediatrics: slip capital femoral epiphysis. You have
22 to suspect this and immediately evaluate an obese

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1 child coming in with a limp. Most of them with SCFE
2 are obese. And you can also see this present with
3 complaints of groin, thigh, or knee pain because of
4 the sensory cutaneous innervation around the hip
5 capsule.

6 It really is medial and posterior
7 displacement of the femoral epiphysis through the
8 growth plate relative to the femoral neck. And you
9 diagnose it on clinical exam with reduced abduction
10 and internal rotation. And you diagnose it on X-ray.

11 You'll see in a minute the X-rays of one of our
12 patients. It can be bilateral in 20 percent.

13 You see here this is a normal hip with the
14 femoral head seated on the femoral neck. This is the
15 slip. This is painful, requires immediate pinning.

16 The preferential site of the slip is
17 within the epiphysis. It's the zone of hypertrophic
18 cartilage cells. It's under the influence of gonadal
19 and growth hormone.

20 And some associated causes, again, you
21 usually can't predict who is going to get this. We
22 don't know exactly why this happens, but these are

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1 some associated causes, continued weight gain, renal
2 failure, history of radiation therapy, hypothyroidism,
3 and then the hormonal effects.

4 So hips and knees need to be checked in
5 every obese child. You can't ignore a complaint of a
6 limp and you can't write off a gait as just due to
7 excess weight. You really need to look for the
8 pathology here.

9 In Japan, the annual incidence is
10 estimated to be 2.22 per 100,000 boys and .76 per
11 100,000 girls 10 to 14. The point here is it's five
12 times higher than the previous estimate. It was hard
13 to find estimates in this country, but this is
14 probably being driven by the obesity epidemic.

15 Blount's disease is another pediatric
16 orthopedic morbidity. It's bowing of the tibia and
17 femur, unilaterally or bilaterally. It results from
18 the overgrowth of the medial aspect of the metathesis.

19 Two-thirds of the patients with Blount's
20 may be obese. And this also requires surgery. We
21 have seen this severe enough to compromise ambulation
22 and cause peripheral neuropathy when you don't treat

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1 it.

2 Obstructive sleep apnea is not a usual
3 complication in obese children. And this is defined
4 as prolonged partial upper airway obstruction or
5 immediate intermittent complete obstruction that
6 disrupts normal ventilation during sleep and normal
7 sleep patterns.

8 The histories you usually get include what
9 you would expect: nighttime awakening, difficulty
10 awakening, restless sleep, daytime somnolence,
11 napping, enuresis, poor concentration, and poor school
12 performance.

13 The etiology is thought to be some
14 combination of increased fat mass, increased muscle
15 relaxation during sleep, exacerbated in kids with
16 enlarged tonsils and adenoids. And there is a link in
17 adults and one study in kids that shows people with
18 elevated insulin seem to have more problem with this.

19 The gold standard of diagnosis is
20 nighttime polysomnography and because the severity of
21 obstruction may not correlate with either the degree
22 of obesity or severity of sleep symptoms.

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1 Abnormal sleep patterns are surprisingly
2 common in the obese children. And obstructive sleep
3 apnea has been noted in obese infants as young as five
4 months of age.

5 The real functional morbidity here is the
6 significant decreases in learning and memory,
7 attention. This can look a lot like ADD in an obese
8 child. The long-term sequelae are pulmonary
9 hypertension, systemic hypertension, and right heart
10 failure. So in school children who are not doing
11 well, this should be one of the things you should look
12 for if they're obese.

13 Weight loss can reduce apneic episodes,
14 hypoxemia, and daytime sleepiness.
15 Tonsilladenoidectomy can buy you some time if you need
16 it. The treatment modality here is a CPAP or BiPAP.
17 It's extremely effective but very hard to get
18 adolescents to use. It's kind of an invasive thing at
19 night. They don't like it very much.

20 So families need to be asked specifically
21 about these symptoms because it may be normative in
22 the family. It should be considered in kids with poor

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1 school performance and concentration difficulties.
2 And it can occur during intercurrent illnesses with
3 tonsil enlargement and with further weight gain.

4 Dr. Dietz highlighted the liver disease
5 due to obesity. This has become a real issue.
6 There's a nonalcoholic fatty liver disease that
7 describes a continuum of conditions that range from
8 simple steatosis through nonalcoholic steatohepatitis
9 to cirrhosis and end-stage liver disease. And you
10 diagnose this when you get increased liver enzymes on
11 blood draw and a fatty liver on ultrasound, but the
12 gold standard of diagnosis remains liver biopsy
13 because you need to see the inflammatory cells and the
14 fibrosis.

15 Twenty to 25 percent of obese children in
16 some series have had evidence of steatohepatitis.
17 Nobody, again, knows why certain children get this,
18 but it's felt to be obesity, fatty infiltration of the
19 liver with a second hit possibly with a genetic
20 predisposition and a second environmental hit causing
21 inflammation fibrosis, which may progress to
22 cirrhosis.

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1 The natural history of this disease is not
2 well-known in children. Here you have a liver biopsy
3 from a ten-year-old. You can see the fat infiltrating
4 the hepatocytes. You can see portal bridging fibrosis
5 already at age ten.

6 In Japan, the prevalence was 2.6 percent
7 has been reported in the population and which rose in
8 their obese children to over 50 percent. So fatty
9 liver is quite common. Obesity and type II diabetes
10 are the strongest predictors of the progression of
11 fibrosis. And the progression of fibrosis is really
12 the pathological event.

13 Age may also be a risk for cirrhosis
14 because it may reflect the increased time you have for
15 that second hit thought to initiate the fibrosis. And
16 a liver with fat in it may be at increased risk of
17 damage from viruses or endotoxins or alcohol or
18 industrial components.

19 Predictors of elevated liver enzymes in
20 some studies have been shown to be male gender,
21 Hispanic ethnicity, and elevated BMI, but these are
22 just in one study. Predictors of fibrosis, BMIZ

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1 score, insulin resistance may be leptin, but still the
2 natural history is not well-known.

3 You can reverse the elevations of the
4 aminotransferases and fatty liver with ten percent
5 weight loss. Because it's hard to get approval for a
6 second biopsy, it's hard to know what is happening to
7 fibrosis that exists.

8 Metformin has been used to treat these
9 children. It can normalize liver enzymes in about
10 half with biopsy-proven NASH and reduced
11 hepatosteatosis by about a third as it improves
12 insulin sensitivity.

13 The caveat here is when liver biopsies
14 were performed in adults after weight loss, all had
15 reduced steatosis, but you can't always reduce the
16 fibrosis if it's preexisting. And in this study,
17 rapid weight loss in some studies has been linked to
18 increase fibrosis. So you have to use caution when
19 dropping the weight rapidly.

20 So nonalcoholic fatty liver disease in
21 childhood now is diagnosed as an exclusion. You want
22 to make sure you're not dealing with any of the

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1 hereditary hepatitis syndromes.

2 Gallstones are just like in adults.
3 They're diagnosed with abdominal pain and tenderness.
4 The obesity accounts for a higher percentage of
5 gallstones in children. Fifty percent of
6 cholecystitis in some series in adolescents were
7 associated with obesity. And it requires surgical
8 intervention.

9 When we move to the chronic
10 obesity-related comorbid conditions, we are really
11 talking about conditions, by and large, linked by
12 insulin resistance, such as type II diabetes,
13 polycystic ovarian syndrome, hypertension, and
14 hyperlipidemia. I also put the psychological
15 conditions. And we're going to talk about those at
16 the end because they're extremely important in the
17 childhood population. Here you see just an
18 illustration of that.

19 Important to think about is
20 insulin-mediated glucose disposal by muscle varies
21 almost tenfold in healthy individuals. So we're
22 coming to the table with different predispositions for

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1 insulin resistance. The more insulin-sensitive the
2 muscle, the less insulin needs to be secreted to
3 maintain normal glucose homeostasis because that is as
4 important. The more insulin-resistant an individual
5 and the greater degree of compensatory
6 hyperinsulinemia, the more likely they are to develop
7 these associated diseases.

8 Energy regulation and control of insulin
9 also occur at the level of the CNS. The CNS
10 integrates afferent signals regarding energy intake.
11 And normally the CNS exerts an inhibitory effect on
12 insulin secretion. And obesity can occur in settings
13 of neuroendocrine pathology, CNS pathology, trauma, or
14 cancer.

15 At the level of the adipocyte, adipose
16 tissue in obesity becomes refractory to insulin
17 suppression of fat mobilization. So there is an
18 increased release of free fatty acids. These fatty
19 acids are linked with the onset of peripheral and
20 muscle hepatic insulin resistance.

21 So postprandially there is an excess of
22 circulating lipid metabolites and leads to fat

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1 deposition in other tissues. And it's sort of
2 intuitive that fat in muscle, fat in liver doesn't
3 belong there and can be pathologic.

4 Hyperinsulinemia stimulates fatty acid
5 synthesis in the liver. Elevated insulin may increase
6 degradation of APOV 100, compromising triglyceride
7 transport out of the liver. And so there you have net
8 accumulation of fat in liver. In muscle, elevated
9 free fatty acid and accumulated triaceglycerol appear
10 to inhibit insulin signaling.

11 The resulting suppression of muscle
12 glucose transport leads to reduced muscle glycogen
13 synthesis. And we have done treadmill studies on our
14 kids with BMIs over 40. Despite normal hearts, by and
15 large, and lungs, their exercise performance is at the
16 level of cardiomyopathy patients. And we think that
17 the muscle impairment in energetics here plays a role.

18 Metabolic syndrome, just to review, the
19 American Diabetes Association came out with a
20 statement they're not sure if we should be using this
21 term or just talking about individual risk factors.
22 But the cluster that you look at here is abnormal

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1 blood lipids, low HDL, high triglycerides, high LDL,
2 and impaired glucose tolerance, along with obesity and
3 elevated blood pressure.

4 There is an increased incidence of
5 impaired glucose tolerance in an obesity clinic
6 population. And this was in a 2002 article, which
7 reported 25 percent of obese children age 4 to 10 had
8 impaired glucose tolerance. Twenty-one percent of
9 obese adolescents in this population had impaired
10 glucose tolerance.

11 This is a physical finding often
12 associated with insulin resistance, although it
13 doesn't have to be all the time, called acanthosis
14 nigricans. And it is a pigmentary excess in the skin.

15 It can appear in the neck axilla and other skin
16 folks. Obese patients have been reported to have
17 higher fasting insulin and lower insulin sensitivity
18 when they have acanthosis. This fades when weight
19 reduction occurs.

20 Diabetes clearly is one of the emerging,
21 rapidly emerging complications of obesity. And this
22 is just how you diagnose diabetes in any child, high

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1 random plasma glucose with symptoms of diabetes, an
2 elevated fasting plasma glucose, or a glucose over 200
3 on an oral glucose tolerance test.

4 In the setting of type II, elevated
5 fasting insulin and hyperglycemia, that's the
6 occurrence. And only 20 percent in a lot of series
7 present with the classic polyuria, polydipsia, and
8 weight loss. It's an emerging problem in the
9 pediatric endocrinology clinic, accounting for a lot
10 of the new diabetic diagnosis. This is just the same
11 kind of track here with insulin resistance, beta cell
12 dysfunction giving rise to diabetes.

13 The defects are excessive hepatic glucose
14 production and defective beta cell secretion and
15 function. And the duration and severity of
16 hyperglycemia dictate the microvascular complications.

17 In an article in 2003, it was noted that
18 the lifetime risk of diabetes for individuals born in
19 2000 is one in three for males and two in five for
20 females.

21 The risk factors for type II diabetes are
22 clearly obesity and having a first or second degree

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1 relative with type II diabetes. Ethnicity also plays
2 a role here, with African American patients, Hispanic,
3 Asian, and Native American descent predisposed to a
4 greater degree.

5 Also, it's not unusual to see diabetes
6 present in puberty when you naturally are more
7 insulin-resistant. Inactivity may contribute to some
8 of the increased insulin resistance, which is
9 predisposing to diabetes as well as visceral facta
10 position and children with polycystic ovarian
11 syndrome. And there is a slight female to male
12 preponderance.

13 As I said before, maternal diabetes or
14 impaired glucose tolerance during gestation may infer
15 an increased risk of obesity and diabetes in that
16 child.

17 Our Native American population is getting
18 hard hit with diabetes, with rates up to 50 per 100
19 thousand in Pima Indians. In a study from Cincinnati
20 in 1994, their estimated rate of type II was 7.2 per
21 100,000 incidence of diabetes. This was a tenfold
22 increase for them over the previous ten years. And in

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1 an article in 2004, it was noted that the worldwide
2 incidence of diabetes type II has tripled since 1985.

3 Associated findings are polycystic ovarian
4 syndrome, acanthosis nigricans, dyslipidemia, and
5 hypertension. Just a point about PCOS, which we used
6 to just think of as an adult disorder, these girls
7 present with dysmenorrhea, oligomenorrhea, regular
8 menses, hirsutism, and acne. You find
9 hyperandrogenemia. They may have cysts on their
10 ovaries. They will develop eventual problems with
11 fertility. And girls with premature adrenariky need
12 to be followed because they seem to be at increased
13 risk for this.

14 In a study of an adult female population
15 study in Atlanta, unselected, the prevalence of this
16 was 6.6 percent, making it one of the more common
17 endocrinopathies in females.

18 Hypertension is common in children with
19 obesity. Twenty to 30 percent of obese children in
20 clinic settings have elevated blood pressure. Obese
21 adolescents had a higher risk of obesity as adults.

22 Obesity is linked to the end organ

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1 morbidity of cardiac hypertrophy. We find LVH on
2 ultrasound not infrequently and long-term renal
3 disease, cardiovascular disease, and stroke. It does
4 respond to weight loss, dietary change, and
5 pharmacotherapy.

6 Hyperlipidemia, the pattern you see in
7 children is hypertriglycemia, elevated LDL, and low
8 HDL. Increased central fat position and
9 hyperinsulinemia are thought to be drivers of this.
10 Overweight adolescents have increased predisposition
11 to lipid abnormalities in adults.

12 I want to spend a little bit of time on
13 the psychological morbidity in obesity,
14 obesity-associated psychological conditions:
15 depression, anxiety, low self-esteem, teasing,
16 bullying, binge eating disorder.

17 There are also additional psychological
18 conditions that may impact treatment. Clearly if you
19 have a patient with undiagnosed ADD or ADHD or bipolar
20 illness, adjustment disorder, or oppositional defiance
21 disorder, treatment and compliance are going to be
22 more difficult. So these are crucial issues to take

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1 into consideration when you evaluate your patients.

2 The study Dr. Dietz alluded to was in
3 depression in obese adolescents from grades 7 to 12.
4 A depressed mood predicted follow-up obesity, but
5 baseline obesity did not predict follow-up depression.

6 This was a study from Appalachia. It
7 talked about obesity trajectories. And I think a lot
8 more thought needs to be given to the trajectory of
9 obesity during childhood.

10 They had four groups. One was a normal
11 weight group. One was a group that was obese in
12 childhood that resolved in adolescence. The third
13 group was obesity in adolescence but not in childhood.

14 And the fourth group was chronic obesity, pretty much
15 since infancy.

16 When they studied these groups as to their
17 psychological morbidity, there was no difference among
18 groups in gender, family structure, parenting style,
19 family history of mental illness, drug abuse, crime,
20 or traumatic events.

21 The chronic and childhood obesity were
22 associated with having undereducated parents and low

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1 family income. The obese children, chronic obesity
2 was significantly associated with higher rates of
3 oppositional defiance disorder and for boys
4 depression.

5 I don't think this is the definitive
6 study, but I think this teases out some of the things
7 we need to be thinking about when we look at the
8 context in which our obese children sit, the context
9 of their families' environment and their own
10 psychological states.

11 When you look at health-related quality of
12 life, obese children and adolescents have likelihood
13 of having impaired health-related quality of life
14 greater than healthy children or adolescents. And
15 this number is comparable to children with cancer
16 undergoing chemotherapy, which gives you an indication
17 of some of the severity of this. They reported lower
18 pediatric quality of life scores in all domains, which
19 were physical, psychosocial, emotional, social, school
20 functioning. Interestingly enough, in this group of
21 children, the parents rated them even lower than they
22 did themselves.

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1 Obese children and adolescents with
2 obstructive sleep apnea reported lower quality of life
3 scores than other obese children. And these scores
4 did not vary by age, sex, socioeconomic status, or
5 race. And BMI scores among obese children and
6 adolescents was inversely correlated with physical
7 functioning.

8 I would echo Dr. Dietz's comments that
9 when you see these children, you realize how complex
10 their situation is and how crucial the understanding
11 is that you need to understand their psychological
12 state, the family dynamics and functioning, the family
13 psychological state, and something about parenting if
14 you hope to have them comply with therapy of any sort.

15 So I think this point can't be overstated.

16 I think I will end there. And I have this
17 obesity being unique, complex, pathologic, and
18 multifactorial. And you see my Freudian slip there to
19 echo complexity because I think it can't be overstated
20 that this is a complex pathologic disorder that
21 requires extremely careful evaluation of these
22 children to know what the right thing to do in their

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1 situation is.

2 Thank you.

3 CHAIRMAN NELSON: Thank you. I wouldn't
4 have thought it possible, but you almost put us back
5 on time.

6 (Laughter.)

7 DR. HASSINK: I take the Chair's comments
8 seriously.

9 CHAIRMAN NELSON: So we actually have over
10 20 minutes that we could spend discussing the large
11 volume of information that you presented to us before
12 going to lunch. So I'll open it up for questions and
13 clarification from anyone on the panel. Tom?

14 COMMITTEE QUESTIONS OF CLARIFICATION
15 FOR SPEAKER

16 MEMBER NEWMAN: Thank you for that real
17 whirlwind tour. Just the one thing that went by
18 really fast that really did catch my eye is it seemed
19 like there was one thing where rapid weight loss would
20 be bad. And that was the alcoholic liver. Can you
21 just back up? It was like 50 percent. I mean the
22 fatty liver.

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1 DR. HASSINK: That comes from one adult
2 study. And it's hard to know what to make of this in
3 pediatrics, but they did notice that there is a
4 metabolic change in rapid weight loss that increases
5 free fatty acids and may exacerbate the nonalcoholic
6 hepatosteatorosis.

7 Since rapid rapid weight loss is not that
8 common in childhood so far --

9 MEMBER NEWMAN: No. But with these
10 devices, it might be.

11 DR. HASSINK: Yes. And I think you just
12 have to take that as a point of interest. It hasn't
13 been reproduced in childhood. And it comes from a
14 study. So I don't really know how to set that in
15 context for you other than it's been noted in adults.

16 MEMBER NEWMAN: Would this be something
17 you could diagnose with ultrasound or would it require
18 a liver biopsy?

19 DR. HASSINK: The diagnosis of fibrosis
20 and inflammation, that component requires a liver
21 biopsy. And that's been the holdup in really
22 understanding what the trajectory of this disorder is

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1 in childhood.

2 So you can see the fat come and go. And
3 that's actually pretty easy to see. Weight loss you
4 can see the fat just disappear out of the liver. And
5 you can see the liver enzymes come down. They can
6 come down pretty fast as soon as you get weight loss.

7 What you really don't know is, is there
8 any residual inflammation in fibrosis. And I will
9 tell you that kids walk into clinic with elevated
10 liver enzymes that are not all that high and have
11 fibrosis already if you biopsy them.

12 So this is kind of a little bit of a black
13 box yet in understanding what the natural history of
14 this is and who goes on to the fibrotic and cirrhotic
15 endpoint. And I don't have a good answer for how you
16 want to --

17 CHAIRMAN NELSON: Dr. Botkin?

18 DR. BOTKIN: This might be covered later
19 in the day, but I wonder if you could tell us what is
20 known about how obese children differ from non-obese
21 children with respect to dietary habits and exercise
22 patterns.

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1 DR. HASSINK: We know there are a lot of
2 epidemiologic links with TV watching, which is the
3 most well-substantiated. So that links with sedentary
4 behavior plus eating behavior. So we know that the
5 more TV watched, the more likely kids are to be obese.
6 So we know that epidemiologically. We know it
7 anecdotally from what we have seen clinically.

8 We know that some eating patterns, such as
9 bingeing or rapid eating, tend to be a little more
10 common and linked to obesity. We know snacking and
11 grazing behaviors are more common and linked to
12 obesity and consumption of highly sweetened sodas and
13 juices are more common or at least take the
14 predisposed individual and can create the obesity.

15 So we do know some things about activity
16 and inactivity. And those are the things that we try
17 to reverse with behavioral modification and lifestyle
18 change.

19 CHAIRMAN NELSON: Bob?

20 DR. WARD: Do we have any clear data
21 showing reversal of these morbidities with rapid
22 weight loss, such as the cardiomyopathy, the sleep

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1 apnea?

2 DR. HASSINK: I think that you have to
3 look at each morbidity. For example, the orthopedic
4 problem is a simple one. When it's there, it's there.

5 If you've slipped, you've slipped. Maybe you can
6 prevent the slip in the other hip if you don't end up
7 pinning it.

8 The liver disease, we know we can get the
9 fat out and the enzymes down. So there is data there.

10 The obstructive sleep apnea, with weight loss,
11 clearly there is data that that can be reversed.

12 The metabolic complications, in adults we
13 know a lot about type II diabetes and that being
14 reversed. So the metabolic complications tend to be
15 amenable to reversal or the severity, dropping the
16 severity of those.

17 The sort of anatomic complications, like
18 the orthopedic complications, once they're there,
19 they're there. Whether you can take it all the way
20 every time, I don't think we know that.

21 CHAIRMAN NELSON: Dr. O'Fallon and then
22 Dr. Lustig.

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1 MEMBER O'FALLON: I was struck by the fact
2 that Dr. Dietz on all of his lists, he had asthma,
3 which, of course, we're aware of as being another
4 exploding incidence.

5 And, yet, you never mentioned it. And he
6 never actually did either. He just had it on his
7 list. And so I'm wondering, is that a mistake or is
8 that something? Do we have any evidence that --

9 DR. HASSINK: No. I had it on my list and
10 still consider it strongly. The prevalence of asthma,
11 the incidence has gone up with the obesity epidemic.
12 So if you look at them, they kind of parallel each
13 other.

14 And a lot of the epidemiologic, sociologic
15 factors that predispose to obesity are also common
16 with asthma. And also the inflammatory kind of
17 situation you're in with asthma may be linked with
18 obesity. And inflammation may also be another link.

19 Is it directly? The reason I took it off
20 is is it directly caused by obesity? Certainly you
21 see obesity-related. There's fatty infiltration of
22 the lung. And you get diffusion problems. And in

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1 some animal studies, there's decreased surfactant
2 production. But that is sort of the bench work.

3 Is it directly linked? I think you can
4 fairly say that asthma is made worse by obesity and
5 obesity is made worse by asthma. And there are a lot
6 of epidemiologic links. And there may be some
7 pathologic links.

8 So it shouldn't have been left off. But
9 if I put one more thing on, Dr. Nelson would have
10 probably burned my slide.

11 MEMBER O'FALLON: But let me ask, is there
12 any kind of evidence yet about whether a weight loss
13 will improve asthma?

14 DR. HASSINK: I think there probably is.
15 I don't know it. I know clinically there is. I know
16 there is a paper out there somewhere.

17 CHAIRMAN NELSON: I'm going to jump the
18 queue. I gather Dr. Kral had his hand up first, and I
19 think he wants to comment on the asthma point and
20 maybe a couple of the other hands.

21 DR. KRAL: Yes. There are several papers
22 showing reduction of asthma after obesity surgery.

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1 CHAIRMAN NELSON: Okay. I'll take
2 comments out of order on asthma for the moment. Any
3 other points? Then we'll go back to Dr. Lustig?

4 DR. LUSTIG: Dr. Hassink, with the 107
5 slides, I guess I'm not too surprised that you didn't
6 address all the issues, but one of the things since
7 we're talking about scientific overview here is about
8 classification and causation. All obesity is not
9 alike.

10 DR. HASSINK: Right.

11 DR. LUSTIG: For instance, Prader-Willi is
12 very different from brain tumors is very different
13 from metabolic syndrome patients, et cetera. How do
14 the comorbidities stack up in various forms of
15 obesity?

16 DR. HASSINK: Good point. I could have
17 spent the hour talking about causes of obesity. There
18 are clearly -- and just to bring the point about
19 genetic obesity, there are clearly monogenetic causes
20 of obesity that are well-known to just Prader-Willi or
21 X-link. We've learned a lot about them. Most obesity
22 is considered to be polygenic, but there are

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1 polymorphisms also related to etiology of obesity.

2 It's a difficult question. One question
3 would be, are there any obese people that are spared
4 certain comorbidities? I think you see that
5 clinically, but I don't know the evidence about what
6 their predisposing factors would be which would allow
7 them, for example, to be spared diabetes until they
8 get to be 400 pounds.

9 DR. LUSTIG: Well, in the adult
10 literature, for instance, the lowest quintile, the
11 waist-hip ratio, has a cardiovascular
12 morbidity/mortality rate.

13 DR. HASSINK: Right.

14 DR. LUSTIG: That is the same as the
15 general population --

16 DR. HASSINK: Right, right.

17 DR. LUSTIG: -- and an increased subcu
18 component with a normal visceral component.

19 DR. HASSINK: there is also some
20 discussion about physical activity and the protective
21 effect and if our fit obese people are at the same
22 risk as unfit obese people.

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1 So I think there is a lot more we need to
2 understand about the heterogeneity of the obese
3 population, which kind of gets back to my point about
4 this has to be taken kind of individually and set in
5 the context of at least the individual and possibly
6 knowing more about that individual's predisposition to
7 obesity and what that bodes for the individual later
8 on. And I think that's a point very well-taken.

9 CHAIRMAN NELSON: Dr. Gorman and then Dr.
10 Diaz.

11 MEMBER GORMAN: You know, in our
12 preparator material, there was some concern in some of
13 the surgical interventions about postoperative
14 malnutrition in terms of inability to get effective
15 micronutrients as well as calories and protein. And
16 in that vein, not particularly that particular issue,
17 is there a risk that we should be aware of in losing
18 weight to fast?

19 DR. HASSINK: I think that in adults who
20 have a malabsorptive component to their gastric
21 surgery and don't take their dietary supplements, you
22 see problems with vitamin deficiencies and

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1 malnutrition.

2 I think slower weight loss at least -- I
3 don't have surgical experience, but slower weight
4 loss, you know, the clinical sine qua non, we use a
5 pound a week or so on a normal diet. Usually you
6 don't see any kind of problems. Even faster than
7 that, you don't see any problems.

8 I think at this point I would be looking
9 at the adult surgical literature and looking at
10 patient compliance with what they have been asked to
11 do in terms of the nutritional supplementation. And I
12 think that has to be a key factor.

13 MEMBER GORMAN: As a follow-up question,
14 is there any evidence in that the rate of initial
15 change of weight predicts the maintenance of that
16 weight loss?

17 DR. KRAL: No, there's no evidence.

18 DR. HASSINK: I'm blanking on that.

19 DR. KRAL: No, there's no evidence.

20 DR. HASSINK: Can anybody help me from the
21 expert panel?

22 DR. KRAL: Yes. There's no evidence.

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1 I've really looked for it.

2 DR. HASSINK: Okay.

3 CHAIRMAN NELSON: I've got Dr. Diaz and
4 then Dr. Inge, Dr. Moore, and Dr. Pories. And that
5 will probably take us to lunch, but we'll see.

6 MEMBER DIAZ: Is the inflammatory picture
7 in child, in obese children, similar to adults?

8 DR. HASSINK: This is sort of emerging
9 work. And it's thought that obesity in terms of what
10 the adipose tissue is doing in children is similar to
11 adults. I mean, it's a very good question.

12 Is the adipose tissue system acting in
13 children metabolically like it acts in adults? But
14 you can say that the inflammatory issues are at least
15 now thought to be similar in children and adults? But
16 I think that is a very interesting question about the
17 whole metabolic function of the adipose tissue system.

18 CHAIRMAN NELSON: Dr. Inge?

19 DR. INGE: Yes. This is just more a
20 comment. I can appreciate the panel's interest in
21 understanding the consequences of rapid weight loss in
22 inappropriate population adolescents.

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1 And, actually, to that point, Dr. Garcia,
2 who will speak later this afternoon, probably will
3 present a great deal of evidence in that regard from
4 our program, which is really using as a model the
5 gastric bypass for rapid weight loss in adolescents
6 and some of the cardiac consequences, some of the
7 obstructive sleep apnea consequences, and some of the
8 consequences in terms of other metabolic responses
9 that will be very informative. For things that he
10 doesn't present I think we can actually come up with
11 some evidence in that regard.

12 CHAIRMAN NELSON: Dr. Moore?

13 MEMBER MOORE: Thank you for that
14 discussion, Sandra. A question. In a family with a
15 child who is obese, what is the data showing that the
16 parents are likely to be obese also?

17 And, as a follow-on to that, what is the
18 likelihood of therapy just targeting the child? You
19 know, behavioral therapy basically can be effective in
20 that environment.

21 DR. HASSINK: Thank you.

22 I think that population over the clinic

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1 data -- and I have looked at this. I can just tell
2 you in my population about a half to two-thirds --
3 about two-thirds of the patients have at least one
4 parent obese. I do have about a third who bring in a
5 kid with no parental obesity at the time, although
6 there may have been parental obesity in the past.

7 So I think we can say that it's not
8 unusual to have multigenerational obesity in these
9 kids, although you can see an obese kid without
10 parental obesity. That's for sure. And I don't know
11 the wider data.

12 Treating children alone, I think I know
13 better the data treating parents alone. And there is
14 some data in the behavioral literature on lipid
15 treatment and obesity treatment that if you just take
16 the parents, especially the younger children, and
17 intervene with them in terms of how to make behavioral
18 and lifestyle changes, you get a weight loss in the
19 kids.

20 Adolescents, if the group is tailored, if
21 you're talking about lifestyle intervention, if it's
22 tailored to the adolescent, there's some success with

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1 adolescent groups, but they also do well. And the
2 parents also have an ongoing component of the
3 treatment as well or at least a discussion about
4 lifestyle change.

5 So mostly this is done in the context of
6 the family. It's hard to tease out the child when the
7 nutritional activity or environment is so impacted by
8 what the family does. And it really nowadays is
9 needing the family to almost protect the child against
10 the sort of adverse nutritional activity environments
11 that exist everywhere.

12 DR. ARSLANIAN: May I add to that?

13 CHAIRMAN NELSON: Go ahead. On this
14 point, sure.

15 DR. ARSLANIAN: Related to this point.
16 The data which is in a research setup has shown that
17 targeting families together with the child, the
18 10-year outcome was better, statistically
19 significantly better, where 30 percent of those
20 children were normal overweight, versus if they just
21 targeted the child or random target. So I think there
22 are very robust data in that area.

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1 DR. HASSINK: Pretty much you can't do
2 this without the family. And I would venture to say
3 you can't do any obesity-related therapy without
4 having involvement of the family.

5 CHAIRMAN NELSON: Dr. Pories?

6 DR. PORIES: This is just a quick
7 follow-up to the comment about malnutrition. It's an
8 extremely important point. If you follow the adult
9 patients long enough, as we have, you can see the
10 polyagra, the beri-beri, the Korsakow Fornicky
11 syndromes. And I think in terms of children, the
12 question of malnutrition is extremely important.

13 CHAIRMAN NELSON: I see no other questions
14 or comments. Let me ask the panel one question and
15 also first thank you for your presentation. I don't
16 know. You're welcome to stay and listen.

17 The first question for the Committee is
18 Dr. Dietz had mentioned Institute of Medicine
19 prevention of obesity report. To the extent that
20 people may refer to that, you may know that by memory.
21 I don't. Would it be worth having a copy of that
22 available for our discussions or not?

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1 DR. ARSLANIAN: Yes.

2 CHAIRMAN NELSON: Okay. So we will talk
3 with the FDA about getting that. I can download it
4 for \$30.50 if you'll reimburse me right now.

5 (Laughter.)

6 CHAIRMAN NELSON: But that is the
7 question. So we'll work on that.

8 Jan has an announcement before we break
9 for lunch.

10 EXEC. SEC. JOHANNESSEN: If people are
11 here who are going to be participating in the open
12 public hearing at 1:30, I think it would be useful if
13 we would just get together right now at the beginning
14 of the lunch break. And we can just decide who is
15 going to speak first and get the times, make sure
16 everything runs smoothly.

17 CHAIRMAN NELSON: Then with respect to
18 lunch, there is a dining room out to the left and to
19 the left. There is a buffet. Timeliness in terms of
20 ordering off the menu if we all did it would be
21 suspect, although some people were having to do that
22 yesterday. So I would encourage you to look at the

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1 buffet.

2 There is a private room that may or may
3 not fit all the panel members. But at least yesterday
4 the place was relatively empty. So we had that to
5 ourselves. So that may not be an important issue.

6 I would encourage people. We're scheduled
7 to start the public session at 1:30. So it would be
8 nice if we're back here at 1:25 since it takes some
9 time to get settled and get organized, which would
10 give us by my clock a good hour for lunch.

11 So see you in an hour.

12 (Whereupon, a luncheon recess was taken at
13 12:24 p.m.)

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S-E-S-S-I-O-N

(1:32 p.m.)

CHAIRMAN NELSON: I'm told by Jan, who is generally correct, not always, that I have something I need to read before we have the open public session.

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"For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

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1 "Likewise, FDA encourages you at the
2 beginning of your statement to advise the Committee if
3 you do not have any such financial relationships.

4 "If you choose not to address this issue
5 of financial relationships at the beginning of your
6 statement, it will not preclude you from speaking."

7 So our first speaker if we're ready is
8 Linda McAfee.

9 MS. McAFEE: You will give me the high
10 sign when my time is low?

11 CHAIRMAN NELSON: No problem.

12 OPEN PUBLIC HEARING

13 MS. McAFEE: I am Director of Medical
14 Advocacy for the Council on Size and Weight
15 Discrimination. The council is a group that does not
16 take any funding from the weight loss industry at all.

17 I have been a patient advocate for a
18 number of years. And this is probably my ninth
19 advisory committee meeting I have gone to, I think at
20 most of them. I've decided to tell you, instead of
21 actually making a presentation, because pediatrics is
22 not an area of expertise for me. Obesity is. And I'm

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1 hoping to learn from this and perhaps put some written
2 comments into the FDA afterward.

3 But I wanted to bring up a few things
4 today that I had heard that I thought needed a little
5 more addressing. And hopefully we'll be able to do
6 the same tomorrow.

7 One of the big problems with anything
8 having to do with obesity, whether it's drugs or
9 devices, is that there is a real problem establishing
10 risks and benefits. And, of course, this is just a
11 risk and benefit analysis.

12 Partly the risk is inherent in the problem
13 of clinical trials. You just can't get everybody.
14 You're already going to find things out after the
15 market. The problem here is benefits because benefit
16 is extremely controversial in the obesity field now.

17 There was a lot of talk this morning about
18 overweight and obese. That's a really important
19 distinction to make just epidemiologically because
20 when the study came out this spring from Catherine
21 Fleagle in JAMA, the year before that, they had come
22 out with a figure of 400,000 people who died from

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1 obesity. Then they were forced to revise that
2 downward to like 360,000.

3 Well, what Catherine found was that
4 overweight itself is actually protective so that they
5 have a long -- it saved 82,000 lives. That's not the
6 same as obesity. Obesity has quite a nasty little
7 punch mortality-wise. So it's really important to
8 remember that, particularly when you are going to do
9 things on children.

10 And we're not talking about pseudo tumor
11 cerebri here. I'm talking about people who have
12 children have a risk factor for a risk factor as
13 adults. And it's really important to understand that.

14 That is a real problem in the workplace,
15 just like when I went to the Redux hearings and
16 fen-phen hearings. There was a concern there, and it
17 turned out to be right. Everybody got those drugs.
18 They found a way.

19 I mean, people are going to Tijuana
20 routinely now for LAP-BAND surgeries. So this is
21 something that because of the social prejudice we
22 suffer it's particularly difficult for us to make that

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1 kind of risk-benefit analysis for ourselves because we
2 have to factor in the social prejudice.

3 That's not something that you should
4 factor in. This should not be a medical solution to
5 social prejudice. And it's really important for you
6 when you deal with this to confront your own
7 prejudices and then think about that a little bit.

8 One of the problems with this field is
9 also that we are not all the same. Again, someone
10 alluded to it today from the panel. There is a very
11 Nineteenth Century view of obesity. And it's based on
12 this is how you look. So you all look the same way to
13 us. So your bodies all work the same way. You all
14 got there the same way. You all get back to thinness
15 the same way. That's extremely untrue.

16 It's clearer and clearer that many of the
17 things that kill us are really related to insulin
18 resistance and not to just adipose tissue. Now,
19 granted, I mean, so much is coming up now about the
20 different sites of the hormone pump. You know, it's
21 very confusing now to know exactly how direct that is,
22 but I can tell you that everything I look at when time

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1 after time you see a headline that says obesity causes
2 this cancer and then a year later, let's say, oh, it's
3 insulin resistance that causes this.

4 So that's a really important distinction
5 to make when you're talking about who to treat. In
6 fact, there's only been one prospective study on
7 weight loss. And this is one of the major problems.

8 People cannot keep weight off long enough
9 for it to be studied, which is astounding when I think
10 about it. So we really don't know half of what we
11 think we know.

12 The one prospective study that was done is
13 not a randomized clinical trial, but it was
14 prospective. And it was large with the American
15 Cancer Society data.

16 What they showed with adults was that if
17 you started out the study without the comorbidities,
18 you did not gain any mortality, no mortality change,
19 by losing weight. But if you had comorbidities, it
20 did change it.

21 So these are just some things to think
22 about. This is an emerging technology. It's really

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1 very difficult to address these at the best of times.

2 But when you have studies with 11 people in them, 33
3 people in them, that's not good enough. We are going
4 to have to have bigger studies.

5 And they are going to have to include the
6 profile similar to the profile that we see. They're
7 going to have to include a lot of diabetic kids
8 because those are the kids who will get the most
9 benefit out of it.

10 I am really looking to see because this is
11 an emerging technology, because risk and benefit are
12 uncertain, I think that you really have to look at
13 allowing these things for only the ones who would get
14 absolutely the most benefit out of it.

15 And later on -- I mean, I know the company
16 is anxious to sell a lot of whatever they have. And I
17 understand that, and I support that. Later on broaden
18 the indication. But in the beginning, I think it has
19 to be a really narrow indication.

20 And it is such an individual thing that I
21 really -- I was talking to someone earlier. One of
22 the problems is you really do need like a board of

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1 people that you present a case to who decide what is
2 the situation here. This is a family of 3 or 4
3 generations of people who weighed 200 pounds. You
4 know, why are you trying to get them to 125? It
5 doesn't make sense. It's very complicated.

6 I know I am almost out of time. I want to
7 talk about the value of the term "epidemic." That's
8 thrown around all the time here. I hope that you
9 understand that has an emotional value that you really
10 have to factor out when something is an epidemic.

11 We're used to infectious disease epidemics
12 and killer epidemics. This is not the same thing.
13 It's a huge number of people who got fat, but putting
14 the "epidemic" label on it is really a sales pitch
15 more than anything else.

16 It's not to say, again, that there isn't a
17 problem that people are getting much fatter. It's
18 just that label that you have to be careful about, I
19 think.

20 One thing also, there is talk about blood
21 pressure today. The one study on weight loss surgery
22 that is really long-term, the Swedish obesity study,

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1 looked at when people did maintain their weight loss.

2 Blood pressure initially went down, but by three
3 years, it went back up to the baseline. Right?

4 So there is something else going on here
5 with hypertension. It's not just that simple as
6 losing weight. Maybe something has been damaged by
7 years of obesity. I don't know. But something is
8 going on. So we can't just say we'll resolve
9 hypertension and associated risk factors by weight
10 loss. It is not that clear.

11 I guess that's all I really had to say. I
12 hope I'll talk to you tomorrow. And I would like to
13 open it for any questions anybody has. I was a fat
14 child. I can tell you about being a fat child.
15 Anybody?

16 CHAIRMAN NELSON: How about if we wait to
17 see if we have time at the end of the open public
18 session if there are questions.

19 MS. McAFEE: Absolutely.

20 CHAIRMAN NELSON: We can address those.

21 MS. McAFEE: I will be here tomorrow, too.

22 Thank you.

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1 CHAIRMAN NELSON: Thank you for your
2 comments.

3 The next presentation is by Vernon Vincent
4 of Inamed. Did I pronounce that right?

5 MR. VINCENT: Yes. Thank you very much
6 for the opportunity to speak.

7 My name is Vernon Vincent. I am the
8 Director of Clinical and Technical Programs, Inamed
9 Health Corporation. I have held this position for
10 quite some time.

11 I do have a financial interest in this.
12 My company did pay my way here. And I have been
13 intimately involved with the field of obesity surgery,
14 specifically the LAP-BAND, for about 15 years.

15 Many of you here, this team and maybe the
16 surgeons to my right, know the LAP-BAND very well.
17 The purpose of this presentation is to provide and
18 introduction to the rest of the panel first to the
19 LAP-BAND, but in the following presentations about the
20 procedure and the data for the surgeons, perhaps an
21 overview of just how it works and what it is and what
22 it isn't could be beneficial.

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1 I want to really consider that we're
2 talking about severe obesity. This is not a cosmetic
3 issue. We're talking about existing illness,
4 adolescents and adults that have severe obesity or
5 have a concurrent form of diseases that are causing
6 disabilities and increasing their risk of mortality.

7 An option does exist for this. And the
8 surgical treatment that I would like to tell you about
9 is the LAP-BAND adjustable gastric banding system.

10 This is preaching to the choir, I
11 apologize, just to set the stage. And I'll use the
12 term "academic pediatric obesity" is continuing to
13 increase. And we're seeing thousands and thousands of
14 very sick young people today. Prevention would be
15 wonderful. We should definitely work on that. We
16 were talking today about kids that are coming now that
17 are overweight.

18 So on many of your minds has to be the
19 question of why a surgical device or a surgical
20 procedure for adolescents for obesity. Well, I think
21 the point I would like to make and that many of the
22 other panel members will make is that there is an

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1 urgent need now.

2 The obesity epidemic has affected children
3 and adolescents today, 200, 300, and 400 pounds or
4 more overweight. Serious illness and physical and
5 psychological disabilities exist as a result of their
6 weight. Severely obese adolescents do not lose this
7 condition with very rare exception. And with that,
8 they carry an increased risk of adult morbidity and
9 mortality.

10 So in surgical treatment for obesity,
11 there is a number of discussions about ideal
12 procedure. I'm not sure that that exists. Goals
13 include it should provide for a safe, significant, and
14 sustained weight loss. It shouldn't kill you to have
15 it done, but it should last a long time. It should be
16 generated, improving a resolution and obesity-related
17 cohort conditions, should improve psychosocial
18 development, should not compromise nutrition or
19 growth, should be reversible and allow for adoption of
20 future advances in obesity therapy, should be
21 acceptable to the patients, and it should be
22 acceptable to the health care providers and health

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1 care community.

2 In the media, obesity surgery, bariatric
3 surgery, has become a catch phrase that is commonly
4 misquoted. Patients that have one procedure are
5 commonly described as having had another. And it's
6 all lumped together.

7 So I would like to point out that there is
8 more than one procedure in this bucket of obesity
9 surgery category. Most common is the gastric bypass
10 and widely practiced around the world and definitely
11 most common in the United States.

12 Stomach stapling from many of your
13 residencies you probably think of the VBG, vertical
14 banded gastroplasty, that is still practiced and still
15 done around the world; and then banding in various
16 iterations and designs. The procedures vary according
17 to surgical invasiveness and alteration and the
18 morbidity and mortality risks, such as to the
19 procedure.

20 The LAP-BAND adjustable gastric banding
21 system we believe provides an alternative that
22 satisfies many of the goals I describe previously.

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1 It's effective. It's safe, no major change to the
2 anatomy for its placement. It's reversible in the
3 worst case. You can cut out, remove, leaving anatomy
4 essentially intact.

5 When appropriately managed, there's no
6 significant effect on nutrition. Normal food can be
7 eaten, much reduced amount. And it is adjustable.
8 This is very appealing for young women of
9 child-bearing age or if you have acute illness that
10 you need to have increased nutrition.

11 This isn't a new device. The original
12 open adjustable silicon gastric band was first
13 implanted experimentally in 1986. These devices are
14 still in people, functioning today.

15 Laparoscopic development began in 1991 and
16 concluded in 1993 with the first placement of a
17 LAP-BAND laparoscopically in Belgium. Worldwide
18 adoption has followed through systematic training and
19 support throughout the world.

20 The clinical trial was conducted here in
21 '95 to '98, with the FDA panel approval coming in June
22 of 2001. And the label currently is very specific

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1 you've got to be 18 years old. Approximately 180,000
2 procedures have been done to date worldwide.

3 Continuous improvement in the technique
4 and patient management nuances, as Dr. Yustein
5 mentioned this morning, continue to enhance outcomes
6 that are constantly moving forward.

7 It's easiest to understand this device if
8 you see one.

9 CHAIRMAN NELSON: I assume these
10 procedures are not used?

11 MR. VINCENT: Correct. So now we watch
12 this short animation. This video clip gives a very
13 simplistic presentation of laparoscopic surgery.
14 Laparoscopic surgery includes access through trocars
15 with a scope and instruments.

16 Ideally this procedure is designed for and
17 intended to be done laparoscopically. Dissection is
18 completed around the top of the stomach in an unlocked
19 position. Every sample you have is locked closed. In
20 the illustration on the screen, you can see the
21 unlocked band being threaded around the stomach and
22 locked in its place.

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1 The access for it is typically planted in
2 a rectus muscle several inches, under the skin
3 additionally in some people. And percutaneous
4 adjustments are available at any time after placement.

5 Typically a month or six weeks after the initial
6 surgery would be the first opportunity for an
7 adjustment. So it's placed in a very loose position,
8 gradually tightened so that you have a controllable
9 outlet.

10 Some people amazingly need very little
11 restriction, and some will need considerably more.
12 And that opportunity for variation is there. As I
13 mentioned, pregnancy, you can completely deflate and
14 get out of the way essentially and let the pregnancy
15 continue briefly after losing weight.

16 Simple picture of the uninflated band and
17 inflated band. All we're doing with this device is
18 creating a neostoma, a new outlet high on the stomach,
19 with a very small pouch so that the intake is greatly
20 reduced and then its transition to the rest of the
21 stomach is delayed. There is no change to the
22 intestinal tract, no anatomical alteration, just a

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1 delay in passage, significant reduction. So by
2 definition, it's a pure restrictive procedure.

3 There are over 1,100 LAP-BAND publications
4 and abstracts to date. I brought a few folders. I
5 apologize. I didn't realize the size of the
6 Committee. I brought a few folders with the recent
7 adolescent publications. They're on the table here.

8 Summarizing all of the publications,
9 international and U.S., -- there are 17 U.S. papers
10 now -- we can expect approximately a 40 percent excess
11 weight loss at one year, 50 percent at 2 years, and 60
12 percent at 3 years and beyond. Five international
13 papers and one U.S. paper on adolescents with the
14 LAP-BAND occur in the press.

15 How do the procedures compare? One very
16 important detail with regards to adolescents or anyone
17 having surgery is the mortality rate of the procedure.

18 What is the risk of the procedure?
19 Surgery March of '04 with systematic review conducted
20 by Australia, citing the literature available at the
21 time, citing a tenfold difference, a one in 200 risk
22 of death with the gastric bypass versus a one in 2,000

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1 risk with the LAP-BAND, interesting difference if it
2 were my child who had the surgery.

3 There are a few small observational
4 studies in print. There are a couple on the
5 JI-bypass, a procedure that is essentially gone,
6 several on the gastric bypass, one on the VBG, as I
7 mentioned, six on the LAP-BAND.

8 All of these studies report positive
9 benefit. Weight loss is sustained. And health is
10 improved for children. All of these procedures work.

11 This is a fairly challenging slide. This
12 is the data from the six publications with varying
13 endpoints, some reporting a percent of weight loss in
14 terms of BMI lost. We have a couple of the authors
15 present today for these people. You'll be hearing
16 personally about them.

17 Informational point. there are other
18 studies ongoing around the world. There is a
19 randomized controlled clinical trial in Melbourne,
20 Australia, LAP-BAND versus the medical therapy in
21 Monash University, Professor Paul O'Brien, Professor
22 John Dixon enrolling adolescents, the LAP-BAND versus

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1 a very intense medical program.

2 There is also a health economics, a
3 cost-effectiveness study funded by the government in
4 Melbourne, and it's being run by the Melbourne
5 University looking at ten modalities, different
6 programs, and one surgery on it is the LAP-BAND. So
7 these are details that a year or two it should be
8 interesting to follow.

9 A small note on Inamed. Inamed Health has
10 maintained the commitment, not only to the letter of
11 the approval letter or FDA in an approval, that we
12 would continue training and providing support, but it
13 is very much our philosophy.

14 The LAP-BAND is provided only to surgeons
15 qualified to give -- they are invited to a certain
16 training program with advanced laparoscopic experience
17 documenting animals in this program.

18 We spend a lot of time helping build those
19 programs so that they, in fact, do provide follow-up
20 and patient support. This is probably more important,
21 definitely more important, for the adolescent
22 opportunity than others.

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1 Again, the surgeons that are here that are
2 in studies with adolescents, the LAP-BAND will explain
3 the components of those teams. We absolutely support
4 that, and we absolutely support current indications
5 and are not supporting or encouraging off-label use.
6 We are supporting investigation in the clinical trial.

7 To summarize, the LAP-BAND system is an
8 effective tool in the treatment of severe obesity.
9 And these principles are applicable to the adolescent
10 population. Lower risk of death and more serious
11 complications than any other surgical option are
12 embodied in the LAP-BAND procedure. Anatomy is not
13 altered or rearranged. It's adjustable and
14 reversible, worst case can be removed or it can be
15 left intact.

16 Thank you very much for your attention. I
17 appreciate this opportunity. Thank you.

18 CHAIRMAN NELSON: Thank you.

19 The next speaker is Joseph Skelton from
20 the Medical College of Wisconsin.

21 DR. SKELTON: I have no financial
22 interest. I am the Director of a multidisciplinary

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1 weight management program at the Children's Hospital
2 of Wisconsin. I am going to give you my two cents as
3 someone who has hung up a shingle about two and a half
4 years ago and has since seen 500 overweight children
5 and families.

6 I'll make two important points in
7 speaking, but I'll be brief. One is something that
8 you have already heard. This problem of obesity is
9 affecting the health of children now. I have some
10 small data to show you from our program.

11 And then also children are little adults
12 is the second big important point I want to make and
13 echo the recommendations from the American Surgical
14 Association that any trial or evaluation of a control
15 group should be a large experience in dealing with
16 children.

17 This is just a short abstract that we had
18 recently presented looking at our first 284 patients
19 that we had seen. I want to focus on -- can I go
20 back, please?

21 Our children are very overweight. We are
22 seeing children with the medical comorbidity of being

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1 overweight. You see that the mean BMI is 35. And
2 this is in children 2 to 18 years of age. For
3 children with a BMI of 40, over a quarter of our
4 children had a BMI of greater than 40, which, as you
5 have heard before, is criteria for bariatric surgery
6 in adults. It's actually now over 80.

7 And you can see just by looking at the
8 laboratory studies this is affecting their health now,
9 with over half of the children having elevated total
10 cholesterol level and nearly two-thirds of the
11 children having evidence of insulin resistance.

12 Even though there are a lot of people even
13 in this room that can report more studies than this,
14 we were very concerned with the children that we're
15 evaluating. I can tie this to NASH. Twenty percent
16 of our children had an elevated ALT. We ended up
17 biopsying eight of those children. All eight had NASH
18 with seven of those eight having fibrosis and
19 cirrhosis. And, like I said, many people across the
20 nation can tell you even worse stories of this
21 problem.

22 The most important point I think I want to

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1 make, in addition to these children being very ill, is
2 these children have significant psychosocial stressors
3 that need to be evaluated by people experienced with
4 this problem. We looked at 58 children that had been
5 in our program for nearly a year. And even though we
6 did some success with the majority of our kids, we
7 found some very interesting things.

8 I'm looking here at the different colored
9 bars. It's kind of hard to pick up. But as far as
10 report of psychological history of having a behavioral
11 issue or a mental health issue, you were necessitating
12 the evaluation by a mental health professional. Even
13 though only about a quarter of our children actually
14 had a history of it, nearly half of the parents
15 reported having some form of psychological history.
16 So this is very important, the concept of children
17 when you are actually having to treat them with the
18 family. There are significant family stressors,
19 including mental illness, that can be a big
20 confounder.

21 As far as previous weight management
22 attempts, this was actually surprising that hardly any

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1 of the children had been in either a formula or even
2 an informal program, including buying over-the-counter
3 books, diet aids, and only a tenth had made a change
4 in weight. About a third of them had done something
5 with the family as far as changing what they were
6 eating.

7 And then their eating activity behavior,
8 this can also be significant when you are looking at
9 something as invasive as bariatric surgery. Children
10 are very picky eaters. And then you even add in a
11 very strict diet that you will put the children on
12 after bariatric surgery that can be even more
13 difficult.

14 Over half the children sneak food, eat
15 large amounts of food, and then have high-level
16 sedentary activity, so my second point being,
17 hopefully you are considering issues like this and
18 need to be with people very experienced in dealing
19 with the overweight children and their families. And
20 the particular mental health, behavioral health
21 providers, not only pediatric psychologists and
22 psychiatrists but those with a history or experience

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1 in health psychology and hopefully in weight
2 management.

3 Thank you.

4 CHAIRMAN NELSON: Thank you.

5 The next speaker is Dr. George Fielding
6 from New York University.

7 DR. FIELDING: Thanks very much. And I
8 would like to thank you for the opportunity to speak.

9 I've got no financial relationship with industry.
10 I've paid my own way here to give this presentation.

11 What I would like to do is just give a
12 brief overview of results that I have for LAP-BAND
13 analysis over the last six years, some of it in
14 Australia, some of it here.

15 I've chosen to use the LAP-BAND in these
16 children because of its gentle nature and its
17 adjustability. The other aspect of this is that I was
18 actually obese myself as a child and adult. I had the
19 surgery seven years ago, which has given me a little
20 bit of advantage to the take on it.

21 There are three phases in the results I
22 would like to present here briefly. I did 41 bands in

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1 adolescents in Australia since between '98 and 2004.
2 Since coming to New York, I have done another 58 in a
3 shorter time frame.

4 If you look at the data from Brisbane with
5 a mean age of 17, it might cut off. At the time it
6 was close to 19. The mean age in that group is 17.
7 And you can see on the left the number of patients per
8 year and their descending weight.

9 And you can see that their BMI actually
10 does fall from a mean of 43 to a mean of 29 by 2
11 years. And then it pretty much stays static. And the
12 excess weight was in the 60 percent. This is being
13 maintained with normal follow-up.

14 In terms of whether this surgery actually
15 offers a successful outcome, one of the measures of
16 the success is how many patients lose half of their
17 excess body weight. And in these children, 80 percent
18 lost at least 50 percent of their excess weight for 3
19 years; likewise, getting the body mass index below 30,
20 which is really a good determiner of success.

21 One of the issues that is always raised
22 about surgical treatment of adolescents is that of

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1 compliance. And I'd just like to report that
2 children, both in Australia and here, their compliance
3 is clearly better than adults. There are a lot of
4 different reasons for that.

5 If you look at it, one way of measuring
6 that is how often that actually turned up before. And
7 we found that they came on average 12 times in the 2
8 years, which is exactly what we asked them to do.
9 Some of them came very frequently. It really hasn't
10 been an aspect of their management that has proved
11 difficult.

12 I then came to New York about two years
13 ago now. We had the largest surgery experience in the
14 world, done over 4,000 LAP-BANDS between the 2 of us
15 doing the surgery there. The key issue with the
16 program, which I will espouse, since I started doing
17 this quite a while ago is the dedication to long-term
18 follow-up. It's the integral component of success
19 with any bariatric surgery.

20 The second integral component is that
21 there are multiple disciplines involved in the
22 provision of the care. And the basic requirements are

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1 obviously in-house nutrition and psychological
2 back-up.

3 When you're dealing with adolescents, it's
4 very important. It's great we now incorporate a
5 pediatric surgeon into the team. We have specialized
6 teenage psychological care at the NYU Child Study
7 Center. So we've got the components in place for a
8 successful team management of this problem from the
9 tour.

10 We look at the -- these were done in New
11 York, done 58, 46. This is an absolutely classic
12 breakdown of sex difference in bariatric surgery in
13 adults as well, 5 13-year-olds, 40 between 14 and 17,
14 which I'm going to concentrate a little bit more on,
15 and 13 older people, who really in many ways I think
16 function more as adults. They are mainly Caucasian, 5
17 Hispanics, and 3 African Americans.

18 They do have comorbidities. And if you
19 look at the breakdown, probably a fifth of the
20 children have dyslipidemia, depression, and diabetes.

21 Low back pain is very common and then the whole host
22 of comorbidities that do appear in adults, including

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1 sleep apnea, requiring CPAP. They have the whole
2 gamut of comorbidities exactly as one would see in the
3 adult population.

4 The average weight of the children who
5 have come to New York has been nearly 300 pounds, the
6 average BMI 47. It takes about half an hour to do
7 this procedure. And the average length of stay is one
8 day, but we're increasingly sending the children home
9 on the same day as surgery. So it's not a major
10 venture physically for the patient. And I would
11 really stress how gentle this really is because there
12 is no intestinal surgery at all.

13 Interlooping perioperative complications,
14 all patients were discharged within 24 hours. As I
15 said, there's an increasing use of the same day.
16 There's no death, no pulmonary embolus, no acute
17 reoperations. One boy came in with a perforated
18 appendicitis a week after his band. He weighed 450
19 pounds. But he is in acute remission and seems to be
20 doing this at NYU.

21 This is pretty hard to read from here, but
22 basically it shows very similar data to what I found

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1 in Brisbane, which is as time goes on, the weight loss
2 is generated and maintained. And it will deliver
3 somewhere between 50 and 60 percent excess weight
4 loss, which can be maintained.

5 One of the things we have looked at in the
6 children who have got longer than a year follow-up --
7 and this is only a small number so far, but you can
8 see that their nutritional panel is on for vitamin
9 B-12, which we maintain during our series.

10 Just for a minute, to look at the 14 to
11 17-year-olds, which I think are the main emphasis of
12 this whole panel, the overall data is the same as I've
13 shown. It's a quick operation, a short length of
14 stay. It's mainly being done in Caucasians, but there
15 is an increasing number of Hispanics and African
16 Americans. This is the breakdown of age, 19
17 17-year-olds, 11 16, 7 15, and so on.

18 We have now performed the surgery in this
19 age group in 15 children in our FDA study and 25 prior
20 to initiation of the FDA study. The weight loss has
21 been great. There have been a couple of
22 complications. The well-known complication of

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1 LAP-BAND is a slipped band and where the stomach comes
2 up through the band, gets stuck, and it generates
3 reflux. And so they require reoperation. We have had
4 two of those. I mentioned the boy who had the
5 perforated appendix.

6 I would just like to spend a short time
7 about reflux because this has been a discussion that
8 has been very prevalent in the adult population. For
9 the 58 children complaining of reflux after the
10 surgery, typically in the evening after an evening
11 meal, they had diagnostic esophagrams, which showed
12 two of them had slips and two of them basically had
13 hiatal hernias.

14 The hiatal hernias were repaired, the band
15 hadn't slipped, and the other two bands had slipped.
16 These were all done as day cases. All four resolved
17 all their symptoms and had ongoing weight loss after
18 resolution of that complication.

19 We have had an FDA-approved study now for
20 about the last five months. It's an ongoing study for
21 five years. Initially it was 50 children. And it's
22 involved psychological assessment repeatedly, yearly

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1 bone scans, and then ongoing observation of weight
2 loss and symptomatology for a five-year period.

3 We're thrilled to have gotten this
4 experience, and we're recruiting patients quite
5 rapidly. As I said, we've recruited 23 already in
6 about the last 5 months.

7 This is just a breakdown of that data, now
8 23. And 18 have had surgery. It's very similar to
9 the previous data I have showed you.

10 This just shows the pre-op weight is about
11 the same. It's about 300 pounds, BMI 47. The
12 operation is half an hour. And they're all home
13 within 24 hours.

14 You can see here 37 percent of them had
15 diabetes or an off glucose tolerance test, likewise
16 with back pain and cholesterol and depression. These
17 children are not well, and they have all the diseases
18 that their parents and grandparents have related to
19 their weight.

20 The lipid panel has been maintained in a
21 short follow-up so far. Likewise, the nutritional
22 panel has been maintained, the early follow-up on the

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1 FDA children. And the weight loss has been nice and
2 steady with 17 percent weight loss at 3 months.

3 So, in conclusion, I would like to just
4 offer a feeling that this surgery is safe in
5 adolescents. And it does produce an effective weight
6 loss. And it's best performed, as many have said, by
7 obtaining a lot of experience in the surgery and in
8 the multidisciplinary studies.

9 Thank you.

10 CHAIRMAN NELSON: Thank you.

11 The next speaker is Jeffrey Zitman,
12 Columbia University.

13 DR. ZITMAN: Thank you.

14 I have no financial connection or
15 relationship with the Committee or the maker as well.

16 I actually had not prepared any slide show, which I
17 guess is both good and bad, but I do have just a
18 couple of comments.

19 I won't repeat everything that Dr.
20 Fielding said about the Band, but what I would like to
21 do is just take a couple of minutes to give you our
22 perspective as to how we put our program together.

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1 Our program is really in the birthing stage as we
2 speak.

3 We decided a little more than a year ago,
4 "we" being a meeting of the pediatricians, pediatric
5 endocrinologists, pediatric gastroenterologists,
6 nurse-practitioners, and psychiatrists, as well as
7 bringing in the adult bariatric surgeons, that there
8 really was a role for adolescent bariatric surgery at
9 our institution.

10 We looked at what was available in terms
11 of surgery. We decided that a Lab-Band was the better
12 choice, as opposed to bypass, simply because of the
13 reasons that Dr. Fielding just went through.

14 And so in putting together our team, we
15 researched the literature that was there in both the
16 adult and population, researched the problem. And we
17 developed a protocol, which we applied for and
18 received permission from the FDA to perform, which in
19 many ways mirrors what George just showed you.

20 Our study involved patients who are
21 teenagers, 14 to 17. We were approved for 15 patients
22 as a pilot study, after which we were invited to apply

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1 for an additional 50 patients.

2 Because of his study, in addition, we are
3 also going to be looking at excess weight loss and
4 changes in BMI. We are also going to be looking at a
5 variety of basic metabolic scientific issues as to
6 what goes on with these patients. So perhaps I can
7 give you some additional insight as to what the actual
8 metabolic changes are. And that's where we are at
9 this point.

10 We have not actually opened our program in
11 terms of advertising. It was just through word of
12 mouth. In the first 2 weeks being in the same city as
13 Dr. Fielding, we had 27 phone calls inquiring about
14 the program from as far away as Tennessee and Indiana.

15 So I stand here simply to say I think
16 there is a clear need for surgical intervention in
17 some of these patients and our job as pediatric
18 surgeons and pediatric practitioners involved in teams
19 who are working with this is to make sure that these
20 patients are screened appropriately and get the best
21 care.

22 I would emphasize that in our program, we

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1 work very closely with the adult bariatric surgeons.
2 We are a children's hospital, and we're part of a
3 large complex. Our bariatric surgeons are part of our
4 team so that when they turn 19, 20, and 21, that care
5 will be continued.

6 Thank you.

7 CHAIRMAN NELSON: Thank you.

8 Let me ask if there is anyone else who
9 would like to speak during the open public session.
10 Could you introduce yourself, say where you're from,
11 and declare any conflicts before getting into what you
12 have to say?

13 MR. DOWNEY: Yes, I will. Thank you.

14 My name is Morgan Downey. And I am the
15 Executive Director of the American Obesity
16 Association. I have a number of conflicts of
17 interest. Our association gets support from the
18 weight loss industry in general, including commercial
19 weight loss programs, like Weight Watchers and Jenny
20 Craig; pharmaceutical industry; biotechs; and a few
21 companies in the surgical area, including Inamed, for
22 one.

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1 I just wanted to touch on a couple of
2 observations from the morning's presentations. I
3 would like to do this in context, though. We opened
4 our office here about eight years ago. I would say
5 it's pretty steady that we get maybe four or five
6 calls or letters or e-mails a day from parents who are
7 frantic to find some kind of service, good,
8 appropriate service, for their children who are
9 suffering with obesity.

10 Most times they have exhausted diet and
11 exercise programs. They are very frustrated that the
12 pediatricians and internists that they deal with
13 oftentimes just won't see an obese adolescent child
14 and if they do don't really have any tools or
15 counseling to give them in terms of weight loss.

16 I think it was Dr. Yustein this morning
17 who presented a very good slide on the spectrum of
18 interventions from device and from diet and exercise
19 pharmacology than this gap in surgery, but that's not
20 really a gap. That gap is being filled, but it's
21 being filled outside of the medical model. That is
22 being filled by drugs and devices, products and

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1 services that are largely unregulated, frequently
2 dangerous, and often fraudulently sold and
3 represented.

4 And the FDA in terms of their enforcement
5 on dietary supplements and the FTC in terms of
6 enforcement of deceptive advertising practices have
7 documented this very highly. So that is not really a
8 gap. That is where people are going in a really
9 desperate effort to find some consistency.

10 I would also like to say that we released
11 last week a survey that we did in connection with
12 Inamed where we interviewed, the company interviewed,
13 adults with morbid obesity. And we looked at kind of
14 two scales. One was the degree of intimacy with their
15 sexual partner. And the other one was their
16 experience with job discrimination.

17 In both categories, as you might expect,
18 there was a very, very high level of poor relations
19 with their intimate partners and a very high level of
20 experience with what they felt to be employment
21 discrimination. That, unfortunately, I think gets
22 conveyed very quickly to children and adolescents who

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1 are overweight of what they have to look forward to.

2 And while we might be very concerned about
3 glucose levels and blood pressure and the other
4 important health indicators, I don't think those
5 psychosocial problems that come with morbid obesity
6 should at all be underrated here in terms of the
7 importance.

8 I will just summarize by saying we have
9 worked for several years on the drug side of the FDA
10 to improve the guidances they have for approval of
11 weight loss drugs. And it's been a frustrating
12 problem because it has gone on for so long without
13 resolution.

14 And I would just encourage the Committee
15 here that we need strong, well-controlled, rigorous
16 studies of interventions for children and adolescents.

17 And time is of the essence. This is a real crisis.
18 And we need to move quickly to develop those and get
19 those out to the research community.

20 Thank you.

21 CHAIRMAN NELSON: Thank you.

22 Let me ask if there is anyone else who

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1 would like to have an opportunity to speak during the
2 open public session. And if you could introduce
3 yourself, where you're from, and any conflicts before
4 launching?

5 DR. BROOKS: My name is Dr. Jeffrey
6 Brooks. I'm an adult gastroenterologist and Chairman
7 of Stats Medical. I do have an interest in one of the
8 companies involved in the program. We are currently
9 testing a second generation balloon. So I do have a
10 monetary interest in this.

11 I just wanted to point out to the
12 Committee because it seems like everyone is talking
13 about LAP-BAND and for good reason -- it's a terrific
14 thing. But I would like you to also think about what
15 Dr. Yustein said today, that there are non-permanent,
16 nonsurgical means that are coming around the pike.
17 And I would like you to keep that in mind when you
18 make your decisions on the four questions tomorrow.

19 CHAIRMAN NELSON: Thank you.

20 Anyone else who is interested in speaking
21 during the open public session?

22 (No response.)

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1 CHAIRMAN NELSON: Seeing none and hearing
2 none, this brings a close to our open public session.
3 And, barring any objections, we can move to our next
4 presentation a little bit early. Jeff?

5 DR. BOTKIN: Are you going to entertain
6 questions for any of the public presenters?

7 CHAIRMAN NELSON: I wasn't planning to
8 unless you had a question you think you would like to
9 ask.

10 DR. BOTKIN: I do.

11 (Laughter.)

12 CHAIRMAN NELSON: Okay. Go ahead.

13 DR. BOTKIN: It's a question for Dr.
14 Fielding. And I wonder whether you could just briefly
15 describe what other components you had to your program
16 in the way of dietary management, exercise,
17 psychological counseling, et cetera, and whether you
18 can ascribe any of the presented benefits to those
19 other components, as opposed to --

20 DR. FIELDING: Sure. The first thing is
21 just to spend a minute on why one thinks the LAP-BAND
22 works. My own feeling is it works by stopping people

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1 being hungry. Above all else, that's what it does.
2 And that's more important than the punitive,
3 restrictive component.

4 You can actually render someone who has
5 been starving their entire life actually not
6 interested in food. It then gives them a chance to
7 set them up to be able to then eat small amounts of
8 food without strength. That's the endpoint.

9 To get from there to the adolescents, I
10 believe it needs to be the kids' idea. The number one
11 thing that I have found that has led to success is
12 that the child has gone to the parent and said, "Mom,
13 I want to do this. I've read about it. I've seen it
14 on TV. I've seen it on the internet," when the child
15 goes to the parent and the parent then goes looking.

16 So in my sense from the people we've seen
17 so far is that the kids are very committed to doing
18 this. So then they come along. And in our
19 population, they've all done everything. They've all
20 been to Weight Watchers. They've all had dietary
21 resources. A lot of them wore the fat hat for every
22 holiday they've ever had. So these are very

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1 experienced people in the world of obesity. And they
2 might be only 14, but they spent most of their life
3 doing that.

4 So when they come to see us, then that's
5 the first thing we find out, how have you really tried
6 to deal with this, yourself, as a family unit,
7 whatever? So they get a sort of evaluation.

8 And, two, with only one exception since
9 I've been in New York, the people at the Child Study
10 Center have said, "This kid is ready to do this" with
11 one exception.

12 We then have a nutritionist that we have
13 on board as part of our team. She sees every patient.

14 And she assesses them preoperatively. And then I see
15 them, and we talk about it all.

16 The key second ingredient of the work,
17 actually, we're doing is seeing them afterwards. The
18 one thing I know, there are people who are very up in
19 odds about how they feel about this. Are these kids
20 going to be difficult to look after?

21 But honestly this is a very different
22 population than, say, someone who is in a transplant

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1 program or somebody who has got cystic fibrosis or
2 chronic disease. These kids if you can make them fit,
3 they become well. They evolve into a well person. So
4 they want that so badly. They have been trying all of
5 their life to do it.

6 And, finally, here is a tool they can use.

7 And they can smell the change. They know what is
8 going to happen. And so they really comply. They
9 come to visits. They come to get their adjustments.

10 They whine to me occasionally. They talk
11 about their food and all that. I chat with them about
12 what it's like being fat, and I chat with them about
13 peer pressure. But it's not usually a formal "You
14 must do this and you must do that."

15 It's just a kind feeling of being looked
16 after, being made not hungry. I don't know if any of
17 you have ever been fat, but the hardest thing about
18 being fat, the reason they're fat is they're hungry.
19 And so this tool gets rid of that. And it's as gentle
20 as anything.

21 But it's one of the reasons, one of the
22 mechanisms of "You have to do it this way. You must

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1 attend 35,000 sessions. And you must walk 50,000
2 steps." All of that continues because most kids want
3 to be part of the peer group. Most kids want to play
4 ball. Most kids want to go to dances. It's just when
5 you're a human being, you can't.

6 And so the natural evolution is to say,
7 well, they consume more life than they do. And that's
8 why they're so compliant, which is different than any
9 other form of chronic illness that you have to manage.
10 That's my take on it.

11 CHAIRMAN NELSON: There seem to be a lot
12 of questions. And I'll point out we have eight
13 minutes for all of them. So I'll go to Dr. Yanovski
14 and then come over this way.

15 DR. YANOVSKI: Really, the crux for many
16 of us is subject selection, which is can you tell us
17 about the characteristics of your patients? Are they
18 paying for this procedure themselves? How much are
19 they paying? Are you rejecting anyone? And on what
20 basis?

21 DR. FIELDING: The main reason for us, the
22 hardest, is it's awful to have to reject someone who

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1 really wants this. But if they just don't get it, I
2 won't give them the surgery.

3 I can tell within five minutes whether
4 they get what this is about. They get that it's going
5 to involve a change in the way they live and change in
6 what they eat, that they can't eat the same way as all
7 their buddies so, and that it's an evolution for them
8 or if I think they are being coerced at all by their
9 parents against their will, then that's the time to
10 say, "Look, no one in this room is ready to do this
11 yet. Go back to the Child Study Center and spend time
12 with them. Think about it some more." That's what I
13 tell them.

14 DR. YANOVSKI: So it sounds like you only
15 take the most willing of the willing.

16 DR. FIELDING: Right.

17 DR. YANOVSKI: And then there was one
18 other question. So the socioeconomic status --

19 DR. FIELDING: Well, the socioeconomic
20 status that I have dealt with so far has been the
21 upper half, rather than the lower half, because
22 they're the ones who have insurance, number one. And

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1 that's who come initially.

2 Surprisingly, quite a few insurance
3 companies have covered this in adolescents.
4 Particularly the ones that cover it in adults cover
5 it, of course. We have a very good relationship in
6 Manhattan with the insurance companies for the
7 LAP-BAND.

8 Once we have set up where is the aid of
9 the FDA, that's out the window simply with insurance
10 companies. And so we have been blessed in a patient
11 of mine who is very wealthy who has helped to fund
12 children who can't pay for it.

13 And so the last five or ten, the last five
14 or ten of these children, are poor African American
15 and Hispanic kids. And so we're starting to get a mix
16 of what is going on in the community. And we have now
17 reached out to the big Harlem children's zone in New
18 York. We're going to be getting children to sit down
19 with us.

20 And so what I hope to go over in time is
21 does it work in really rich kids, does it work in
22 really poor kids, and how does it all work. So to

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1 date, it has been what you would expect. Ours are
2 really intelligent kids. These kids really are
3 suffering. They're bright, and they're the ones going
4 to their moms and dads, saying, "I want to do this."

5 CHAIRMAN NELSON: All right. There were
6 some hands to my right. Are they still up? Bob?

7 MEMBER NEWMAN: Your follow-up looked like
8 it stepped off fairly quickly by 12 months. Is that
9 because some of the kids are just not 12 months out
10 from the surgery?

11 DR. FIELDING: No. That's what we've been
12 doing so far in Manhattan. What we do is we see them
13 monthly to two-monthly depending on where they live.
14 The adjustment schedule, typically we make three or
15 four adjustments in the first year. Then we keep them
16 coming for the first two years. And then afterwards,
17 we drop it back to three-month intervals.

18 MEMBER NEWMAN: Have either children in
19 New York or in Brisbane undergone pregnancies after
20 this? What has been your experience with that?

21 DR. FIELDING: One girl at Brisbane got
22 pregnant at the age of 15, had the baby, and kept

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1 doing follow-up. One of the really great things about
2 this band is that you can manage your pregnant with
3 the band inflated so they don't gain weight or you can
4 deflate it or whatever.

5 And I've actually published on this one
6 about 50 women who have had babies with Bands who had
7 previously had babies showing a statistical
8 improvement in theory and the same body weight and
9 attributes of the children.

10 The biggest difference is you just don't
11 get the follow-up deficiency that you get with the
12 bypass. So the incidence of some of that sort of
13 stuff is much less.

14 CHAIRMAN NELSON: Thank you.

15 So we'll now transition to our regular
16 presentations and call the question period after the
17 open public comment period to a close. And the
18 presentation is from Dr. David Wendler on subject
19 selection and assent in pediatric research.

20 DR. WENDLER: Thank you.

21 ASSENT IN PEDIATRIC RESEARCH

22 DR. WENDLER: I was asked to speak about a

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1 couple of things in a short time. So, rather than try
2 to give much in-depth analysis about any of this, what
3 I thought I would do instead -- hopefully this will be
4 helpful to the group -- was to try to present a
5 framework for thinking about both of these issues.
6 I'm going to focus on subject selection and assent in
7 particular, just give a framework for thinking about
8 both of them. And I won't try and answer too many
9 questions. Then if people want to go into more depth,
10 we can do that during the questions if we have time.

11 Okay. So, just to let you know, I work
12 for the NIH, but I make up everything that I say. And
13 the people who give me money don't approve of what I
14 say, and they typically don't agree with what I say.

15 Okay. So, first of all, quickly on
16 subject selection, the way that I think about this is
17 to think about framework. I'm trained as a
18 philosopher. So in the trying to think about
19 framework, we first ask ourselves, well, what are the
20 goals of the project? What is it that you are trying
21 to accomplish? Try to think about and get clear in
22 your head what the goals are and think about what

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1 happened and ways to achieve those goals.

2 So at least when I sit down and scratch my
3 head and try to think about the goals of subject
4 selection, this is basically what I come up with, that
5 you want to distribute benefits and burdens fairly and
6 assure the value of the research, validity of the
7 research, minimize risks, risks to both individual
8 subjects and also aggregate subject support as well,
9 maximize the benefits and protect.

10 So I think that's basically the framework.

11 And for this part, I'll just give a quick point on
12 each one of these goals and then go on to assent.

13 So one way to think about this, as people
14 in this room know, there has been a big shift in the
15 psychology of research and research ethics. Twenty
16 years ago, everybody talked about protection,
17 minimizing risks, protecting people from risks. While
18 those things are still obviously important, there's a
19 lot more emphasis these days on ensuring access,
20 making sure people have fair access to participation
21 in clinical research.

22 So a quote from about ten years ago from

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1 Levine, "People are clamoring for access to clinical
2 trials. And Fannie Mae and others like them are owed
3 such as a matter of justice."

4 So if you think about it from this
5 perspective, the way I think about this is to start
6 out very simply assuming that everybody in the world
7 is eligible for your study and then exclude
8 populations or individuals from that set only when you
9 have a good reason to exclude them. That's one way to
10 ensure that you're resulting inclusions and exclusions
11 are fair.

12 So a couple of obvious reasons why you
13 might exclude people, the first one is you're doing
14 research and trying to do science and you're trying to
15 learn something. So the first thing you should do is
16 you should exclude people who can't help you answer
17 the question that you're trying to answer. So this
18 puts forth the value in the study, obviously simple
19 things.

20 If they don't have the disease that you're
21 studying, you can't enroll them and also things about
22 validity. And these are questions that get tough for

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1 researchers. So somebody who doesn't come back to the
2 clinic every time, they're supposed to come back once
3 a week, and they miss a day, they miss two visits.

4 When does a helpful subject become one who
5 is endangering the validity of the study and becomes
6 in practice one of the harder questions with respect
7 to subject selection.

8 At least initially you should make sure
9 that these are people are in position, whether or not
10 they're going to achieve that, but at least the
11 physicians that carry out the demands of the study.

12 A simple example in terms of the value, at
13 least typically studies about different kinds of
14 cancer trials exclude people with brain tumors who get
15 drugs are not able always to determine whether the
16 symptoms are a result of the tumors or a result of the
17 drug. So sometimes you have to exclude people or that
18 reason.

19 This is an example I was just talking
20 about. You also have a set number of clinic visits.
21 We'll have to come back to it. You're not going to be
22 able to do good science if you can't make your clinic

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1 visits.

2 Physical risks. There might be physical
3 risks. Obvious cases. One of the things I'll just
4 mention briefly we can talk about more if people are
5 interested, I think typically when people talk about
6 minimizing risks with respect to subject selection,
7 they think about it with respect to the risks to
8 individual subjects. They think about minimizing
9 risks to this person, minimizing the risks to that
10 person.

11 I think that's obviously important. I
12 think that leaves out an important consideration,
13 namely minimizing the aggregate risks of a research
14 study. You do that by choosing some subjects over
15 other subjects. And I think that becomes a valid
16 reason for exclusion, although some people worry about
17 that as discriminatory.

18 So maximizing benefits, I sat on an IRB
19 when they were first starting to roll out protease
20 inhibitors. And we had a big debate about who we were
21 going to allow in these initial studies. Should we
22 allow people with high CD4 counts who tended to be

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1 relatively healthy or should we enroll people with
2 lower CD4 counts who needed the access to the drugs
3 and were sicker and had less time to get them, which
4 brings up one of my key points and I think is the
5 hardest to get these goals? But the problem is that
6 what we find out when we start thinking about
7 individual cases is that these goals aren't always
8 consistent. You can minimize risks by choosing one
9 population. You can maximize value by choosing
10 another population.

11 Protecting the vulnerable. You guys are
12 talking about kids. In one sense, all of them are
13 vulnerable. But there are different levels of
14 vulnerability depending upon the status of the kids,
15 kids who are very young, kids who are particularly
16 sick.

17 As some people know, there's been a big
18 debate lately about research on wards of the state.
19 Some of that was going on in the last 15 to 20 years.

20 And depending upon who the guardians are for the
21 wards of the state, I think I would consider them in
22 most cases to be more vulnerable than kids who have

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1 attached families.

2 So this is a point that I was making, that
3 in a lot of cases these different goals come into
4 conflict. So you might want to say let's enroll older
5 kids because they understand more and more and are
6 able to make their own decisions, but at least in some
7 cases they face greater risks than little kids do.
8 And so you're faced with balancing off minimizing the
9 risks versus maximizing their understanding.

10 Another example of this is, as people
11 know, that there are some regulations that vary the
12 level of risk to which you can expose a kid depending
13 upon whether or not the kid has the disease that
14 you're studying. And one of the justifications that
15 some people who agree with this have offered is that,
16 well, even if there is no prospective direct benefit
17 in the study in front of you, for sick kids, there is
18 more likely a benefit from the result of the studies
19 in the future. You might think that's important, but
20 then, on the other hand, if they are sick, they may be
21 more vulnerable than healthy kids, so another kind of
22 concept you have.

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1 Unfortunately, although I am a
2 philosopher, I like to come up with tricky sorts of
3 concepts. In this case I have never been able to
4 figure one out. So you fall back on relatively
5 unhealthy metaphors, like balancing competing goals.
6 I think you just have to look at the individual cases
7 and see what's more important.

8 So that is sort of the framework for
9 thinking about subject selection. And I will try to
10 give a simple sort of framework for thinking about
11 assets in pediatric research.

12 So as people here know there are a few
13 exceptions, but in most cases kids are enrolled in
14 research, it doesn't offer any compensating potential
15 benefit. They have to have the permission of their
16 legal guardians. It could be their parent.

17 Also, most guidelines -- this is true of
18 the U.S. It's also true of most guidelines that I
19 have been able to find around the world, also require
20 what is called the assent of what is called the U.S.
21 vote, the affirmative agreement of children. And you
22 can here italicized "who are capable of providing."

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1 That is one of the big things to date that I'll come
2 back to in just a minute.

3 So there is a lot that we need to know.
4 I'm going to focus on capacity to give consent, but I
5 think there are a lot of important issues that we know
6 very little about in this area. And we need a lot
7 more research.

8 One of them is just the appropriate
9 process. If you've decided you're going to get assent
10 to a particular study, what is the right way to do it?

11 One of the obvious questions is whether or not you
12 salute the assent of the kids in conjunction with the
13 parents.

14 There are some people who think that is
15 the right way to do it, the families or units. It's a
16 part of families, and that proper respect applies
17 given how these decisions are made as a group.

18 Other people worry that kids who are in
19 that context are not going to feel free to say they do
20 and they don't want to be in research. And that's a
21 reason to get their essence separately.

22 I'll just give you one quick little bit of

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1 data. Sorry this doesn't show up very well here.
2 This is just a study that was published very recently
3 from a group out of Penn, American Journal of
4 Bioethics. They took a bunch of kids who had come
5 into emergency rooms and they were asking them to be
6 part of research. You can't see the bottom. It gives
7 you a response rate. Seventy-five percent of the kids
8 were 11 to 19. The mean age was just about 14.

9 Most of them are African American males
10 because this was a study of violence. Kids were
11 brought into the ER who had been injured as a result
12 of violence in New York City.

13 One of the things they did was they asked
14 kids at the end whether or not they felt that it was
15 their decision to enroll in the research or not. And
16 there were two groups. There were kids who had a
17 family member in the room with them at the time they
18 were asked to give assent, and there were kids who
19 were alone in the room. And you see pretty clear
20 differences here.

21 So when there is a family member in the
22 room, 17 of the kids said it's your choice, but 10 of

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1 them said maybe it was or that it wasn't. When they
2 were alone, almost every single one of them said that
3 it was their choice.

4 Here's at least some suggestion for the
5 not surprising fact that maybe when kids are in the
6 room with the family members, they don't feel
7 necessarily comfortable to make their own decisions.

8 Now, one of the things that I think is
9 just a slight caveat on that, I think a reasonable
10 question about the extent to which why we're asking
11 kids to make their own decisions, one of the
12 interesting pieces of data I think in this study was
13 that there are 16 participants who said that it was
14 not or may have not been their choice to participate.

15 They then asked those kids whether or not
16 they were glad they were participating. Almost every
17 single one said that they were. Fourteen of the 16
18 said that it wasn't their choice, but they were glad
19 they had been in the study as well. Two of them said
20 they may have been glad.

21 So you get some sense, one, about the
22 pressure kids are exerting, having exerted on them,

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1 but maybe sometimes just the pressure that's being
2 exerted is steering the kids in the right direction.

3 Another thing with respect to the process,
4 I think that in research ethics, we've gotten so
5 focused on consent forms and, by implication, assent
6 forms that I think one of the mistakes that
7 investigators more often in IRBs make is that they
8 conflate giving kids information with obtaining their
9 assents. And one implication is that what often
10 happens is in studies where they're not getting
11 assent, the kid doesn't get information, assent to be
12 provided as part of a consent form or part of an
13 assent form.

14 And I think almost unconsciously sometimes
15 it ends up when you're waiving the requirement for us
16 and kids aren't getting the information, there's no
17 form. People don't have any other way of getting
18 information to them.

19 I think that's a big mistake. I think the
20 reason why you give information and the reason why you
21 ask them to make their own decisions are very
22 different and shouldn't be run together.

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1 Another thing that is not in the federal
2 regulations surprisingly but it is in some other
3 regulations is the notion of dissent. That's distinct
4 from assent. So there are some regulations that
5 happen. I just gave an example here from -- we were
6 in Tanzania last year discussing some people with
7 this.

8 So Tanzanian regulations say the
9 researchers must recognize when a child is very upset
10 by a procedure and accept that as genuine dissent from
11 their being involved.

12 Now, I suspect, though, somebody else
13 knows better than I do why this isn't a U.S.
14 regulation. One suspicion is that what was going on.
15 People thought, "Well, if you have an assent
16 requirement, then you don't need a dissent
17 requirement." Assent is required. Then dissent is an
18 objection. So it's not assent.

19 The problem is that it doesn't seem to
20 provide sufficient protection when the assent
21 requirement is waived. At least some people,
22 including myself, think there are good reasons to

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1 respect dissent, even when you don't require assent.
2 To do that, you need a separate requirement, which is
3 in the U.S. federal regulations.

4 But from what I know, I think respecting
5 dissent is important, but I think it is important also
6 to assess it. I don't think that requiring dissent
7 means that you knock a kid out of a study the first
8 time they get a little upset, they get nervous, or
9 they cry.

10 I think the first move is to assess, try
11 to address and remove the source of distress.
12 Sometimes just stopping for a minute, letting a kid
13 take a break, letting a kid decide when they're going
14 to have a procedure can make a big difference. I
15 think that ongoing more than minimal stress is a
16 reason to take kids out of research, even when they're
17 not capable of providing assent.

18 A topic I would suggest at the beginning,
19 I think there is a moderate debate, an interesting
20 debate, going on about this now, which is the question
21 of which kids are capable of assent. As I mentioned
22 in the beginning, the U.S. regulations, like most

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1 others, say you've got to get the assent of kids if
2 they're capable of giving assent. Then there's very
3 little guidelines for either investigators for IRBs in
4 terms of what constitutes capacity to give assent.

5 So here are the U.S. regulations. They
6 say in making this determination, you should look at
7 the age, maturity, and psychological state of the
8 children, obviously not very helpful. What about the
9 age? What about the maturity? What about the
10 psychological state our investigators supposed to be
11 looking at?

12 So there is more debate going on in this
13 recently. Surprisingly, there hasn't been that much,
14 but in the last couple of years, there has been a fair
15 amount. This is my attempt to try to cull out the
16 various arguments that people have been making.

17 So I think in order to figure out what the
18 right age is for assent to figure out the point at
19 which children are capable of giving assent, you've
20 got to ask fundamental, conceptual, theoretical, moral
21 questions about why is it that we're asking for the
22 assent of some kids but not other kids. We need to

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1 ask that fundamental question before you can figure
2 out which kids are capable and which kids aren't
3 capable of giving assent.

4 I think there are a couple of arguments,
5 bases for assents. So here are a couple of them.
6 I'll just go through these very quickly. I'll tell
7 you my preferred one without arguing for it. And then
8 we can discuss it if people want to.

9 So a lot of people that I talk to on this
10 just say it's respectful. In order to put a kid in
11 research, it's respectful to ask their decision.
12 Other people talk about respect for families. There's
13 this rule of sevens, which goes back at least 1,000
14 years, which I will talk to briefly.

15 The National Commission talked about two
16 things: respect for what they called developing
17 autonomy, respect for ability to understand. I don't
18 think any of those have been arguments for basis of
19 assent, ability to make their own decisions, which,
20 although I think it seems like the obvious right, I
21 think it's probably the right one.

22 So, first, respect for children, I think

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1 this is a powerful ones for IRBs, for investigators,
2 for parents. And the argument is basically that
3 getting people and allowing people to make their own
4 decisions is central to respecting that.

5 Then the problem with this argument is
6 just that respect as a general ethical requirement
7 doesn't have a lot of content. I think what respect
8 tells you is that you should treat people in the way
9 they deserve to be treated. And that just begs the
10 question about the age at which proper treatment of
11 kids involves asking them for their assent. I don't
12 think it gets you very far.

13 Another one is respect for the family
14 unit. People who focus on this I think draw different
15 conclusions. One conclusion you could draw is kids as
16 long as they are a part of families have parents,
17 parents made decisions for them. It's not up to the
18 kids. It should be up to the parents. I think that's
19 one way to look at it.

20 Another way to look at it is to say, well,
21 families have different processes. Maybe what we
22 should do is we should figure out what the average

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1 does, what a typical family does or maybe what we
2 should do, we should let parents do it in whatever way
3 they do.

4 So, one, I think it's not clear to me what
5 the implications of this are. Secondly, the fact that
6 families do it one way or another way isn't clear to
7 me as a compelling argument that that is the way we
8 should do it in the research projects.

9 Rule of sevens I mentioned briefly goes
10 back a long time. I think I've seen some people cite
11 this. And I think people who cite it actually cite it
12 inaccurately.

13 If you look back through history, what the
14 rule of sevens says, it comes with a legal doctrine
15 which says up until about the age of seven, kids can't
16 be held legally responsible. So that if they commit a
17 crime, you can't put somebody who is under seven in
18 jail. They're not responsible for what they do. From
19 7 to 14, the assumption is they are not rational, they
20 are not responsible, not able to make their own
21 decisions. It's not until 14 that the presumption
22 gets to their being rational.

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1 For some reason, people seem to conclude
2 from this that the age of seven is ripe, but the way I
3 understand, if you went with the rule of sevens, I
4 don't know that there is a reason to do it, but if you
5 did it, it seems like 14 is the right one.

6 I was giving this talk a year ago in
7 Cairo. Somebody at the end told me that a lot of the
8 sayings of Mohammed about the way you treat kids
9 actually tracks this breakdown of 7 and 14. So if
10 anybody is an historian and wants to track back, you
11 can find out about it.

12 The National Commission made two arguments
13 when they started giving suggestions and
14 recommendations that ended up being a basis for the
15 U.S. federal regulations. The first one was when they
16 called respect for developing autonomy.

17 So the idea here is that as kids get
18 older, they start being able to make certain decisions
19 for themselves. They get better at this. And the
20 assumption according to the National Commission was
21 that around seven is a time at which you should start
22 respecting this developing autonomy by giving kids

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1 their own decisions.

2 I don't see why seven is the right age,
3 but, again, all of these are going to be caricatures
4 of these views. So anybody who holds these views, I
5 apologize I'm not doing justice to any of them. I'm
6 just going to get through them right now.

7 Another one that the National Commission
8 gave was in terms of ability to understand. They
9 commissioned a couple of child psychologists to do
10 some studies on when kids understand what. And what
11 they found out is that by about the age of seven, kids
12 can understand certain aspects of the research
13 participation. Not surprisingly, for some reason, the
14 National Commission concluded from that that that was
15 the age at which you get kids' assent.

16 The problem is I don't see any special
17 reason why the information that kids learn at seven --
18 if you look at the data, there are lots of things kids
19 can understand before seven. Three-year-olds know
20 that needles hurt. They know what it is to stay
21 overnight someplace. And most of the data suggest
22 that seven to nine-year-olds have a very poor

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1 understanding of long-term risks. So it's again
2 unclear why the break hits at age seven.

3 This is just a brief summary of my own
4 literature, not anybody else's. I think that the only
5 compelling arguments I can think for having kids make
6 decisions, one is what is standardly called the
7 biomedics literature. The other is nonmedical.

8 You don't want to hurt kids. I think the
9 way that you incorporate that requirement isn't by
10 asset. I think it's by the assent requirement that I
11 mentioned earlier. If the research is causing kids
12 serious distress, they should plan on taking them out.

13 But I don't think that's a reason to get
14 the prospective assent to the research. The only good
15 reason I can come up with for doing that is that the
16 simple standards are bread and butter respect for
17 autonomy, which suggests that that is the basis that
18 you don't start getting assent from kids until they
19 are able to make these decisions.

20 So based on that conceptual analysis, I
21 went through the literature and tried to figure out
22 what that age might be. There is very little data.

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1 There's a little bit that has been done. The
2 literature that exists right now in my reading
3 suggests that at some time between about 12-15,
4 obviously with a great exception, -- some kids don't
5 get it by 15, there are really smart kids who get it
6 before 12 -- sometime in that age is when kids are
7 able to make these decisions for themselves.

8 That's it.

9 CHAIRMAN NELSON: Thank you.

10 So let's open up for questions and
11 discussion. Over to Dr. Kral.

12 COMMITTEE QUESTIONS OF CLARIFICATION
13 FOR SPEAKER

14 DR. KRAL: The way you pose the problems
15 here, it begs the question whether there should be
16 some kind of testing of the kid to decide whether they
17 on the Vineland scale, for example, have a social
18 intelligence or I didn't want to use the word
19 "intelligence" testing.

20 DR. WENDLER: Right. Yes. I think that
21 is a great question. So one of the responses that's a
22 perfectly right response to this talk, you might say,

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1 "Okay. Your argument is that you require assent to
2 the point at which the kids are able to make decisions
3 for themselves. Kids get to that point at varying
4 ages. So isn't the implication of your view what we
5 should do is we should do individual testing for every
6 single kid? You're at the point at which they are
7 able to make these decisions, require the consent of
8 those kids but not of the other ones."

9 I don't think that's a crazy way to go.
10 It's not the very that I nurse for a couple of
11 reasons. One, as far as I know, no one has yet come
12 up with such an instrument that's really going to
13 work, research-specific. This is the problem as
14 people are saying now. The buzz word is that consent
15 and assent are task-specific. So the fact that you
16 can understand one study doesn't mean you are going to
17 be able to understand another study.

18 The implication of that is that although
19 general kinds of tests may be helpful for knocking out
20 the extremes, they are not going to be very good
21 gauges of which kids really can understand this study
22 versus that study.

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1 So these are individualized tests people
2 are trying to work on. None of them are very good
3 right now. They take a lot of time. My view
4 basically is that you have a dilemma here. You could
5 put your resources in towards testing every kid or
6 not.

7 My view would be if you didn't have a
8 dissent requirement, so if you were going to say that
9 kids who can't pass this test, we're not going to pay
10 attention to what they say at all, then I think you
11 have a really strong reason to assess every individual
12 kid.

13 But I think if you have a dissent
14 requirement in place, then the analysis looks very
15 different. With a dissent requirement in place, I
16 think what you basically then do is what I think you
17 should do is pick an age toward the upward end of the
18 range, so 14 or 15. I think 14 is probably the right
19 age. You are going to miss a couple of kids. There
20 are going to be some kids who can really understand
21 and they're not respecting it. I think that would be
22 a big deal if you're not paying attention to what they

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1 say at all. But as long as you have assent
2 requirements in place, all they have to then do is
3 start objecting or asking questions. And you stop at
4 that point. And, in effect, by default, they end up
5 getting respected.

6 So I think that sticking with the upper as
7 a general default and then having a dissent
8 requirement in place is the way to go. Something
9 could come up. I have actually argued this in adult
10 research that we're really serious about informed
11 consent, we should try to develop instruments for
12 assessing every single person. In adult literature,
13 we have estimated that probably between 30 to 35
14 percent of people don't understand key elements of the
15 research and they participate. That would worry all
16 of us.

17 I think one way to do it is to try to
18 develop really simple tests. I don't think they're
19 there yet, but I think there is a possibility of doing
20 that. And I think if you came up with those
21 instructions, we should use them.

22 CHAIRMAN NELSON: Dr. Champagne?

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1 DR. CHAMPAGNE: The study that you had of
2 the Cohn study of the kids in the ER, these are
3 randomized for whether they were asked with a parent
4 in the room or without a family member in the room
5 versus whether they had a family member to be in the
6 room with them?

7 DR. WENDLER: My understanding is it
8 wasn't randomized. It's just as a default as the kids
9 came in. Some of them did, and some of them didn't.

10 In fact, I don't know if you could use --
11 I probably went too fast for you to see the numbers.
12 But the numbers don't even fully add up. They had an
13 n of 70, but my --

14 DR. CHAMPAGNE: Twenty-seven in each
15 group.

16 DR. WENDLER: Yes. It looks as though
17 they didn't come around to thinking about this
18 question until they had done the first bunch of kids.
19 That's only 54 that they made this assessment in.

20 So one thing to say about that is that
21 it's, at most, very, very preliminary data. I think
22 it is interesting data for these purposes, but it's

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1 not definitive at all.

2 DR. CHAMPAGNE: I guess it just concerns
3 me. I think kids who don't have other family around
4 them to make decisions, if you force them to make
5 decisions, they will make decisions. They may not
6 make the best decisions.

7 So I think when we're talking about things
8 where you have family involved, I mean, you're looking
9 at very different things there, I think. So I think
10 whether they have a parent in the room with them
11 versus whether they have an arret available to help
12 them make those dieticians is different cohorts.

13 DR. WENDLER: And you say whether
14 randomized, you've got to believe that kids who show
15 up to the ER with the parent versus kids who don't are
16 very different kids who have very different sorts of
17 lives. So the fact that they have answered
18 differently isn't surprising at all. I think it's
19 absolutely --

20 CHAIRMAN NELSON: Dr. Fost?

21 DR. FOST: Your last slide suggested that
22 children in general over 12 to 15 are capable of

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1 understanding things well enough. So with regard to
2 our task, let's say we have a 13/14-year-old child of
3 normal developmental maturity who has got severe
4 obesity who is at high risk for a comorbidity soon or
5 later, diabetes and so on, and there is a trial going
6 on which his parents want him to be in, he doesn't
7 want to be in.

8 Now, normally when we have children with
9 life-threatening diseases, Hodgkin's disease,
10 leukemia, and so on, and they don't want to receive
11 arduous treatments, you say, "Shut up," and they get
12 pity. And courts will generally order treatment over
13 a child's objections.

14 And that is, what is your view of what the
15 guidance should be with regard to obesity and clinical
16 trials?

17 DR. WENDLER: That's a great question. I
18 like the pediatricians shut out there. I think on
19 this point -- and I disagree with the regulations in a
20 lot of cases, but I think on this point they have got
21 it pretty much right.

22 I mean, I think the crucial question you

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1 first have to ask yourself is, one, is being in this
2 trial offering some very important potential medical
3 benefit to the kids, yes or no? If the answer is no,
4 that's important. Secondly, if it is, is that
5 potential medical benefit available outside of the
6 research context? And if it is, then I think that's
7 obviously more reason why you should respect your
8 assent and not try to force kids into this study.

9 The hard cases are cases where -- we'll
10 take some of these studies. Let's imagine that they
11 look really good. So do some clinical trials on it.
12 We think there is very important professional medical
13 benefit.

14 Can you imagine cases where you wouldn't
15 be available outside of the research context?

16 DR. FOST: Suppose it is. The child just
17 doesn't want any kind of surgery.

18 DR. WENDLER: Suppose it is available?
19 Well, I mean, for the research efforts, I think it's
20 easy. I really think that the research adds an
21 important additional ethical concern. I think that we
22 should try very, very hard not to force kids to be in

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1 research studies. I think there are good reasons for
2 that, not only for the kids but for the people who are
3 doing the research, the general public.

4 So my first response would be what you
5 should do is you should put that kid into a research
6 trial. Then you should take them to the clinic, and
7 you should have some very good, astute pediatrician
8 try to work with them and try to get them to do it.
9 Maybe if not, you force them into it. But I think you
10 can.

11 Once the kid is that age and they
12 understand, I think my suggestion is not of the
13 researchers, the study, not in a research context, do
14 it purely on clinical grounds. At least then
15 everybody can feel confident that if you're forcing
16 this kid, you're doing it for what everybody believes
17 is their interest.

18 CHAIRMAN NELSON: Before going to Jack,
19 practically speaking, in some settings, you need a
20 willing adolescent, even if it's a treatment that the
21 parent says ought to be done. So you end up, for
22 pragmatic reasons and ethical reasons, in sort of the

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1 same position as to whether you would honor assent or
2 not.

3 And one question, which you don't have to
4 answer now, would be given the previous presentation
5 about the willing participant and it's got to be the
6 kids' idea whether efficacy is going to track assent.

7 This is a question that we may discuss at length
8 tomorrow, which would be a pragmatic resolution to how
9 you would deal with this particular conflict.

10 I believe it is a question. It sort of
11 goes to Dr. Yanovski.

12 DR. YANOVSKI: So as someone who obtains
13 consent and seeks assent a lot in adolescents, in
14 younger children, it seems to me that we have to be
15 very careful when we talk about obesity therapies that
16 we differentiate them from therapy for cancers that
17 are going to kill people in the next three to six
18 months because they're not in general going to cause
19 mortality in the short term; rather, in the long term.

20 Because of that, most, almost all, of the
21 adolescents or even younger children who are suffering
22 even quite severe complications of weight will get to

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1 be at the age of consent before they would reach a
2 point where any of the surgeons in this room would
3 choose not to treat them.

4 And I think it's very important to realize
5 that we must respect the autonomy and potential
6 autonomy of those subjects in a way that may not be
7 certainly appropriate for conditions that are lethal
8 in the short term.

9 DR. WENDLER: Yes. I think that is a
10 really important point. So, one, you could postpone
11 in a way you can't with other conditions. And I
12 think, to go back to Norm's question, I think it makes
13 the question of whether this is an important medical
14 benefit to proffer the decision was make because
15 wasn't that applicant A versus next month, next year?

16 CHAIRMAN NELSON: Dr. Gorman?

17 MEMBER GORMAN: It seems in some way that
18 you've turned our paradigm of us seeking assent into
19 thinking that perhaps dissent is a more potent way of
20 determining a subject's willingness to participate in
21 this study. Do you have any thoughts on actively
22 seeking out dissent or do we have to wait until

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1 they're squealing?

2 DR. WENDLER: Here is a great question. I
3 don't know if I have a good answer. Here is my
4 general philosophy when people ask about how you
5 implement this in practice. I think what you should
6 do is let's say you have a kid that -- at least in my
7 view, I don't think we should be asking consent from
8 an eight-year-old.

9 What you should do, both in terms of
10 respect and also to the point that Skip is making,
11 just in terms of getting their cooperation, kid
12 understanding, kid not being afraid, I think you sit
13 them down. You try to explain as clearly as you can
14 in a way that that kid can understand what you're
15 proposing to do, what you are planning to do. And
16 then you say to them, "Okay. Here we go. And if at
17 any point you're confused, if at any point you have
18 any questions, if at any point you get scared, you
19 want us to stop, if there's anything you need, you
20 just let us know." And then you just start them off
21 basically keeping an eye on the kid.

22 And if the kid starts to complain, if the

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1 kid starts to have problems, as I mentioned, you stop
2 and you try to assess it. If not, you just keep on
3 going.

4 So it's sort of the here we go with an eye
5 on the kid and a good clinician who works well with
6 kids by their side to make sure things are going okay.

7 And maybe at least for younger kids, if you could do
8 it, have a parent around, the parent is a good
9 barometer of how well the kid is doing.

10 CHAIRMAN NELSON: I guess I would just
11 like to point out -- and I see some other hands --
12 that to the extent that one argues in favor of an
13 active solicitation of dissent versus a
14 developmentally adjusted process of assent, where
15 you're not looking for all the elements of informed
16 consent, it may end up that those two positions are
17 practically the same, you know, whether you view it as
18 asking them to say yes in a simple way, the way that
19 you stick them with a needle, versus all of the other
20 risk-benefit, et cetera, versus actively asking them
21 if they want to say no to you doing that.

22 So it may be it doesn't make a difference

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1 depending on how you implement either approach.

2 DR. WENDLER: I think asking sort of
3 prospectively for protestations is the equivalent of
4 asking for assent. I wouldn't do it that way. And I
5 think although in some cases it becomes pretty similar
6 practice, I think it's helpful to keep the sort of
7 conceptual grounding for the two practices. I think
8 that they have fundamentally different justification.

9 I think that the reason why you are
10 respecting dissent isn't something about autonomy.
11 When philosophers talk about autonomy, basically what
12 they mean is they mean allowing people to control the
13 course of their lives, allowing them to control what
14 they do and what they don't do.

15 I don't think that is what Myer is saying.

16 That's I don't think how you ground this. I think
17 what dissent is grounded in, dissent is grounded in
18 the context of non-prospective drug benefit research.

19 You shouldn't be causing harm to the kid. And you
20 shouldn't be causing more than minimal distress.

21 So the reason why I think you should
22 respect assent is because it's an indication that

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1 you're starting to cause harm to a kid, that they're
2 starting to suffer in one way or another.

3 And the idea is that how are the kids
4 going to know? Typically -- I mean, this isn't always
5 the case, but typically in a research setting, kids
6 are undergoing things that they are not that familiar
7 with in a setting.

8 If they are not familiar, I think the
9 appropriate thing isn't to ask them up front
10 prospectively, "How do you think this is going to
11 affect you?" It's "Here we go. And let us know how
12 it's affecting you as you go along."

13 MEMBER GORMAN: So your process would
14 really be in slightly different terminology, assent
15 with a very low threshold for voluntary withdrawal,
16 not to throw in any more terminology?

17 CHAIRMAN NELSON: Yes. I mean, Dave is
18 alluding to a debate that is going on. In many ways,
19 the debate is between him and I on precisely the point
20 you are raising. So we could go on if you'd like. Is
21 that fair?

22 Was there a hand over here? Dr. Lustig,

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1 go ahead.

2 DR. LUSTIG: I have two related questions.

3 The first question, obviously the obesity therapies
4 that are currently available and effective that we
5 know about from adults are clearly high-risk in terms
6 of implantable surgery, are you suggesting that we
7 should not be considering patients under 14 for those
8 procedures because of the issue of assent?

9 DR. WENDLER: Oh, sorry. No. For me,
10 right here all I am saying is picking a cutoff for
11 when you should acquire assets, I think the question
12 of who is appropriate for human study is a different
13 question. That for me is the question of the subject
14 selection that I talked about a little bit earlier.

15 I think if you end up concluding for one
16 of these studies, that the appropriate population to
17 do it in is five to eight-year-olds, then in my view,
18 you shouldn't be asking for the assent to those. But
19 you should be respecting their dissent.

20 DR. LUSTIG: Also part of that question
21 is, do you believe there is an age gradation based on
22 risk? In other words, let's say there was an obesity

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1 therapy that was minor risk. Could you potentially
2 offer that to kids at a lower age and still expect
3 appropriate assent?

4 DR. WENDLER: Yes. I think that's a great
5 question. As people know, there are sort of minimal
6 risk standards comparing risks to the risks of the
7 others' daily life.

8 We posted a paper recently on the actual
9 risks in daily life. And one of the things that you
10 find out for kids is that there is a big increase in
11 the risks that kids face once they become early
12 teenagers for two reasons mostly: because of playing
13 sports and because now they and their friends are
14 driving cars and kids are dangerous behind the wheel.

15 I think what that data raises, it raises
16 an interesting question of whether or not you should
17 have age-relative interpretations of minimal risk. If
18 it's true that the risks in the daily lives of older
19 kids is higher than the risk in the daily life of
20 younger kids, does that imply that you should allow
21 riskier non-beneficial research in older kids?

22 In the end, I think maybe the answer is

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1 yes. I mean, I think that the fact that they just
2 have higher risks in their daily life, I don't think
3 that's a good reason to expose them to greater risk.

4 But what is interesting is that increase
5 in the risks the kids get in daily life, when they get
6 into their early teens, that correlates with the point
7 at which most kids get to the point where they can
8 understand and make their own decisions.

9 I think that the fact that the kid can
10 understand and make those decisions, I think that is a
11 moral reason for considering allowing slightly higher
12 risk in older kids.

13 So, for instance, if you had a
14 hypothetical study where it's going to be risky, you
15 don't know if you could benefit the kids and you could
16 do it in anybody from 5 to 18, I would say I think
17 there is a good reason assuming risks are equivalent
18 and the value is equivalent across the populations. I
19 think the fact that the older kids can understand
20 better is a reason to do what the older kids and
21 exclude the younger kids, at least first.

22 CHAIRMAN NELSON: I've got Dr. Diekema,

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1 Dr. Newman, and Dr. Inge. And we do have a break
2 depending upon when you guys want it. Dr. Diekema?

3 DR. DIEKEMA: Hi, Dave. I wanted to
4 reiterate that I think it's important to distinguish
5 between dissent and assent. I actually chair an IRB
6 where we will oftentimes have a different age for
7 those two. We'll require assent in, say, kids above
8 10 or 12 but then tell the investigators, particularly
9 in a study that doesn't offer the prospect for direct
10 benefit, that dissent needs to be respected, with the
11 difference being in assent we see, in part, a vehicle
12 for communicating what is going to happen to a child.

13 My other comment is that I think it is
14 important to recognize that assent is different from
15 consent in a number of ways, but one important way I
16 think is that assent, really, we should be properly
17 focusing on what children care about, as opposed to a
18 comprehensive view of what the research project is
19 about.

20 Most eight-year-olds don't care if you're
21 going to bank their data, for example. I think it's
22 silly to ask them if that's okay. But they do care if

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1 you're going to put a needle in their arm. They do
2 care if you're going to do a surgical procedure.

3 So I think assent is sometimes interpreted
4 more broadly than it should be, that somehow the child
5 has to be told about the entire research study and
6 everything that's going to happen in that study;
7 whereas, in reality, I think the proper question is,
8 what does a ten-year-old care about? And that's what
9 you talk to them about.

10 CHAIRMAN NELSON: I see that as a comment.
11 So in the interest of time, unless David wants to
12 expand on it, we'll go to Dr. Newman and then we'll go
13 over to Dr. Kral.

14 DR. WENDLER: Go ahead.

15 MEMBER NEWMAN: I am trying to visualize
16 very, very concrete situations where the dissent
17 process would happen with the obesity devices. I'm
18 just thinking, you know, so here is a child. He's
19 scheduled for surgery. He's on the OR schedule. And
20 someone doesn't get the ID the first try.

21 I'm just trying to think, in what way
22 could you actually practically do that because, I

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1 mean, I've seen kids where it doesn't go well and then
2 they don't cooperate. And then they say, "No. I only
3 want her to do it, not him," I mean, that kind of
4 manipulation.

5 And then if this is a research thing and
6 as soon as the kid says, "Stop," you have to stop, how
7 does that play out or if they say, "No. I don't want
8 to do the follow-up visit. I'm sick of this. I don't
9 want to go there," but they're in research?

10 DR. WENDLER: Yes. That's a good
11 question. The first thing I think with surgery
12 trials, it's sometimes is hard to figure out how
13 you're going to -- as long as the anesthetist is doing
14 his job, it's hard to figure out maybe how you can get
15 dissent.

16 I think that is something that maybe
17 you're not going to get, but for me that is okay
18 because I said before the reason why I think you
19 should justify and the reason why you're getting
20 dissent and respecting dissent is the extent to which
21 it's an indication of the kid suffering. If the kid
22 is out and really isn't feeling anything, then the kid

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1 can't get dissent, but we also assume that the kid is
2 not suffering. So that I am not too worried about.

3 I just wanted to emphasize one point is I
4 think this is really important. I think respecting
5 dissent is very important, but I think it's also very
6 important not to confuse it with the first time the
7 kid objects, the first time you get any fighting, you
8 completely take the kid out of the study. I think
9 that's a mistake.

10 What you're trying to do is you're trying
11 to protect the kid from distress and harm. Sometimes
12 it turns out that the only way to do that is to take
13 the kid out of the study. In those cases, I think you
14 should take the kid out of the study.

15 A lot of cases, the kinds of cases that
16 you describe, there's other ways of doing it. You
17 know, if the kid really does want person A, rather
18 than person B, to sort of push the GERD or put their
19 central line in and you can do it, why not? And if
20 that's a way to address their distress, then I think
21 that's the appropriate response to take. And then you
22 just go ahead with them.

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1 CHAIRMAN NELSON: I think I had forgotten
2 to write down Dr. Kral's name when he raised his hand
3 earlier. So Drs. Kral, Inge, and then O'Fallon.

4 DR. KRAL: Every now and then, in despair
5 or otherwise, people have questioned there should be
6 some kind of competence testing before allowing
7 anybody to become a parent or procreate.

8 I would like to get back to the first
9 question, the same question I asked from the
10 beginning, but this time I'm going to ask about
11 parents. Should there be a testing of the parents'
12 ability to take upon them the responsibility in the
13 assent process of their offspring?

14 DR. WENDLER: I think that the way that we
15 do it with adults, whether they're making decisions
16 for themselves or they're making decisions for other
17 people, right now is we have a default that they're
18 competent and they are able to understand and make
19 decisions.

20 Now, I think that's the default we still
21 go with, but if we look at the literature, as I
22 mentioned, -- I had written on this a couple of times

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1 a couple of years back -- if we start looking at the
2 literature, there has now been a fair amount of
3 empirical data on understanding. They take people
4 into the study and they ask about the risks or they
5 ask about could they have said no.

6 You find out that understanding is a lot
7 -- it's not what you hope it is. It's a lot less. I
8 mean, I estimated at the time that 30 or 40 percent of
9 people don't understand at least one key element of
10 the research participation, like the risks in it, like
11 the fact that they could say no, things that I think
12 we all think are important.

13 I take it that what that suggests is that
14 this default is under pressure. I think we should. I
15 mean, I would advocate what we should try to -- we
16 don't have them right now. But what we should do is
17 we should try to develop very simple tests to assess
18 whether or not people understand. And if they do,
19 then we go ahead. And if they don't, then we stop.

20 What it shows is that the first time
21 around, people are impoverished. About two-thirds of
22 people will get it, but at least a third of people

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1 won't.

2 But if that third, if you just do a
3 remedial educational step with them, you find out you
4 identify what they didn't get. They didn't get that
5 they could say no. They didn't get the risk. They
6 didn't get this is a randomized study. If you then
7 focus on that aspect of the study, the vast majority
8 of them will get it just the second time around.

9 Just to give you one really quick example,
10 I sit on the IRB for the National Institute on Drug
11 Abuse in Baltimore. For every single one of the
12 studies, we require the investigators -- we sent out a
13 list of questions that they have to ask the subjects
14 and the subjects have to get right after the consent
15 process to go in the study. If they don't get any of
16 those right, they have to go back. They can't get an
17 anonymous study.

18 So I think we need to develop the method.
19 They're not there yet. But I think if we get the
20 right methods, it's not going to be that onerous of a
21 process. And I think it will make a difference.

22 CHAIRMAN NELSON: Dr. Inge?

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1 DR. INGE: Yes. I think, you know, that
2 it is important to point out and to see if we have
3 agreement that this is a treatment trial we're talking
4 about, but for an elective surgical procedure, that
5 there probably are chances for direct benefit for each
6 subject and that because we need the long-term
7 participation in agreement of the subject for what we
8 might consider optimal outcomes, that I just would ask
9 the question, is there a reason to or is there a
10 disadvantage to requiring assent at even the lowest
11 age at which you will be enrolling patients, so even
12 younger? If indeed the decision is made to have
13 younger patients participate in such a study, is there
14 a valid reason not to require or disadvantages to
15 requiring their assent?

16 I would advocate that that would be what
17 we should do.

18 DR. WENDLER: Right. Well, I would think
19 the obvious disadvantage is you might get a no. And
20 you might get a no based on somebody who doesn't
21 understand a study, doesn't understand what they're
22 saying no to.

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1 I guess maybe here is the fundamental
2 question. A couple of people have said before you
3 need the cooperation of these kids, but I don't think
4 that soliciting their assent and getting their
5 cooperation are the same thing.

6 I mean, I think you can solicit their
7 cooperation. You can give them information. You can
8 answer their questions. You can tell them what you
9 can do. I think you can do all of that for ethical
10 reasons. And when you have to get their compliance,
11 there's an added pragmatic scientific reason to do all
12 of that.

13 I think that is all very important. But
14 the question of assent is an additional question.
15 Then the question of whether or not you stop and you
16 say, "Okay. We explained it all to you. We're about
17 to go forward. You give us a thumbs up and a thumbs
18 down. And if you put your thumb down, we're not going
19 to go ahead."

20 Now, I think if you've got this sort of a
21 puzzle, you've got a medically beneficial study,
22 there's more reason to think the kid is going to say

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1 okay if they understand the benefit to them, but if
2 they say no, then there are more worries, particularly
3 if, as I had said earlier, I think one of the crucial
4 questions is whether or not the potential benefit they
5 can get is one they can get next month, as Jack was
6 saying, or whether or not this is an operation that is
7 also available outside of the research context.

8 I think that makes a big difference, as
9 the regulation states, so that you can only waive the
10 assent when it's both for important medical benefit
11 and that potential for medical benefit is not
12 available outside of the research products.

13 I know we're running out of time. Let me
14 give you one really quick example of a case that I saw
15 at the clinical center. This is a kid who had an
16 inborn immune deficiency, immune apheresis of the
17 kidney. They had to get some cells.

18 I think it's similar to surgery in the
19 sense that the kid had to cooperate. They had to roll
20 him down to the pheresis unit. He had to sit in the
21 chair. He had to let them put the blinds in. He had
22 to stay relatively stationary, couldn't pull the

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1 things out. He had to be there for about a half an
2 hour.

3 We had a couple of kids we did this with.

4 One of the kids, the assent was required. He was an
5 eight-year-old kid and explained the whole procedure,
6 explained the whole procedure to the kid. He said,
7 "Okay. All right.

8 "Have you got it? Do you understand? Do
9 you have any questions?

10 "No."

11 I was actually the consultant at the time.

12 And I said to the kid, I said, "Okay. Now it's up to
13 you. Do you want to do this?"

14 The kid said, "Absolutely not. I want to
15 play basketball with my friends in the hallway."

16 In that case, we didn't do that procedure.

17 But I don't think that -- I think it's clear, and I
18 should talk to his mother about this afterwards.

19 And we did it with his brother. His
20 brother was younger. So we didn't have to get the
21 assent of his brother afterwards. And his brother
22 went along fine.

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1 I think in these cases, again, the
2 difference between asking them to make an affirmative
3 agreement is very different than asking them to
4 cooperate. And I think it was clear in this
5 eight-year-old, who ended up saying no.

6 If we hadn't said, "It's up to you," if we
7 had just said, "This is what we're doing. We're going
8 along," everybody I talked to who knew this kid, had
9 been taking care of this kid for six years, his mom,
10 his older sister, were convinced he would have gone
11 along, he would have been fine, he would have
12 cooperated, he was a good kid. But we had to sap him,
13 "Is it okay with you?" Once he's given that choice,
14 he said no.

15 So I think there's a difference between
16 the two. I think if you do it right, you can solicit
17 cooperation. You can give kids the information you
18 want. You can reassure them in the way you need to
19 without asking them to make this prospective decision
20 about yes or no.

21 We sort of do this all the time, right?
22 Your significant other makes a decision about what

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1 you're going to do on Friday night or where you're
2 going to go to dinner. If you had a choice, you would
3 say no, right, but you will go along.

4 (Laughter.)

5 CHAIRMAN NELSON: We're going to have the
6 opportunity to dig into these issues when we tackle
7 the various questions tomorrow since they're all
8 wrapped up with each other. So I want to thank David
9 for his presentation and for stimulating conversation.
10 And we now have the opportunity to take what I hope
11 is only a ten-minute break.

12 (Whereupon, the foregoing matter went off
13 the record at 3:20 p.m. and went back on the record at
14 3:34 p.m.)

15 CHAIRMAN NELSON: We have two more
16 presentations to go before the end of the day. And I
17 might say I'm buying time as people get into their
18 seats.

19 About the two presentations, the panel and
20 those in the audience will note that we do not have
21 physical handouts of the slides. We will have those
22 available for tomorrow I am told. Part of the reason

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1 you don't have them now is we just got them. And
2 they're only in display format at the moment. But
3 we'll make sure we have copies of those for
4 distribution for reference if you so choose during our
5 discussions tomorrow.

6 So we have two presentations this
7 afternoon, one on conservative intervention and one on
8 surgical intervention, which one might think are two
9 ends of the poles, although I know many surgeons who
10 think often surgery might be the most conservative
11 approach. But we'll see how this dichotomy plays out,
12 at least in the presentations.

13 Our first presentation on conservative
14 intervention is Deanna Hoelscher from the University
15 of Texas in?

16 DR. HOELSCHER: Houston.

17 CHAIRMAN NELSON: Houston. There are many
18 Universities of Texas, but in Houston.

19 DR. HOELSCHER: Thank you. I would like
20 to thank you all for inviting me here.

21 CONSERVATIVE INTERVENTION

22 DR. HOELSCHER: I see a few friendly faces

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1 in the audience, most particularly Dr. Klish, whom I
2 spoke to when I was putting this presentation
3 together. We didn't realize we both were going to be
4 here at the same time. Thank you very much.

5 What I would like to do today in my talk
6 is just give you a brief definition of child
7 overweight. I know you have seen this before, but I
8 just want to kind of establish the parameters I am
9 using, give you some rationale on why we use
10 conservative approaches and then talk about different
11 methods.

12 I'm loosely basing that on least invasive
13 to most invasive, although I've got protein-sparing
14 modified fasts there, which is a little bit more
15 invasive than perhaps use of pharmacologic agents, and
16 then some conclusions and recommendations.

17 Just an overview of child overweight and
18 interventions. During my talk, I'm going to be using
19 the same nomenclature that I'm sure you've heard this
20 morning already to define overweight and at risk of
21 overweight with kids, the 95th percentile or greater
22 based on the CDC growth charts, and then between the

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1 85th and 95th percentile.

2 Just a few points for you to keep in mind.

3 The prevalence of overweight among children varies by
4 gender and race, ethnicity, and there are disparities
5 in the rates among different groups.

6 Another thing, another important feature
7 of this, is the prevalence of overweight is not a
8 normal distribution, but there is a skew towards
9 heavier weights.

10 We just collected data on over 23,000 kids
11 in Texas in schools. If you look at their heights,
12 you get this great normal distribution, just like in
13 textbooks. But you look at weight, that's not what
14 you see. And you see the tails skewing to the heavier
15 weights.

16 The primary aim of these overweight
17 interventions is energy balance. So you want to
18 balance energy in versus energy out. What there is is
19 very little data on preschool children. And because I
20 have such a short time for my presentation, what I'm
21 going to try and do is group these different types of
22 interventions together and kind of give you a broad

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1 overview and point out a couple of studies so you can
2 kind of see the literature that we're working with
3 here. In general, I'm not going to be talking about
4 preschool children because they're not highlighted in
5 most of this work.

6 And then, finally, practice is not
7 evidence-based in the strictest sense. And that
8 reason is because there is not enough data. As you
9 can see, we really are lacking in a lot of data about
10 conservative interventions.

11 We just did a review that looked back 20
12 years about interventions for treatment of childhood
13 obesity. And we came up with 44 studies that had done
14 that. So that's really kind of a small literature.

15 So how do children differ from adults?
16 You heard a little bit about that with some of the
17 other presentations, but I would like to point these
18 out again as they have implications for interventions.

19 One is there is reliance on parents as
20 gatekeepers for both food and physical activity. So
21 when you talk to the kids, you have to talk to the
22 parents as well in most cases.

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1 There's also consideration of growth and
2 development from a biological standpoint. And I'll
3 give you an example of that in just a moment. With
4 adults, you don't have to worry about them getting
5 taller, unfortunately.

6 There's cognitive and emotional
7 development that plays into this. One of the things
8 that we have just heard about since is at about the
9 age of 14. Well, about the age of 12 is when children
10 start to distinguish concrete abstract concepts from
11 concrete concepts. So that is a very important age
12 there. You've got to take that into account.

13 Another thing that is important with kid
14 sis their peer relationships, very important, more so
15 than in adults. The degree of overweight is different
16 in kids the way it is classified currently. And you
17 have heard a lot about that already.

18 Another thing about children is they have
19 a big social environment going on, which is the
20 schools, that we have the workplace, but the workplace
21 varies a lot more in adults than the school
22 environment does. And the kids interact within that.

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1 Also, when you're looking at interventions
2 for kids, you have to consider eating disorders,
3 development of eating disorders, disordered eating
4 patterns. And then there are critical periods of
5 adiposity increases, adiposity rebound in puberty or
6 two.

7 So if you look at the rationale for
8 conservative approaches to child overweight, the
9 traditional view has been that overweight in children
10 is benign or cosmetic and that kids will grow out of
11 it. So the treatment paradigm has been to keep the
12 weight stable so that the kids could grow into the
13 weight and that weight loss, if any, should be modest
14 and you should use diet together with physical
15 activity and behavioral counseling.

16 And if you look, what I have here -- let
17 me go back just a second. This is one of the CDC
18 growth charts. This is the height, and this is the
19 weight. So if you look along those percentiles, I
20 will be talking about that next.

21 What I have mapped here is I took the CDC
22 weight chart along the 75th percentile from age 6 and

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1 a half to 18 and a half. And I looked at the
2 difference in weight. This is in pounds each year.

3 So you can see from age 6 to 7, kids
4 depending on whether it's boys or girls gain from 6 to
5 7 pounds if they follow along that 85th percentile.
6 That's a one-year gain.

7 The reason why this is useful is for a
8 couple of reasons. One is you can see how growth
9 might assist you. Because these kids are gaining this
10 much weight and you can kind of equate five pounds to
11 one BMI unit, then you can see that if you can hold
12 the weight constant, that you can change BMI because
13 they're growing along with that. So that's one
14 concept you can look at.

15 Another thing, if you look at this, the
16 periods where you can have the most effect on a
17 treatment or prevention are when they're gaining the
18 most weight. So this tends to be right around puberty
19 here. The girls go through it first, and then the
20 boys go through it second, as you well know.

21 Then when you look at this, you say, well,
22 is there empirical evidence to back this up? Nancy

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1 Butte from the Children's Research Center and Ken
2 Ellis have a study ongoing. They looked at 337
3 Hispanic kids, and they followed them for a year.

4 They followed them, and they looked at
5 kids who were normal weight who remained normal weight
6 at the end of the year. They were normal weight.
7 They became overweight at the end of the year. And
8 then there were kids who were overweight and remained
9 overweight at the end of the year. And they looked at
10 how much weight they gained.

11 If you look at the red line here, these
12 are the kids that were normal weight at the beginning
13 of the year and at the end of the year. You can see
14 that that is within these growth parameters here.

15 The kids who were normal weight who became
16 overweight, they gained 15 pounds. This is a mean of
17 15 pounds. So you can see that's well above kind of
18 the growth trajectory there.

19 And the kids who were overweight and
20 remained overweight gained a mean of 16 pounds. So
21 you can see that that is outside of the normal growth
22 curve, at least this one, which is the 75th

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1 percentile.

2 Now, the current view on conservative
3 approaches for child overweight say that overweight in
4 children is associated with both morbidity and
5 mortality and that it leads to increased risk for
6 severe obesity in adulthood. And BMI tracks over
7 time. We've got data that show that pretty clearly.

8 With children extreme weights, growing
9 into weight is not an option. And I'll show you an
10 example of that in a second. So treatment paradigms
11 need to change to reflect that.

12 This is using some of that data from that
13 chart I showed you before. And if you look at it, you
14 have a boy. This is just looking at boys because the
15 boys and the girls are different. But if you have a
16 boy who is 6 and a half and if he weighs at the time
17 he's 6 and a half 115 pounds more than where the 75th
18 percentile is on the chart, chances are he will not
19 grow into it because chances are he will gain more
20 weight than that throughout time. You would want to
21 keep that 115 pounds constant if you wanted him to end
22 up at the 75th percentile when he was 18 years old.

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1 As you can see, you get to about 10.5. If
2 a child weighs 83 pounds over what the percentile is
3 on the growth chart, then chances are they will not
4 grow into this.

5 So this kind of gives you an idea of the
6 type of weights that we're talking about and what can
7 be achieved and what can't when you look at some of
8 the results obtained from these conservative
9 interventions.

10 One more thing. The determination of
11 energy intake in children, to lose weight, you have to
12 determine how much change you need in energy intake.
13 And with kids, you have to figure growth into the
14 equation, which can be difficult because they go
15 through different growth periods.

16 Estimates from Butte and Ellis, again,
17 from this same technical paper that they did show that
18 there is probably a deficit of about 300 calories a
19 day that you need to have to prevent further weight
20 gain in overweight children.

21 So 300 calories a day, just to let you
22 know, is about 2 12-ounce sweetened beverages. And

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1 it's equivalent to walking about about 60 to 120
2 minutes a day depending on the intensity.

3 Just an overview of behavior modification,
4 diet and physical activity programs is most diet and
5 physical activity programs, which I will talk about
6 now, generally have behavior modification components
7 in them. Most programs have all three. And when I
8 speak about physical activity, I am also talking about
9 sedentary activity, too, because a lot of times
10 they're seen as two different constructs, the time
11 kids spend in media use, computer time, TV time, and
12 then the time they spend actually being active. But
13 you kind of go about some of those interventions the
14 same way.

15 The other thing about a lot of these
16 programs is there is intensive parental involvement in
17 this. The studies to date have mostly been conducted
18 in clinic settings. There's a few that have been
19 conducted in schools. And I'll show you those.

20 For diet, when you look at diet as a
21 conservative intervention, as a definition, basically
22 what you're talking about is you're restricting food

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1 intake, either through a change in macronutrient
2 composition, if you change the fat or the carbohydrate
3 composition, or you're reducing energy intake.

4 The duration if you look at trials with
5 adolescents and children, it ranges from several weeks
6 to about three years. The maintenance of effects,
7 there's limited data. There have been very few
8 studies that have followed up over time.

9 The compliance varies among studies. Side
10 effects with a regular diet, like if you're put on a
11 stoplight diet, a traffic light diet, or following the
12 dietary guidelines, there's relatively few side
13 effects. With a protein-sparing modified fast, the
14 side effects can be more dangerous, can include
15 protein losses, hypokalemia, hypoglycemia, inadequate
16 calcium intake, and orthostatic hypotension.

17 The weight loss achieved with the
18 protein-sparing modified fast, you can get weight
19 losses of one to two kilograms, which is 2.2 to 4.2
20 pounds per week. And with diet alone, you can obtain
21 up to one kilogram per week. A lot of times that's
22 not consistent. You go through plateaus throughout

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1 that.

2 The pros of a diet approach, dietary
3 approach, is it's safe for most of the more moderate
4 diets. The cons are you need to get the parents
5 involved. That can also be a pro that you get the
6 parents involved in that as well.

7 They're costly. They're long-term.
8 There's limited data on effectiveness of diet by
9 itself. Usually diets paired with physical activity
10 is part of a behavioral program. And there are side
11 effects for a protein-sparing modified fast.

12 There are also some diets with altered
13 macronutrient content that people are looking at now,
14 but they have mainly been evaluated only in small
15 trials for limited periods of time. And I'll show you
16 an example of those.

17 One of the diets that is used most often
18 -- and you will see this come up with Lynn Epstein's
19 work -- is the stoplight or the traffic light diet.
20 And it uses a traffic light concept to characterize
21 foods. So gold foods or green foods are low-calorie,
22 high-fiber, no restriction foods. The yellow foods or

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1 amber foods, as they're known, they are essential
2 foods, but they have a higher nutrient density. And
3 so you eat those in moderation.

4 And then the red foods are foods to limit.

5 Generally in Epstein diets, they have been limited to
6 less than four servings. In other diets, they have
7 been more restrictive.

8 The energy goals tend to be about 900 to
9 1,300 calories per day. A lot of times
10 self-monitoring is involved, where they write
11 everything they eat and drink. That's a very
12 effective behavioral technique.

13 This guide has been adapted in various
14 forms. How it is written, it's pretty complicated,
15 but it has actually been used in many different
16 settings, a little bit more simplified. It also
17 follows the U.S. dietary guidelines, where
18 appropriate. So it's consistent with that.

19 One of the new promising directions looks
20 to be reduced carbohydrate or glycemic load diets.
21 There aren't a lot of studies that have looked at this
22 to date. A lot of these come from the work of David

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1 Ludwig.

2 They're smaller studies. The first one,
3 Kara Ebbeling study, was a randomized controlled trial
4 that involved 16 obese adolescents. Fourteen of them
5 finished the trial. And they got a difference of two
6 BMI units between the control group and the
7 intervention from. Now, again, this is a very small
8 group that we're looking at.

9 The Spieth, et al., study was a
10 retrospective cohort, which was looking at 107 obese
11 kids. They did a load glycemic index diet. Basically
12 what these are, they're diets that are limited in
13 sugared beverages and sweets. And they found a
14 difference of 1.12 BMI units, which is about 2.6
15 kilograms.

16 In summary, it looks like what these
17 studies are, they're relatively small. All the
18 evidence isn't in. They're very preliminary. But one
19 of the reasons they might work is they restrict
20 calories because you're eliminated sugared beverages,
21 sweets, things that kids eat a lot of and that they
22 tend to like to eat a lot of.

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1 The protein-sparing modified fast involves
2 about 1.2 to 2.2 grams of protein per ideal body
3 weight. For children, this usually involves a
4 hospital stay. And they need to be given vitamins and
5 minerals, potassium, and calcium along with this.
6 They need to have consistent monitoring of ketones as
7 well.

8 There's a gradual reintroduction of
9 carbohydrates. And this should be done as part of the
10 behavioral program. So they should be learning how to
11 eat in the real world as well as doing the
12 protein-sparing modified fast.

13 This is for a limited period of time. In
14 one study with 8 adolescents, they found a mean weight
15 loss of 13.5 kilograms over 5 weeks. But, as you can
16 see, it's a very small sample size. There was no
17 control. Five of those kids continued on for an
18 additional period of time and gradually lost up to I
19 think it was 30 kilograms over time. Two of those
20 maintained that over a year. Three of those gained
21 weight back. With the published trials, with
22 children, as you have seen, there are few subjects.

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1 There are no randomized control trials. There's
2 relatively little data on this.

3 With physical activity, sedentary
4 activity, interventions in children, what these are is
5 programs designed to promote adolescent weight loss by
6 increasing activity or decreasing sedentary behavior.

7 And the duration of treatment in trials has been 3
8 months to 54 weeks. A lot of them have been around
9 eight months. They generally tend to increase
10 physical activity from 30 to 60 minutes a day for 3 to
11 7 days a week.

12 The maintenance of effects, there's really
13 not a lot of data on this. The compliance, again, it
14 varies. The weight loss achieved, from these studies,
15 it's kind of difficult to quantify. And the reason
16 why most of these are done with exercise
17 physiologists. And they tend to look at change in
18 percent body fat. And there are significant changes
19 in percent body fat. It's kind of hard to equate
20 those to BMI or weight, as I have done with some of
21 the others.

22 The pros are that exercise is generally

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1 easier to maintain than diet over time, at least in
2 adults. And it builds on usual child activities. The
3 cons for these include safety issues, which can be a
4 concern; time and money if the parent is involved.

5 A lot of determinant studies show that the
6 parent needs to be involved. Some of our own work has
7 shown that girls who are involved in sports teams tend
8 to get more physical activity, but that involves a
9 parent getting involved again.

10 Sedentary activities are very
11 self-reinforcing. If any of you all have done video
12 games, you know that you never win the first time you
13 sit down, that you are always encouraged to go on to a
14 new level. So it's really hard to break away once you
15 get in to that.

16 Here are a few examples of physical
17 activity. Actually, these are both physical activity
18 interventions. A lot of these are out of Gutin's lab.

19 And both of these were looking at obese children.

20 The Owens study looked at 74 obese
21 children that were 7 to 11, so elementary school age.

22 They did four months of training. And the training

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1 consisted of 5 days, 40 minutes per day. And they
2 found significant decreases in visceral adipose tissue
3 and then total body fat mass over that time.

4 A more recent study, in 2002, looked at 80
5 obese adolescents. The obesity was classified by
6 tricep skin folds. These kids were 13 to 16 years
7 old. This was an 8-month, or school-long,
8 intervention, 5 days per week, 30 minutes per day.
9 And there were significant decreases in visceral
10 adipose tissue and percent body fat. They found no
11 differences between moderate and high-intensity
12 exercises.

13 A more recent publication by this group
14 shows that these effects are dose-dependent. So the
15 kids who participate more in the physical activity
16 program had better results as far as decreases in body
17 fat.

18 The third type of intervention,
19 conservative intervention, is the use of behavioral
20 modification. And here we're talking about behavioral
21 modification strategies and counseling techniques.
22 And so these involve goal setting, stimulus control.

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1 Motivational interviewing is used a lot now.
2 Self-monitoring is used. And modifying dietary
3 habits, physical activity patterns.

4 It is also used to address underlying
5 psychological issues related to food and physical
6 activity. The duration of treatment ranges all the
7 way from one session to three years. Most tend to be
8 about six months in length.

9 Maintenance of effects, this is the one
10 area where there has been relatively good follow-up.
11 And there has been some maintenance of effects,
12 particularly in some of Lynn Epstein's work. The
13 compliance, again, varies. And I'll talk a little bit
14 more about that later.

15 Side effects are few. The weight loss
16 achieved tends to be about 4 to 15 pounds overall if
17 you look at the whole range of studies done. It tends
18 to be safe. Again, another pro could be that the
19 parents get involved with this. You have to have the
20 parents involved.

21 The cons are that it's costly,
22 personnel-intensive. Results aren't consistent. And

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1 it's long-term. And it involves considerable family
2 involvement. So you're getting everybody involved
3 with this.

4 The most successful work in this field has
5 been done by Lynn Epstein. And as one example, if you
6 look across 4 RCTs that he did, there were 154
7 overweight kids ages 6 to 12.

8 In general, when you look at the
9 behavioral modification, just in the side on this, it
10 tends to be most of the data are for kids in
11 elementary school. So they tend to be 6 to 12 years
12 old. There's less data available on adolescents 13
13 and above and kind of the effects of behavioral
14 interventions on them.

15 In these, there was involvement of
16 parents. There was family counseling. And there were
17 different levels of family counseling. So in some
18 cases, both the parent and a child received an
19 intervention. In some cases, it was a non-specific
20 target.

21 With long-term effects, 30 percent of the
22 kids from these studies were no longer overweight

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1 after 10 years. And then 34 percent of them had a
2 decrease in percent overweight of at least 20 percent.

3 Another thing is when you looked at them
4 at five and ten years out, what was kind of
5 interesting is in some of the studies, both the
6 parents and the kids were targeted and the parents
7 lost weight.

8 The parents regained weight at five years.

9 The kids maintained their weight. So it looked like
10 these interventions were more effective for the kids
11 than they were for the parents and that maybe parental
12 monitoring wasn't the only way that they were -- they
13 were an important component but not the most important
14 component.

15 One of the criticisms of Epstein's work or
16 several of the criticisms have been that he focused on
17 a specialized population. So it's mostly a white
18 middle class population. He omitted anybody who had
19 psychological problems. A lot of his interventions
20 aren't very well described in the literature. And the
21 kids all had two parents at home. So it was kind of a
22 specialized population.

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1 One of the things when we were conducting
2 this review a while back was we looked at school-based
3 tertiary prevention studies, interventions, and you
4 can translate this to be treatment studies.

5 What we found, there were five that met
6 our criteria for this review. And when we looked at
7 them, we were kind of amazed because all of them
8 showed effects on percent overweight, percent Rohrer's
9 index, percent obesity index.

10 And one of the things that we found --
11 now, again, this is not an adequate body of literature
12 to make, to base a lot of evidence on, but it is
13 pretty promising when you look at it. Only one of
14 these was an RCT, though. So there really needs to be
15 more work in this area.

16 But if you look at it, if you think about
17 why they might have been successful, there are a
18 couple of reasons. One is most of these were done in
19 the school level. So there was peer support. So the
20 only way kids might have been pulled out, but the
21 whole school was getting some sort of intervention.
22 So it was framed within a broader social context

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1 there.

2 Another thing is there is a consistent
3 intervention effect because they were there at school
4 every day. So it was a place that you could reach
5 them.

6 Another type of intervention that maybe
7 shows a promising direction is weight loss camps.
8 Kirschenbaum and Craig are conducting three of these
9 camps. They're in North Carolina, California, and New
10 York. And they range from ages 10 to 23 depending on
11 which camp you're looking at. The camps include diet,
12 physical activity, behavioral therapy four times a
13 week, a family program. And then there is an
14 after-care program.

15 Now, one reason this is specific for kids
16 is most of us adults can't pack up and go to a camp
17 for an extended period of time, but they actually have
18 courses at some of these camps that the kids could
19 take courses along with that. And then there is peer
20 support because the other kids are overweight there as
21 well.

22 They have presented some preliminary

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1 results at NAASO. The preliminary results look very
2 promising. Now, it remains to see what happens when
3 these get into the published literature.

4 The final conservative intervention that I
5 will be talking about is the use of pharmacotherapy.
6 And that is the different kinds of drugs that are
7 used. It's actually a real short part of the
8 presentation because there aren't a lot of drugs that
9 are approved.

10 The duration of treatment in trials has
11 been from 3 months to 54 weeks. There's little data
12 on the maintenance of effects. Actually, this should
13 be attrition for Orlistat. In the Orlistat trial, the
14 attrition was 35 percent. Sixty-five percent remained
15 in the study. The side effects range from
16 hypertension to loose stools to risk of fat-soluble
17 vitamin-deficiency depending on which pharmacologic
18 agent you're using.

19 The weight losses, if you look at the
20 Orlistat study, there was a mean difference of 2.6
21 kilograms weight change between placebo and control.
22 And I'll talk a little bit more about that later. You

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1 can expect to see about a one to two-pound-per-week
2 loss in clinical practice.

3 The pros are there is consistent weight
4 loss, little parental involvement, and little
5 behavioral change necessary, although in most cases
6 these drugs have been tested in trials where
7 behavioral treatment was a necessary adjunct to the
8 pharmacologic treatment.

9 The long-term safety in children has not
10 necessarily been evaluated. And there are side
11 effects. There are other drugs currently proposed.
12 Some are being used in practice. One of them includes
13 metformin. There are others. Leptin is being looked
14 at.

15 Most pharmacologic regimes, as I said
16 before, work best in combination with behavioral,
17 diet, and physical activity changes. And that is true
18 in the adult literature as well.

19 These are the drugs currently approved for
20 treatment of obesity in adults and children in the
21 U.S. Actually, the only one that is approved for kids
22 is Orlistat, which is the last one. The two most

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1 important ones used are Sibutramine and Orlistat,
2 which are the last two. Sibutramine is an appetite
3 suppressant. And it works through the not adrenergic
4 and sertranergic pathways in the brain. Orlistat is a
5 gastrointestinal lipase inhibitor.

6 Orlistat, there was a randomized control
7 trial published in JAMA just this year. It was a
8 multi-center 54-week RCT. And, actually, the results
9 of this were released in 2003, which is why Orlistat
10 went on the market at that point in time.

11 It was a double-blind study. They looked
12 at kids with BMIs that were greater than 2 units above
13 the 95th percentile, 12 to 16 years old. They got a
14 120-milligram dose of Orlistat 3 times a day plus a
15 mildly hypocaloric diet, exercise, and behavioral
16 therapy. The parents also had to agree to participate
17 in this with the kids.

18 So the results at the end of the time were
19 a difference in placebo and control of 2.61 kilograms
20 after a year, which is about .66 BMI units. There was
21 35 percent attrition, as I said before. And the
22 compliance was actually pretty good. It was about 70

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1 percent of the kids taking the drugs.

2 With Sibutramine, there was a randomized
3 control trial published in JAMA a couple of years ago.

4 There have been a couple of other trials since then.

5 Again, the other trials have been relatively smaller
6 trials. This was with 82 kids between 13 and 17 years
7 of age for 6 months. And then they got an open label
8 for an additional six months. This was done within
9 the context of a family-based behavioral treatment
10 program.

11 So you had the control with the behavioral
12 treatment plus placebo versus the behavioral treatment
13 versus Sibutramine. And there was a difference of 4.6
14 kilograms between the groups. And that was after six
15 months. That difference was not as large after 12
16 months, after the open label part.

17 So, in conclusion, there are limited data
18 right now on obesity treatment and our prevention
19 studies conducted with preschool kids. Pharmacologic
20 treatment has been evaluated on adolescents only, age
21 12 and older. So we have no data on elementary school
22 kids.

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1 Behavioral modification programs that
2 target diet and physical activity have been evaluated
3 and are effective in children younger than 12. The
4 evidence there is pretty good, but you need intensive
5 family involvement along with that.

6 Increases in physical activity and
7 decreases in sedentary activity are promising
8 intervention strategies. One of the problems with
9 that is if you have kids who are too large, it's
10 difficult for them to move in the first place. So
11 they have to be at a point where they can move. And
12 preferably you would want them with a group of peers
13 when they're engaged in physical activity
14 intervention.

15 Children with extreme BMI weight or that
16 have associated morbidity may need to engage in more
17 aggressive interventions than those presented here.
18 You have seen the data on how much weight kids gain
19 from year to year. You have seen what the
20 conservative interventions do.

21 So, for example, the other day we're out
22 measuring kids in Texas. And there was a girl who was

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1 10 years old who was 115 kilograms, or 250 pounds. At
2 that point you're not going to grow into the weight,
3 and it's hard to begin some of these other
4 interventions.

5 Currently conservative interventions are
6 not complemented by a supported environment for food
7 availability and physical activity in most schools and
8 communities.

9 So you might have a great program. The
10 parents might be very supportive. But then the kid
11 has to go out and live in the real world and real
12 world that's not often supportive of the changes that
13 they need to make and the decisions they have to make
14 as well.

15 I would like to acknowledge some of my
16 colleagues who helped with this presentation and
17 offered some consultation, which include Dr. Klish and
18 some colleagues from the Children's Nutrition Research
19 Center at Baylor College of Medicine.

20 Thank you very much.

21 CHAIRMAN NELSON: Thank you.

22 We do have some time for clarifying

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1 questions. Dr. Yanovski?

2 DR. YANOVSKI: Just a couple of questions.

3 So my read of Epstein's work, including the ten-year
4 follow-on data, are that, indeed, he reports that
5 maybe 30 percent are no longer overweight.

6 DR. HOELSCHER: Right.

7 DR. YANOVSKI: But he also reports that 50
8 percent of those children have not really lost at all
9 in their relative BMI percentile or however he
10 expresses it.

11 DR. HOELSCHER: Right.

12 DR. YANOVSKI: Would you say that is
13 correct?

14 DR. HOELSCHER: Yes, yes.

15 DR. YANOVSKI: So it's sort of a half
16 empty and half full glass that those studies can be
17 looked at as either partially successful or really at
18 least in half the time not even successful for those 8
19 to 12-year-olds that he studies with intact families,
20 high SES, the most advantageous race, and so forth.

21 DR. HOELSCHER: No. You are absolutely
22 right. I think my take on it is from what we have

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1 seen to date, that is the most effective. But even
2 that is not maybe what we would like to see in terms
3 of effectiveness. You are absolutely right.

4 DR. YANOVSKI: The second question is, at
5 least if I recall correctly, Figueroa published a
6 randomized control trial of low-fat diet versus a very
7 low-calorie diet and found that, although in the short
8 term weight losses were greater by -- it's either a
9 year or maybe it's a year and a half. The weights
10 were exactly the same. And, if anything, the low-fat
11 group had done slightly better. Am I remembering
12 correctly?

13 DR. HOELSCHER: Yes, yes. I didn't
14 include that in this.

15 DR. YANOVSKI: So I think there is an RCT
16 in the LCTs.

17 DR. HOELSCHER: Yes, you're right. Sorry.

18 DR. YANOVSKI: And the last thing is I
19 believe that Berkowitz, et al., at the last NAASO
20 meeting released data from a multi-center Sibutramine
21 study. Did you have a chance to find out about that?

22 DR. HOELSCHER: I didn't see that at

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1 NAASO.

2 DR. YANOVSKI: Yes. He presented the data
3 a couple of places over the last year; again, a large
4 multi-center study, finding essentially the same
5 results as in the single-arm study, single-site study;
6 in fact, large differences. But also there still
7 continued concerns about pulse rates not really coming
8 down and blood pressure not really coming down in
9 proportion to the weight loss.

10 But I think it's important that none of
11 these therapies are without potential harm.

12 DR. HOELSCHER: Right. And I didn't
13 mention but in the Sibutramine trial, there were a lot
14 of kids that were discontinued or they had to decrease
15 the meds because they had side effects.

16 DR. YANOVSKI: And I guess one last thing,
17 Gutin stated, if I recall also correctly, that since
18 he stopped the exercise intervention, which is really
19 very intense, pretty much all of the advantages go
20 away from the exercise.

21 DR. HOELSCHER: The cardiovascular, yes.

22 CHAIRMAN NELSON: Drs. Klish, Lustig, and

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1 then Inge.

2 DR. KLISH: Deanna, when we talked -- and
3 I didn't bring this up. Perhaps you can answer it
4 now. I'm not aware of any studies that show that
5 significant weight loss in children that are
6 overweight actually interferes with linear growth as
7 they're losing weight. Did you run into any studies
8 that would imply that? I think it may come up in
9 discussion sometime tomorrow about rapid weight loss
10 and linear growth.

11 DR. HOELSCHER: No. Even the
12 protein-sparing modified fast, the linear growth was
13 not affected in those studies. In the pharmacologic
14 agents, it didn't show it. In Epstein's work, it
15 didn't show that that was affected. In some of the
16 prevention studies, it wasn't shown. Yes, you're
17 right.

18 DR. KLISH: Thanks.

19 CHAIRMAN NELSON: Dr. Lustig?

20 DR. LUSTIG: Yes, a comment and a
21 question. One, the comment is that there was a paper
22 that was released earlier this year from Sao Paulo,

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1 Brazil on Sibutramine, where they used a lower dose,
2 got equal efficacy to Berkowitz without the
3 hypertension tachycardia problem. And there were no
4 --

5 DR. HOELSCHER: That was the 60 --

6 DR. LUSTIG: Sixty adolescents, correct.

7 DR. HOELSCHER: -- kids in that study,
8 yes.

9 DR. LUSTIG: So there may be a dose effect
10 that may be important there.

11 My other question was, do you have any
12 data on predictors of response? In other words, is
13 there any information out there as to who benefits
14 from what?

15 DR. HOELSCHER: There are some studies
16 that have assessed readiness to change. And I didn't
17 mention that in here. I haven't seen a lot. In the
18 behavioral literature, a lot of times we do stages of
19 change, where we look at how ready are they to change.

20 I know that is being used a lot in
21 clinical practice. There may be a study out that's
22 done with weight loss. I'm not familiar with it. I

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1 know it's been done in adults. I don't know so much
2 about the application in kids. But I know in behavior
3 literature, we look at readiness to change, the stages
4 of change, pre-contemplation, contemplation,
5 preparation, and so on.

6 Do you know of some? Are there some?

7 DR. LUSTIG: I was thinking more about
8 biochemical variables.

9 DR. HOELSCHER: Oh, yes. You know, when
10 you look at the studies, it seems that the kids that
11 are at the lower -- they do stratify them. I can't
12 tell you right off the top of my head who and which
13 strata respond better. Someone else probably knows
14 that better than I do here.

15 DR. LUSTIG: I assume the readiness to
16 change translates roughly to the kids' idea in the
17 presentation we heard in the public session. It's got
18 to be the kids' idea. Is that a fair statement of
19 readiness to change in preparation for change?

20 DR. HOELSCHER: Yes. The way we assess it
21 in a behavioral manner is, you know, are you ready to
22 make a change within a certain time period, within the

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1 next six months, within the next three months. So the
2 child would say yes.

3 CHAIRMAN NELSON: Dr. Inge?

4 DR. INGE: I think anecdotally many of the
5 investigators and researchers in pediatric weight loss
6 would admit that the extremely obese population of,
7 say, children or adolescents represented a somewhat
8 different population in terms of their treatment
9 outcomes.

10 Do you have any evidence, really, or any
11 data which you have run across that specifically looks
12 at that group either in a primary study population or
13 as a subgroup analyzed separately to look for
14 treatment effects for behavioral therapy?

15 DR. HOELSCHER: Actually, that's a good
16 question because a lot of times they limit the people
17 who are in these studies. For example, the drug
18 studies, I mean, based on the data we saw earlier,
19 they stop at an upper BMI of 44, which, as we have
20 seen, it kind of goes on past that. And that's very
21 large. But even in some of these behavioral studies
22 that went back, they kind of truncated the top as far

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1 as the super obese that you might be referring to.

2 CHAIRMAN NELSON: Dr. Yanovski?

3 MEMBER YANOVSKI: I think that there might
4 be two groups that would be relevant for Tom's point.

5 I was actually going to ask pretty much the same
6 question with a twist. VLCDs have been used with kids
7 who have been quite heavy. And so that might be more
8 relevant in terms of their outcome. Unfortunately,
9 it's not all that good after a year. And then, you
10 know, we published an open label study with Orlistat
11 with kids whose average BMI was 45 kilograms per
12 meter².

13 But more to the point is are there any of
14 these studies who have combined not only severe
15 overweight but with complications of weight, which is
16 the group that I think maybe that would be proposed to
17 be offered, these kinds of medical devices and
18 surgery?

19 Our Orlistat study did that, but it's an
20 open label study and shouldn't really be mentioned.
21 But do you know of any others?

22 DR. HOELSCHER: Most of these, I don't

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1 recall that they had, you know, that that wasn't an
2 endpoint or they weren't really looking at -- I think
3 what's important to remember here is this child
4 overweight is relatively recent.

5 And we didn't even classify it, really,
6 until 2000. So when you look back, you have to kind
7 of interpret how they classified it. I mean, we had
8 it classified, but it wasn't as standardized as it is
9 now.

10 And so I think people weren't necessarily
11 looking for complications so much in some of what has
12 been published to date. So I am sure there are trials
13 ongoing.

14 I know there are several type II. I'm
15 more familiar with the prevention trials, actually,
16 than the treatment trials, but I know that those look
17 at cardiovascular risk factors. But I'm not aware of
18 any of these because Epstein's really didn't look at
19 that. That wasn't the primary focus.

20 Southern's work, Gutin's work, I think
21 they really didn't know.

22 CHAIRMAN NELSON: Dr. Fant and then Dr.

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1 Botkin.

2 MEMBER FANT: Yes. This is a spinoff from
3 Dr. Lustig's question. As we think about surgical
4 interventions over the next couple of days and the
5 requirement, the general requirement that the kids
6 failed more conventional, conservative approaches to
7 managing the weight, is the data robust enough or do
8 you have any feeling about how that should be defined
9 in a way that is meaningful?

10 All of the approaches that you talk about,
11 one is as good as the other or should there be a more
12 standardized process that they go through as they
13 march toward surgical intervention or do we just not
14 know enough to say, "Well, as long as they make a good
15 faith attempt to do one or two that are available,
16 then that is good enough"?

17 DR. HOELSCHER: When you said that, what I
18 thought of was Bray's algorithm for treatment. And I
19 know that the Texas Pediatric Association has an
20 algorithm for treatment that has you go through
21 behavioral therapy for so long, assess their
22 readiness. If they're ready, you wait. At a certain

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1 point, you add pharmacologic treatment. At a certain
2 point, then you consider surgery.

3 So it's an algorithm that kind of looks at
4 how well they do at a certain point. And it's a
5 certain flowchart. So there is a certain pathway that
6 you go down.

7 And I don't know. Dr. Klish, you might
8 want to talk more about that. That might be useful
9 for you to look at because I think it's incorporated,
10 both evidence-based medicine as well as perhaps
11 clinical experience, which at this point is the state
12 of the art, I think.

13 MEMBER FANT: Are we learning anything
14 about which kids are likely to benefit or which kids
15 are likely to fail based on certain characteristics or
16 are things at the state where we just need to see how
17 they do as they go through this process?

18 DR. HOELSCHER: I don't know a lot of
19 literature that is doing that. I mean, this last
20 study I was talking about is even -- well, one of the
21 studies I was talking about, it was a Yan study with
22 Gutin where he was looking at the kids who

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1 participated, had different levels of participation in
2 the physical activity and there was a dose-dependent
3 effect.

4 You know, even those were just kind of --
5 a lot of people do the before and after outcomes and
6 don't necessarily tease it out to see what are the
7 determinants, kind of the post hoc analyses that you
8 need to do to follow that up.

9 So I'm not aware of a lot of that work
10 being done right now and who is the best candidate.
11 How can you assess them? Some of the best work
12 actually might be done in hospitals right now, but
13 it's not published. So I don't know unless anybody
14 else has.

15 CHAIRMAN NELSON: Well, we may if we
16 explore that question in any depth start answering the
17 questions we're going to discuss in detail tomorrow.
18 So I'm not sure how much we need to go further on this
19 unless, Dr. Klish, you have a quick question.

20 DR. KLISH: Well, I was just going to
21 comment. I think within those of us who treat obesity
22 medically, there is a submerging feeling that obesity

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1 does have phenotypes and does have markers that allow
2 us to perhaps distinguish ahead of time which kids
3 might be more successful and which aren't two
4 psychological markers.

5 I know right off the top of my head, in
6 our experience, angry kids tend to do better in
7 medical management, behavioral management, than those
8 that have an internal locus of control, you know, the
9 ones that feel responsible for themselves. And those
10 are markers of success.

11 CHAIRMAN NELSON: Let me go to Dr. Botkin
12 and hopefully to our next and last presentation.

13 DR. BOTKIN: Two questions. I wonder if
14 there is a period of time that you would say
15 conservative measures have to sort of run their
16 course. In other words, how long would you enroll a
17 child in a conservative measure or approach before you
18 would determine that it was ineffective for that
19 child? Is there such a time period that you think is
20 reasonable?

21 And then, secondly, have folks used any
22 quality of life measures in this domain with

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1 conservative measures that have been reported?

2 DR. HOELSCHER: I know there are some
3 studies that have done that. I'm not real familiar
4 with that aspect of it. As far as the time period, I
5 would say based on most of the studies, it looks like
6 six months is a good time period at which you should
7 see an effect. And if you don't see an effect after
8 six months, you probably need to change course.

9 A lot of these studies have been done six
10 to eight months when you look across the gamut of
11 them. So that should be enough time to see an effect.

12 In some of them, you will see an effect in three to
13 four months, but six months is probably a better time
14 frame, I would think.

15 CHAIRMAN NELSON: Thank you.

16 DR. HOELSCHER: Thank you.

17 CHAIRMAN NELSON: And thank you for the
18 presentation and the answers.

19 So we have one more presentation and
20 discussion and questions before the end of the day,
21 which has been a long day. And that's Dr. Victor
22 Garcia from the University of Cincinnati, who is going

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1 to be speaking to us on surgical intervention
2 including devices, and who is using his own laptop.
3 And we just need to switch over to the technology.

4 Go ahead.

5 DR. GARCIA: Thank you for the opportunity
6 and for the invitation to discuss surgical
7 intervention as well as devices in addressing
8 adolescent obesity.

9 SURGICAL INTERVENTION INCLUDING DEVICES

10 DR. GARCIA: My charge as I was directed
11 was to review the various procedures and relevant
12 anatomy, the assumption being that there were many
13 members in the audience who were not familiar with the
14 surgical procedures. I understand, though, that you
15 have already had a discussion or a display of the
16 LAP-BAND. So in the course of my presentation, I
17 won't dwell on that.

18 I will take the time that is allotted to
19 me to go over briefly the outcomes and allow
20 opportunities for questions and specifically focus on
21 the safety of bariatric procedures as well as the
22 effectiveness. And in discussing these procedures, I

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1 am going to be somewhat all-encompassing in talking
2 not only about the most common ones but also the
3 devices that are available and in use not here
4 necessarily but throughout Europe and Australia and
5 Latin America.

6 I'm also going to pursue the advantages as
7 I view it as far as doing bariatric surgery in
8 adolescents and then, finally, give you somewhat of a
9 personal note but also somewhat justified by the
10 literature out there as far as what my concerns and
11 issues are about doing bariatric surgery in this
12 population.

13 For purposes of discussion as far as the
14 surgical procedures that are available, there is a
15 plethora of them, not all of them as effective as the
16 other, but I think that in most instances, the
17 surgical procedures will restrict caloric intake
18 and/or increase malabsorption.

19 If we go, then, with the first or the most
20 severe as far as the malabsorptive procedures, the two
21 that are in existence and are used some more so than
22 other are the biliary pancreatic diversion, with or

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1 without duodenal switch. And then there is the distal
2 roux-en-y gastric bypass.

3 We then I think logically would look at
4 truly restrictive procedures. And the first one that
5 was developed was the vertical band or gastroplasty.
6 There was then the introduction of the gastric band
7 and then with the use of laparoscopy and adjustable
8 gastric band.

9 And then recently because of interest in
10 trying to decrease their attendant risk in operating
11 on super obese patients, there has been, then, an
12 interest in sleeve gastrectomy, recognizing that it
13 really only offers at least just temporary weight
14 loss.

15 And then there are the more common
16 procedures. Certainly the one that is most commonly
17 done here in the United States, it's a combination of
18 the restrictive and malabsorptive. And that's the
19 roux-en-y gastric bypass.

20 There are two other procedures that are
21 performed throughout Europe, Italy, for example. One
22 is the intragastric balloon. And the other one is the

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1 gastric stimulator, the implantable gastric
2 stimulator. In both these instances, the morbidity
3 and mortality is considerably lower than with the more
4 invasive procedures, but as you will see in the course
5 of this presentation, with the lower morbidity, lower
6 risk, the excess weight loss and the durability of
7 that weight loss are somewhat limited.

8 Let's talk in a little bit more detail
9 about the vertical band, the gastroplasty. There are
10 those proponents of it who feel that this is actually
11 quite effective. It certainly does not have the
12 micronutrient deficiencies that one sees with the
13 biliary pancreatic diversion or with the roux-en-y
14 gastric bypass.

15 But, as one recognized quite readily,
16 while the weight loss was quite admirable for the
17 first year or so, there was regain. And one found
18 also that, particularly for patients who tended to eat
19 high caloric foods, one could easily bypass the effect
20 of the rather small gastric pouch as well as the
21 outlay. The other finding with time is that this
22 outlet would dilate again, allowing the individual to

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1 eat quite a bit.

2 The sleeve gastrectomy we touched on.
3 It's resection of a good portion of the stomach. It
4 does result in weight loss, again weight loss with a
5 lower morbidity and mortality. As a matter of fact,
6 in those who had the most experience with it, the
7 mortality is zero. The complication rate was also
8 relatively low.

9 And then we have the adjustable gastric
10 band. The way this mechanism works, then, as I think
11 you have already been told, is it creates a small
12 pouch through which there is a limited amount of food
13 intake and is tight. The mechanism of this, we are
14 still open for discussion. It's of interest that,
15 despite I think significant weight loss, that there is
16 increase in relin levels, as opposed to with the
17 gastric bypass.

18 The malabsorptive procedures are really
19 the distal gastric bypass as well as the biliary
20 pancreatic or duodenal switch. This procedure as well
21 as the distal gastric bypass are associated with such
22 significant nutritional deficiencies that I don't

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1 think that they are appropriate for discussion for the
2 adolescent patient population.

3 However, the biliary pancreatic or
4 duodenal switch is clearly the gold standard in the
5 sense that it has the best weight loss in the sense of
6 70 to 80 percent depending on the series that you
7 read. Again, the complication rate makes it not
8 suitable for the adolescent.

9 Let's very briefly talk so that we're I
10 think complete in our discussion about these devices
11 about the intragastric balloon as well as the
12 implantable gastric stimulator.

13 There have been two consecutive studies
14 done here in the United States looking at this device.

15 Again, as one would imagine, just with simply putting
16 a device or wires on the stomach, the complication
17 rate is actually very, very low. But, as one would
18 imagine, the excess weight loss is mild to moderate in
19 the sense of 23. With a sort of enhanced screening,
20 that excess weight loss in this study was increased to
21 40 percent.

22 Well, then there is this phenomenon of

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1 putting in a balloon endoscopically. One inflates
2 this with about 500 to 700 cc of saline. It dwells in
3 the stomach. And, again, one can enjoy some decrease
4 both in BMI as far as weight, but, again, the weight
5 loss is moderate.

6 There are some studies, case reports, that
7 suggest that with the retrieval of this device, that
8 the weight loss is sustained, but the vast majority of
9 patients who have this taken out regain their weight.

10 The most common procedures, then, that are
11 available to us in the armamentarium are really the
12 two. The biliary pancreatic or duodenal switch, as I
13 mentioned, is not really suitable for adolescents,
14 though it is considered a procedure for the super
15 super obese. Individuals who with this procedure in
16 its standard form may not achieve the weight loss that
17 they would desire.

18 So we have, then, the roux-en-y gastric
19 bypass. There are a number of approaches. We'll
20 discuss, then, both the open approach and the
21 laparoscopic approach. And you'll see that the weight
22 loss as well as the complication rates are comparable,

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1 despite using the laparoscopic approach. And we'll
2 also discuss, then, the adjustable gastric band.

3 I will not, then, since you have already
4 had a discussion as far as the gastric band dwell on
5 the video, but I did think it would be worthwhile for
6 this audience, particularly those who are
7 non-surgeons, to appreciate, then, the complexity of
8 this procedure.

9 Although it is quite effective as far as
10 achieving weight loss, it is one that in the scale of
11 zero to 10 with 10 being the highest degree of
12 difficulty to perform the operation laparoscopically,
13 experts in this field feel that this is something on
14 the order of about 9.5 in difficulty.

15 I emphasize this because it will touch on
16 some of my concerns about bariatric surgical
17 procedures, who should be doing them and in what
18 context.

19 But in performing this operation, one
20 would vary the roux-en-y. The longer this limb, then
21 the greater the risk of nutrient deficiencies. That
22 having been stated, as long as this limb is in the

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1 order of 75 to 150 centimeters, at least in the
2 studies that are published to date, one does not see
3 the significant protein/calorie malnutrition.

4 However, because one bypasses, then, a
5 segment of the jejunum as well as the duodenum, there
6 is still fairly common iron deficiency anemia as well
7 as impaired calcium and a number of other
8 micronutrients.

9 As this procedure is being performed more
10 and more frequently, one sees increasing reports of
11 the consequences of these micro deficiencies via-a-vis
12 beri-beri, encephalopathy, increased bone turnover,
13 osteoporosis. I suspect the list will go on and on.

14 As a result of this approach, one then
15 makes the stomach the size of a football into about a
16 20 to 30 cc pouch. An additional component of this
17 procedure is to narrow the connection between the neo
18 stomach and the small intestine so that the stomach or
19 the food can empty at a much slower rate. Because of
20 the smaller stomach, the patient then gets full much
21 more quickly.

22 Of interest is that, even though we were

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1 all excited with the fact that grunion levels had
2 decreased, perhaps this was contributed to the
3 mechanism subsequent to these, there are some
4 conflicting reports that the sense of satiety does not
5 have any relationship to grunion levels, either pre or
6 post.

7 Here's the completed operation with these,
8 now stomach as well as the intestine. We won't dwell
9 on the LAP-BAND, but I did want to then direct your
10 attention to the next question is what is the outcome?
11 What is the comparative effect of these procedures?

12 This is the study from the Swedish obese
13 subjects study published in the New England Journal of
14 Medicine. It compares for you, then, a controlled
15 population that received considerable therapy as far
16 as the management of obesity as well as a group of
17 patients who underwent an adjustable band as well as
18 vertical banded gastroplasty and the gastric bypass.

19 And what I'll draw your attention to is
20 the fact that while this study is one of the longest
21 studies, it has the advantage of having the control
22 group, be it a randomized control group, it does then

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1 demonstrate to us the findings that are I think
2 duplicated in a number of other studies published
3 throughout the world as well as here in the United
4 States. And that is that the gastric bypass procedure
5 offers us a much more dramatic, much more rapid, and
6 much more sustained weight loss compared to the purely
7 restrictive procedures.

8 Nonetheless, with that weight loss in this
9 study, one found that there was not only resolution of
10 comorbidities, which we in our own experience at
11 Cincinnati Children's comprehensive weight management
12 program have also seen, but of interest is that when
13 compared to the control group, there was a lower
14 incidence of certain comorbidities, specifically
15 diabetes, hypertriglyceridemia, and hyperuricemia.
16 There were not significant differences noted as far as
17 hypercholesteremia and hypertension.

18 The conclusion of these authors is that
19 long-term weight loss was a consequence as far as
20 bariatric surgery. It also helped as far as improving
21 their lifestyle and the amelioration with some of the
22 risk factors known to be associated with excessive

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1 weight.

2 There was a subsequent study, more so a
3 meta analysis, looking at the surgical treatment of
4 obesity. And given that the viewing of this slide is
5 not perhaps the best in this room, let me just simply
6 summarize that what it demonstrates is, again, what
7 was demonstrated in the Swedish obesity subject study.

8 And that is that roux-en-y gastric bypass had a much
9 greater weight loss. Biliary pancreatic diversion had
10 the best. And then following that was the vertical
11 banded as well as the adjustable gastric band.

12 What is the cost of these procedures?
13 That is to say, what are the consequences from a
14 standpoint of morbidity and mortality? As I alluded
15 to in the beginning of my remarks, with the procedures
16 that offer you or more weight loss or rapid weight
17 loss, more sustained weight loss, one sees, not
18 surprisingly, a higher complication rate, specifically
19 mortality rate, as well as morbidity rate.

20 However, the authors of this study in
21 their analysis felt that there was not a statistically
22 significant difference in mortality between these

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1 procedures, even though the data here, the numbers,
2 the absolute numbers, here would suggest otherwise.

3 So we could summarize, then, on this more
4 easily seen cartoon the bariatric surgical outcomes
5 for adjustable gastric band, roux-en-y gastric bypass,
6 the sleeve balloon, and the inflatable gastric
7 stimulator that the morbidity, the mortality is lowest
8 with the adjustable gastric band.

9 The excess weight loss is on the order of
10 about 47 to 50 percent, again depending on who the
11 author of the series is. The roux-en-y gastric bypass
12 has a higher excess weight loss, but, again, the
13 complication rate and mortality rate, .5 percent, is
14 somewhat higher. Even higher yet but, yet, with much
15 greater excess weight loss is the biliary pancreatic
16 duodenal switch. None of these are available in the
17 United States except for the inflammable gastric
18 stimulator, which is part of a trial.

19 The additional I think important finding
20 or demonstration as far as bariatric surgery is a
21 number of studies. And I know of three to date.
22 There is only one here that I have decided to display

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1 again in the interest of time.

2 There are three studies that would suggest
3 that as a result of the weight loss associated with
4 surgical weight loss, there is improvement in
5 survivorship; that is, that long-term mortality is
6 decreased. And this is the work of Christou in Canada
7 where he found that there was a significant reduction
8 in mean percent excess weight loss, that bariatric
9 surgery resulted in that, that these individuals then
10 also had significant risk reductions as far as
11 developing cardiovascular disease and the other
12 comorbidities we recognize associated with obesity.

13 But I think of particular import to this
14 audience as it pertains to the adolescent, who is less
15 likely, then, to lose weight when they're in the
16 morbid obesity stage of super obesity is that their
17 relative reduction in the risk of death.

18 I think this is of particular interest for
19 those subgroups who perhaps are at greatest risk who
20 are a shortened life span as a result of obesities,
21 particularly minorities, black males, Hispanics, who
22 are not perhaps available or have access to some of

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1 the sort of robust and conservative management
2 programs we just heard about.

3 In 2001, when presented actually with a
4 number of patients with severe obstructive sleep
5 apnea, so severe that they were going to be
6 trach-dependent, we were approached then to
7 contemplate doing a bariatric surgical procedure.

8 We are a result of that initial
9 experience, then, developed with then one of your
10 members of your panel the first children's
11 hospital-based bariatric surgical program in the
12 country.

13 And we have at the time of this slide
14 presentation preparation 63 adolescents with a mean
15 age of 17.5, and I want you to note a BMI of 58.1, a
16 range of 44 to 85. Ladies and gentlemen, these are
17 not adolescents who are just simply 10 or 15 pounds
18 overweight.

19 Now, fortunately, our experience was
20 comparable to that with adults. We had no
21 procedure-related deaths, though we did have one death
22 of a child who nine months afterwards while

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1 convalescing in a nursing home for his
2 osteoarthritis developed infectious colitis, which
3 was unrecognized, and he then went into hypoglycemic
4 shock and multi-organ failure and died as a
5 consequence of that.

6 We did have two children who had severe
7 complications, beri-beri with sequelae over two
8 months. And I think that that was related to severe
9 vomiting. It was not really appreciated. And we had
10 a number of minor complications.

11 Of particular interest to those of us when
12 we developed this program were some of the findings
13 that I am going to share with you now in this sequence
14 of slides. When performing a roux-en-y gastric
15 bypass, these children were obviously concerned of how
16 detrimental or deleterious this may be as far as a
17 child's body composition.

18 We looked at 13 patients, though all of
19 our patients, then, we asked them to have DEXA scans
20 as long as they can fit within the DEXA machine. We
21 looked at 13 patients at 3, 6, and 12 months and
22 looked at their weight, fat, and lean mass, again,

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1 asking the question, does this rapid weight loss have
2 a detrimental effect and adverse effect on their body
3 composition?

4 We were intrigued to note that at 3
5 months, the fat loss was about 19 percent and lean
6 mass loss was about 17 percent, but at 3 to 12 months,
7 we still continued with significant fat loss but with
8 very little nonsignificant lean body mass loss,
9 suggesting to us that despite, then, this rapid weight
10 loss and probably as a result of our regimen as a
11 result of high protein intake, that lean body mass was
12 preserved in adolescents.

13 We looked at then also how obstructive
14 sleep apnea was or was not affected by the weight
15 loss. We have 34 patients to share with you, 19 of
16 whom had undergone both pre and post-op sleep studies.

17 Now, of note, what we found in this cohort
18 of patients is that there was a fairly high prevalence
19 of obstructive sleep apnea in these patients, 55
20 percent. But what we also were pleased to see is that
21 as a result of the weight loss, that there was in all
22 patients either resolution or improvement of their

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1 obstructive sleep apnea and that when compared to
2 adults, that the apnea hypoxia index improved nearly
3 20-fold compared to at least the literature would
4 suggest 3 to 5-fold in adults, suggesting that perhaps
5 earlier intervention would result in a better outcome.

6 I don't need to sort of educate this
7 distinguished group about the consequences of
8 obstructive sleep apnea as it pertains to the changes
9 as far as the cardiac hypertrophy and that that in and
10 of itself is an independent risk factor for sudden
11 death. So this is clearly a very, very critical
12 finding.

13 We also looked at left ventricular
14 hypertrophy in this group, five patients who had pre
15 and post-operative echocardiograms. There are more
16 details to this. What we did find is that as a result
17 of the weight loss, there was decrease as far as left
18 ventricular wall thickness as well as a decrease in
19 ventricular mass, a decrease.

20 Compare this, then, this figure, with the
21 only adult study that we were able to find that only
22 demonstrated about a 14.5 percent decrease in left

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1 ventricular mass after surgical weight loss, again
2 suggesting that perhaps intervening earlier will
3 result in the better outcome.

4 Dr. Inge has been quite instrumental in
5 looking at the metabolic profile. And as a result of
6 his stewardship, we have some I think rather
7 interesting findings suggesting that insulin
8 resistance, which was elevated in a significant
9 percentage of these patients, decreased by 70 percent
10 overall in completely normalizing all but one. In
11 addition, there was a twofold improvement in beta cell
12 function.

13 Now, related to the metabolic syndrome in
14 diabetes, I think it's important to look at what our
15 adult colleagues have demonstrated and specifically
16 that the duration and the severity of diabetes
17 directly determines whether weight loss will help
18 improve or resolve.

19 This is Bill Schaueser's work, which
20 looked at, then, a cohort of patients. What he
21 demonstrated and what I just want to point out to you
22 is that the duration of diabetes was a highly

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1 significant factor determining whether a patient had
2 either resolution or experience improvement as well as
3 the amount of weight loss, the excess weight loss,
4 suggesting, then, or prompting, then, a number of
5 distinguished individuals, to include Dr. Pories, to
6 publish this sort of editorial or article in Diabetes
7 Care just recently, giving us the sort of provocative
8 question, surgery as an effective early intervention
9 for diabetes, combining, then, diabetes and obesity,
10 why the reluctance.

11 And, again, he simply corroborates, then,
12 the findings of Schauer and Paul O'Brien and others
13 that early intervention in the management of these is
14 really a subject for type II diabetes, will help
15 achieve and maintain significant weight loss and that
16 remission was predicted by greater weight loss in a
17 shorter history of diabetes. Improvement in insulin
18 sensitivity following surgery was best predicted by
19 the extent of weight loss as well as improvement in
20 beta cell function.

21 Recently Bill Schauer and his group
22 published on again, another aspect of the metabolic

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1 syndrome and the effect of weight loss. And that is
2 the fatty liver.

3 In our own patient population, where we
4 perform liver biopsies on all the patients who undergo
5 roux-en-y gastric bypass, over 90 percent of them have
6 some form of nonalcoholic fatty liver disease and a
7 fairly significant percentage have already fibrosis.

8 So this is of a particular concern to us,
9 recognizing that some gastroenterologists, pediatric
10 gastroenterologists, feel that nonalcoholic fatty
11 liver disease and NASH may be the next indicator for
12 liver transplantation.

13 What Bill Schaueser and Mattar did is that
14 they biopsied not only at the time of surgery but had
15 a cohort of patients that actually underwent biopsy
16 afterwards.

17 Again, these findings are perhaps not
18 surprising but certainly very reassuring. And that is
19 that with weight loss, there was reduction of the
20 prevalence of metabolic syndrome but that there was
21 also marked improvement in the liver steatosis.
22 Again, this was a biopsy after weight loss. That was

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1 about 15 months afterwards. And in some 37 to 20
2 percent, inflammation or fibrosis resolved.

3 Now, the question, then, given the fact
4 that bariatric surgery or surgical weight loss is in
5 many respects salutary, what would be the appropriate
6 timing of it? Well, first off, it's our contention
7 that the child should have attained physiologic as
8 well as skeletal maturation, that they will have
9 reached the stage of cognitive development that will
10 have them acquire formal operations. That is to say
11 that they are capable of thinking about the
12 possibilities and consequences of what happens if I do
13 or do not take my nutritional supplements. And then,
14 finally, they are of acceptable psychological health
15 as well as looking at the weight-related quality of
16 life.

17 The advantages, then, are that there are
18 procedure-related benefits as a result of bariatric
19 surgery, which suggest that it is safe and effective
20 long-term, that there is as far as the comorbidities
21 resolution and amelioration of most, if not all, but
22 that this is the function of the duration of the

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1 disease and that there is also the reducing of the
2 incidence of these comorbidities as well as an
3 improvement in the quality of life. There is also
4 some suggestive evidence again in adult studies that
5 there is increased survival compared to a medical
6 management.

7 But there are some concerns. And I will
8 just dwell on just a few of them. Of particular
9 concern is that of metabolic bone disease. A recent
10 study, then, published in 2004 would suggest that
11 there is an increase in bone turnover and decrease in
12 bone mass.

13 The authors looked at urinary telepeptides
14 as well as osteocalcine. But the question that still
15 remains and why this is certainly an area further for
16 research is, is this simply a phenomenon as a result
17 of the super obese and morbidly obese child patient
18 losing that excess weight?

19 There are concerns as far as the
20 nutritional deficiencies. They are more common with
21 bypass procedures. And there are those of us who
22 might think that they don't exist with the clearly

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1 restrictive operation. That's not the case. There
2 are some future deficiencies associated with fairly
3 restrictive operations. But clearly they are more
4 common with the bypass procedures.

5 Even with the roux-en-y gastric bypass,
6 there is a fairly high incidence of iron deficiency
7 anemia as well as choline deficiency, vitamin B-12
8 deficiency, and thiamine deficiency, again, requiring
9 nutrient supplementation, not just in the short term
10 but lifelong. And that sort of begs the question
11 about compliance.

12 Now, I mentioned about the fact that this
13 operation is an operation of some degree of
14 difficulty. One has to then take this into
15 consideration when one looks at what would be the
16 threshold for operating on an adolescent.

17 There are two schools of thought. One
18 would be a conservative higher BMI threshold. Another
19 school of thought would accept the NIH guidelines.

20 Let me suggest to you, then, that one
21 should look at a conservative guideline as one
22 offering an operation, particularly one where we're

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1 not clear as far as the outcome, when in the course of
2 the life course that the complication rate or the risk
3 of complication is lowest, when medical therapy
4 clearly is ineffective, when the outcomes are likely
5 to be the best and when the likelihood of recidivism
6 is the lowest.

7 If I make the assumption that you then
8 agree with that as a definition, we look at, then, a
9 higher BMI threshold and what the outcomes are related
10 to operating on a patient who is heavier.

11 And one sees that as early as 1987, noted
12 experts in this field noted that the super obese
13 individual was less likely to lose their excess
14 weight, but they were more likely to gain and that
15 also they were more likely to experience
16 procedure-related complications.

17 BMI, preoperative weight, is an
18 independent risk factor for procedure-related
19 complications and death. We need to conclude that by
20 having a higher BMI threshold to operate, whether it's
21 the laparoscopic adjustable band or roux-en-y, might,
22 in fact, have an opposite-than-intended effect in

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1 terms of the outcomes we want for this adolescent
2 patient population.

3 Experience does matter. One of the
4 consequences of, then, the burgeoning of bariatric
5 surgery as a discipline is that many individuals who
6 were not qualified entered into the field. And as a
7 consequence of that, the complication rate belied what
8 was seen in the published literature.

9 This is an article from the Harvard
10 Business Review that for coronary artery bypass, for
11 coronary angioplasty, for esophageal cancer surgery,
12 complex procedures, that who does it and in the
13 context and in what setting have a direct impact on
14 mortality risk. I would propose or submit to you that
15 adolescent bariatric surgery would also fall in that
16 category.

17 This is work done by Dave Flum that simply
18 supports that contention. Even though the mortality
19 rate for roux-en-y gastric bypass is on the order of
20 about .5 percent, when we looked at the state
21 registry, he found then, again, that the mortality
22 rate was considerably higher, on the order of about

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1 1.9 percent, and that for the surgeon who in his first
2 30 to 40 cases had a 40-fold higher mortality rate
3 than if he had done 200 or 150 cases.

4 There is an argument for reasonablization
5 of complex procedures. And in my estimation here, the
6 literature is nearly incontrovertible, that for
7 certain complex operations -- and I would submit that
8 for very active surgery, that outcomes are directly
9 related to surgeon as well as hospital volume.

10 This is something that is not just shared
11 by those of us here. This is a conclusion or
12 recommendation of Lars Sjostrom of the Swedish obesity
13 subject study, who felt that, really, an obesity
14 center for every 500,000-person population would be in
15 order and that this center would perform 500 to 1,000
16 operations per year and that the center would be
17 mandated to perform life-long follow-up.

18 What are the attributes of the bariatric
19 surgical program for adolescents? I think that,
20 despite the fact that there is no evidence out there,
21 we can still borrow from our colleagues who have done
22 remarkable work in diabetes, cystic fibrosis, and base

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1 our bariatric surgical program for adolescents on
2 those best practices.

3 But it also should be a multidisciplinary
4 team providing comprehensive evaluation standard,
5 standardized care as far as surgical intervention, as
6 well as postoperative medical, psychological, as well
7 as surgical surveillance. And I submit that there
8 needs to be a support group, not just for peers but
9 also for the parents.

10 One needs to recognize that incomplete
11 data is worse than no data. It is essential in
12 embarking on the clinical trial of the one that
13 perhaps we're postulating that one look at maximal
14 retention as far as study participants because our
15 ability, then, to draw definitive conclusions about
16 the absolute and relative efficacy and safety of
17 whatever procedure you're entertaining is limited.

18 So to have a 50 percent follow-up is in my
19 estimation unacceptable. We would have to have
20 complete evaluation of all enrolled patients as a
21 critically, if not absolutely essential, aspect of any
22 clinical trial for barriers of surgery in adolescents.

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1 I'll read this for this, but this is a
2 response from Paul O'Brien, a respected bariatric
3 surgeon, a major proponent of the adjustable gastric
4 band. In preparation for this presentation to this
5 distinguished group, I queried him, given the fact
6 that he is in the midst of a randomized study looking
7 at LAP-BAND and optimum nonsurgical therapy.

8 His response is as follows, "On compliance
9 of adolescent, awful, much worse than adults, maybe
10 just because they're adolescents or it may be that
11 they just don't sense the severity of the problem as
12 do adults. It may be that they are always dependent
13 on mum, m-u-m, or dad bringing them along. And so the
14 logistic catches it.

15 "For whatever reason, I would guess they
16 would score about three to four out of ten on
17 compliance test scores; whereas, our adult patients
18 would probably average around seven to eight.

19 "On effectiveness, this is a good
20 operation. It's good if they attend, better rate of
21 weight loss than the adults. Bad habits. They're
22 probably more susceptible to peer pressure than the

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1 adults and so have episodes of social eating and
2 drinking, which destroy the good results so quickly.

3 "And with a lack of attention to the
4 eating rules, eating too much too fast, the incidence
5 he feels is going to be much higher as far as
6 prolapse. Clearly there is a need for a carefully
7 randomized control trial." And then, of course, there
8 is always the salutation, "Good luck."

9 I would conclude that the success for
10 adolescent bariatric surgery is an imperative. These
11 children are desperate. They suffer more than one
12 could imagine as far as their so-called medical
13 comorbidities. Their quality of life is abysmal.

14 But what I would suggest is that to those
15 surgical hospital volume is a critical component and
16 the choice of operation may be a component as what we
17 do here is really going to guarantee the success of
18 whatever operation we propose. The basis for that is
19 going to be blue ocean strategy.

20 I will conclude my comments and take any
21 questions anyone might want.

22 CHAIRMAN NELSON: Thank you.

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1 One quick comment before we start the
2 questions. I think a number of your slides probably
3 would be worth the panel being able to refer back to
4 in our deliberations tomorrow.

5 So I hope we can get a copy to make
6 printed copies for the panel, be able to distribute
7 for tomorrow's discussion, if we can solve that as a
8 technical issue, even if it's a .pdf file or
9 something, because I gather you're using something
10 other than PowerPoint. If we could figure that out?

11 DR. GARCIA: That's not a problem.

12 CHAIRMAN NELSON: Good.

13 DR. GARCIA: We have the technology.

14 CHAIRMAN NELSON: Perfect. So just to
15 give you timing, and then I'll to our first question.
16 We're scheduled to go until 6:00. What we'll do is
17 we'll either go until 6:00 or until exhaustion,
18 whichever occurs first. Okay? So start over with Dr.
19 Kral.

20 DR. KRAL: Two comments and a
21 comment/question. Comment number one, you did a very
22 good job of presenting this wide array of information.

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1 Second comment for everybody to note, Dr.
2 O'Brien's from Australia, from Melbourne, ideas about
3 adolescents' performance after LAP-BANDING contrasts
4 that to Dr. Fielding's presentation before. Are we
5 talking about the same population and the same people?
6 And I will let you draw your conclusions.

7 The comment/question is I was rather
8 surprised that you juxtaposed the outcomes of the
9 super obese adult with projected outcomes of the super
10 obese adolescent. Do you not believe that these are
11 very, very different phenomena?

12 The super obese adult comes in end-stage
13 disease with prolonged chronic disease and certainly
14 does not have any of the resilience of the younger
15 individual, any pediatric surgical patient, compared
16 to the adult, and particularly when it comes to this
17 type of surgery.

18 In other words, I think it's unfair, and I
19 wonder what your opinion is. Do you think they're the
20 same?

21 DR. GARCIA: Well, certainly the super
22 obese, one would have to stratify that population.

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1 The super obese has had tumor or has coronary artery
2 disease. Yes, that's a different individual.

3 But the super super obese adolescent who
4 by virtue of his mass, if that's what you're alluding
5 to, still represents a technical challenge that I
6 think is not addressed when we look at our guidelines.

7 Is that the question you were asking?

8 DR. KRAL: Yes. I mean, there's no
9 contest that the earlier you intervene so that you
10 don't even allow a progression to that extent is
11 better. That wasn't the basis of the question.

12 DR. GARCIA: Okay.

13 DR. KRAL: The basis of the question is
14 that the adolescent has not had as severe a eating
15 disorder, has not had as long a period of time to
16 evolve any of the occult or other comorbidities that
17 are involved as the adult does.

18 Certainly we should have highly
19 technically proficient surgeons doing this and it
20 should be centralized, but --

21 DR. GARCIA: I don't know the question to
22 that. I don't know the answer to that question. What

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1 I do know and I think raises a number of concerns is
2 that within a much shorter period of time, that
3 adolescent has achieved super obesity.

4 So one has to wonder what consequences
5 that has, both metabolically as well as
6 physiologically. And they're not even addressing the
7 psychosocial.

8 But the other thing that we are noticing
9 is that the incidence of metabolic syndrome and
10 diabetes is certainly much, much greater, much higher,
11 in our pediatric population. As a matter of fact,
12 Cincinnati was one of the first institutions to
13 publish a tenfold increase in diabetes. And, again,
14 most of those individuals were obese.

15 So to suggest that because they're
16 adolescent they don't have the comorbidities that an
17 adult has I don't think is accurate.

18 DR. KRAL: No, but it's not accurate to
19 compare the obvious resilience of the younger
20 individual. And let's not even discuss pediatric.
21 Even in adults, the younger the patient, even at ISO
22 B's; in other words, at the same level of obesity, the

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1 outcomes are better.

2 DR. GARCIA: The outcomes in what respect,
3 Dr. Kral?

4 DR. KRAL: Any one, any kind you want.

5 DR. GARCIA: So weight loss?

6 DR. KRAL: The significant one is the
7 safety and the operative safety, the safety of doing
8 the surgery. That's what we're discussing, right?

9 DR. GARCIA: Right. Well, certainly that
10 adolescent who does not have coronary artery disease
11 and lung disease, if he were to have a complication --

12 DR. KRAL: Can take the joke better.

13 DR. GARCIA: Yes, yes.

14 DR. KRAL: Yes. Okay.

15 DR. GARCIA: But why suggest them to that
16 risk?

17 DR. KRAL: Oh, I agree. Prevention is
18 even better.

19 CHAIRMAN NELSON: If you want to pursue
20 this line of discussion, we could continue, but we
21 want to go to Deborah. And then I'll come back.

22 MEMBER DOKKEN: I also was struck by what

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1 seemed to me as a lay person a pretty dramatic
2 difference between hearing that compliance was no
3 problem and that compliance was awful. And it brought
4 me back to our discussions about assent that we have
5 had earlier in the day.

6 So I guess, again, as a lay person and not
7 a clinician, where is the true picture about
8 compliance on two ends of the spectrum that said it
9 was no problem and that it was awful?

10 DR. GARCIA: I don't believe that
11 compliance is no problem. That's all I'll say.

12 CHAIRMAN NELSON: Anyone else want to
13 answer the question?

14 MEMBER DIAZ: When it comes to adolescent
15 behavior, just look at normal adolescents and draw
16 your conclusions.

17 DR. GARCIA: But that is not to say that
18 it is insurmountable. That is not to say that it is
19 insurmountable.

20 MEMBER DOKKEN: That it is important to
21 address.

22 DR. GARCIA: And, if anything, it requires

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1 more attention than perhaps many of us are giving it.

2 DR. PORIES: We run a children's camp and
3 try very hard between the camps during the year to
4 follow these kids. Our success rate is about 35
5 percent. This is with the buddy system and all sorts
6 of ways. So I fully agree. Follow-up is a problem.

7 CHAIRMAN NELSON: Before going over here,
8 there were three hands that came up. Were we
9 continuing the compliance theme basically? Okay. So
10 Dr. Gorman and then Dr. Garofalo.

11 MEMBER GORMAN: I think this might
12 emphasize for us tomorrow in our discussion to focus
13 on multidisciplinary approaches to this, even inside
14 the surgical arena. Dealing with children with
15 chronic diseases and adolescents with chronic
16 diseases, be they diabetes or other, has given
17 pediatricians a large body of information of how to
18 deal with adolescent noncompliance, sometimes
19 successfully.

20 CHAIRMAN NELSON: Dr. Garofalo?

21 MEMBER GAROFALO: Yes. So my question is
22 you showed some data about morbidity and mortality

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1 comparing the different surgical operations. So some
2 of the data might be more limited. Some there is
3 longer experience.

4 So can we generalize from what we know
5 about the banding, you know, if it has been very
6 carefully done? And do we think that data is going to
7 hold us and it's more generalized and it's more
8 available?

9 DR. GARCIA: I think that, as with any
10 surgical procedure -- and I think that it would be
11 oversimplification to say that this is something that
12 you can see one and then just do it.

13 So I would anticipate that with
14 generalization, even though the learning curve is not
15 as steep as with roux-en-y gastric bypass, that you
16 will see a higher complication rate than what one sees
17 published with a Paul O'Brien or a George Fielding.

18 And that's why I'm a strong proponent of
19 regionalization in centers of excellence. If we're
20 doing that now as an afterthought for adults, it
21 should not be an afterthought for the adolescents. It
22 must be a priority.

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1 CHAIRMAN NELSON: So we're going to go
2 back to Dr. Choban and Dr. Klish.

3 DR. CHOBAN: I had two things. I may have
4 missed something. What is blue ocean strategy?

5 DR. GARCIA: I was hoping somebody was
6 going to ask.

7 DR. CHOBAN: Oh, okay.

8 (Laughter.)

9 DR. CHOBAN: Was I not paying attention
10 earlier?

11 DR. GARCIA: No. You know, when dealing
12 with this issue of adolescent compliance, have you
13 ever just wondered why the makers of sneakers are
14 doing so well or the makers of jeans? What is it that
15 allows a business to market so successfully to an
16 adolescent?

17 It's peer, but there's also a science
18 behind this. On another venture, we're working with a
19 collective marketing firm that markets for -- what is
20 it? Abercrombie. What is it called?

21 MEMBER GAROFALO: Abercrombie and Fitch,
22 Limited.

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1 DR. GARCIA: Abercrombie and Fitch. They
2 know how to push the button, and they know how to get
3 that teenager to come back. They know how to
4 establish brand loyalty.

5 And as physicians and health care and
6 medical personnel, I think we need to look at blue
7 ocean strategy. Blue ocean strategy is really looking
8 at the development of iPod and Sonys, not looking at
9 what the evidence demonstrated but also looking at how
10 Cirque de Soleil, for example, in looking at the
11 circus, how it was done. And Cirque de Soleil used
12 blue ocean strategies. And now we're willing to pay
13 \$150 to go to the circus.

14 That's blue ocean strategy and what needs
15 to be applied as part of this comprehensive program.

16 DR. CHOBAN: That sort of actually brings
17 me to my second issue, the Abercrombie and Fitch
18 reference anyway. If you've seen the ads, you know,
19 it's kind of like I find a few of them a little askew.

20 In my adult population, we have seen a
21 fair degree of they can get a little promiscuous.
22 I've done some younger people, 16, 17, 18. And they

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1 have been primarily the children of my other patients.

2 Two of them I can think of when you ask mom, you
3 know, when you see mom, you also, "Oh, how is" so and
4 so?

5 "She's pregnant." And mom is not very
6 happy and sort of looking at me like I'm responsible.
7 You know, sorry.

8 How do you address that? I mean, I think
9 it is a real issue for people who have been somewhat
10 socially isolated because of how they appear and
11 suddenly it's like "I'm like everybody else, and we
12 can kind of swing a little too far the other way."

13 DR. GARCIA: Tom, how many pregnancies
14 have we had? Four? Something like that? Yes.

15 DR. CHOBAN: Sixty-three?

16 DR. GARCIA: Yes.

17 DR. CHOBAN: That's a lot. I mean, in a
18 pediatric adolescent population is that?

19 DR. GARCIA: So what you touched on is
20 that you now have this metamorphosis. I mean, they
21 have now lost weight. But I think we have ignored the
22 fact that they have been ostracized, stigmatized,

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1 marginalized. And now that they are this new being,
2 they don't have the life skills, they don't have the
3 sort of concrete formal operations to really think
4 about what the consequences are that when "Sam decides
5 to ask me out and says, 'I love you,'" that it's not
6 true love.

7 I really think that this compliance issue
8 is not just compliance with eating a five, three, one
9 ratio or getting your protein first, but it's looking
10 at, really, life skills globally.

11 In addition, in addition, a good
12 proportion of our patients, their parents are super
13 obese, if not morbidly obese. But, in their defense,
14 when they come in, they'll tell us, "I don't know how
15 to cook. I didn't know about eating a bagel and why
16 I'm so hungry shortly thereafter."

17 When you take this on, you take on more
18 than just doing an operation. You take on really a
19 true education of both the child as well as the
20 family. And it's not insurmountable.

21 CHAIRMAN NELSON: Dr. Klish?

22 DR. KLISH: I don't want to talk about

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1 blue oceans or sex, but I have a totally different
2 question. You described several studies where they
3 are comparing medical management to surgical
4 management. And the conclusion was that there was
5 more mortality and morbidity in the medically managed
6 group than the surgical managed group.

7 You may have said it. I may have missed
8 it. But how were the medically managed patients
9 selected in these studies? In other words, were they
10 the medical patients that were successful in early
11 weight loss or did they just take all comers to a
12 medical therapy which has, at best, maybe anywhere
13 from 15 to 20 percent success rate?

14 The reason I'm saying that is I think if
15 you had a fair comparison, you would only compare to
16 the successful medical managed patients if you're
17 truly trying to go head to head looking at how well
18 bariatric surgery works.

19 DR. GARCIA: Well, but if you took it --
20 none of these studies were randomized controlled
21 trials. If you then look at them as intent-to-treat
22 analysis, then whether they were successful or not,

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1 then you would still I think have a valid comparison.

2 For the Swedish obesity, it was
3 individuals who were then part of an obesity
4 treatment. Now, it wasn't an Epstein aggressive, but
5 it was still an obesity management.

6 DR. KLISH: I agree. When you look at it
7 from the terms of intent to treat. That may be fair
8 at this state of the art, but if we become better
9 medically to handpick our patients that we think are
10 going to be more successful, then those kinds of
11 studies aren't going to be relevant, I think.

12 I'm trying to grasp this in my own mind as
13 well because theoretically if we get more successful,
14 you have to somehow know how to compare these things
15 head to head.

16 DR. GARCIA: I truly hope, Dr. Klish, that
17 you do become much more successful soon.

18 DR. KLISH: Well, I think it is happening.
19 Success is increasing. Every year our success gets a
20 little bit better.

21 CHAIRMAN NELSON: I'm not surprised that
22 our statistician wants to comment on intent-to-treat

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1 analysis.

2 (Laughter.)

3 MEMBER O'FALLON: Well, not necessarily
4 comment on that, but, rather, I have been sitting here
5 listening to you and trying -- I mean, you're saying,
6 in essence, that they are -- O'Brien or whatever his
7 name was from Australia was saying that they are
8 terrible at compliance but the way they don't even get
9 to the surgery until they have already "failed" the
10 medical management or behavioral management. Is that
11 not correct?

12 Okay. So already the people that get the
13 surgery have already shown that they can't follow the
14 medical management. And, yet, you're turning -- I
15 mean, it seems that we're kind of in a loop here.

16 And then I wonder, are you saying -- in
17 essence, we really do have in these centers for
18 adolescent overweight or obesity, don't you have to
19 have more effective programs for delivering
20 behavioral? I mean, it's important, both before and
21 after they get the surgery.

22 DR. GARCIA: Yes. And, yes, you are there

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1 because you have not done well with the behavior. But
2 one recognizes that once you reach a certain level of
3 adiposity, that there are physiologic drive, stimuli
4 that just make that behavior just not possible.

5 So, even though if I weigh 300 pounds or
6 400 pounds, even though I may know and want to or have
7 a desire to not eat that extra, there are drives that
8 I'm not going to be able to control. And that's where
9 surgery comes in to play, where it will limit not only
10 the amount. Depending on the procedure, it will limit
11 what kind of foods that I can eat. Otherwise I'll get
12 sick or have dumping syndrome.

13 MEMBER O'FALLON: One of our earlier
14 speakers made the point that there are different kinds
15 of hunger, that a great deal of the time it isn't
16 really physical. It's in some senses up here that
17 they are hungry. And that part maybe hasn't been
18 fixed by the surgery.

19 CHAIRMAN NELSON: I didn't realize you
20 were Cartegian.

21 DR. KLISH: Can I make one other comment?

22 CHAIRMAN NELSON: Continuing this line of

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1 --

2 DR. KLISH: In the same line because you
3 also implied with your last comment that it is
4 impossible for a super obese individual to get back to
5 normal weight using medical management.

6 DR. GARCIA: It's unlikely.

7 DR. KLISH: That's not true because we all
8 have experienced that.

9 DR. GARCIA: It's unlikely. It's very
10 difficult.

11 DR. KLISH: But it does happen?

12 DR. GARCIA: It does happen, yes, but it's
13 very difficult vis-a-vis the --

14 CHAIRMAN NELSON: On my list, Dr. Daum,
15 Dr. Kral, and now Dr. Botkin.

16 DR. BOTKIN: First of all, I want to say
17 thank you for that talk because you've certainly
18 enlightened me about a lot of technical aspects and
19 outcome aspects of surgical management of these
20 patients.

21 I had two questions that sort of will help
22 me at least prepare for tomorrow's discussion. The

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1 first one is, do you have any experience with this
2 operation in younger people?

3 You talk about adolescents a fair extent.
4 What about preadolescents or even younger children
5 than that? Is there an experience with it? And have
6 people attempted it and as good as what you showed?

7 DR. GARCIA: I do not have any personal
8 experience. Our age limit is 13. There have been
9 some reports or at least if not reports, I've been
10 told by bariatric surgeons much wiser or at least
11 older than I am that they have done even bypasses on a
12 number of younger patients, but I have not seen
13 reports in the literature or preadolescents. Sorry.

14 DR. BOTKIN: Thank you.

15 My second question goes to the children,
16 the adolescents, you reported to us. It sounded like
17 you selected extremely obese people for this
18 operation. I wonder if you would comment on your
19 thoughts about choosing less obese individuals for
20 this kind of surgery.

21 DR. GARCIA: I personally think we should.
22 I think that as a result of that higher BMI

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1 threshold, besides the concerns that I outline in my
2 presentation, that you will have some adolescents who
3 will strive to gain weight in order to meet that
4 threshold.

5 I think that when you look at the
6 comorbidities and we say, "Oh, we have to have
7 comorbidities," I am always struck by the logic there.

8 There was a point in time that you waited until an
9 individual had a heart attack before you perhaps
10 intervened.

11 So now we know we don't wait. We look for
12 other risk factors for the markers. We developed
13 those markers by looking very critically at what were
14 the precursors for these sentinel events.

15 Do you wait for the adolescent, then, to
16 do knee replacement therapy before you consider
17 osteoarthropathy when there is an indication or do you
18 wait until you have a reversible cardiac chamber
19 before you must intervene?

20 If we know that, again, the assumption or
21 the observation is that this individual has failed
22 efforts to lose weight and you know the natural

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1 history, as the previous speaker alluded to, that once
2 you are a certain BMI at a certain age, you are not
3 going to suddenly grow into it. Then why wait, then,
4 until that individual is super obese to perform a
5 procedure that has risks that are directly associated
6 with or directly related to the size of the patient?

7 So in many respects, it's kind of
8 intuitive to wait until --

9 DR. BOTKIN: As just a final follow-up on
10 the same issue, could you comment on how far down you
11 turn the knob if you are charged with patient
12 selection for this?

13 DR. GARCIA: How low?

14 DR. BOTKIN: Yes.

15 DR. GARCIA: Well, I could very
16 comfortably and safely say I would go no longer than
17 the NIH criteria. But I would also suggest that given
18 the chronicity of this disease, knowing that there are
19 ethnic and racial differences, there are some Italians
20 who are obese who don't have diabetes, that there are
21 many Hispanics and African Americans who as a result
22 of their obesity are going to lose 20 years of their

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1 life, it suggests to me that we need as a discipline
2 to look more critically, then, at predictors and
3 markers of adverse outcomes and use that as a
4 criteria, not absolute BMI but the reactive protein.
5 Let's look at that and see if that is something that
6 we should look at as a marker for that individual who
7 has failed, despite multiple attempts has failed, not
8 wait until they are insulin-dependent or hypoglycemia
9 or have nonalcoholic steatolipitoids.

10 CHAIRMAN NELSON: Dr. Kral?

11 DR. KRAL: A comment to the discussion
12 between Dr. Klish and Dr. O'Fallon about selection and
13 patients selected for failure and do we really have
14 criteria for selecting patients. I have looked at
15 that throughout my career. It isn't getting much
16 better, and we are not very good at it.

17 Ben Italy and I wrote in JAMA around 1980
18 about the dilemma of what we then called morbid
19 obesity, severe obesity. The dilemma was that the
20 patients who probably most needed the surgery are
21 those with the least resources to be able to follow
22 through and do everything that is necessary. We had a

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1 mini discussion about the adolescents here before,
2 whether they have the means to pull it off well.

3 You mentioned among the devices -- and
4 this is the point I wanted to make -- the
5 electrostimulator. The failure with the
6 electrostimulation was absolutely abominable in the
7 beginning until they came up with what they called a
8 selection algorithm which selects around 30 percent --
9 correct me if I am wrong on this. It's around 30
10 percent. Only about 30 percent of their candidates
11 are eligible and fulfill the selection criteria. Only
12 then will they improve and get some kind of
13 effectiveness out of the electrostimulator.

14 So the devil is really in trying to find
15 selection criteria. And they're not that difficult.
16 They're the same, actually. And I don't use the word
17 "conservative" but conventional or nonsurgical
18 treatment. The selection criteria are the same. It's
19 the stable family. It's the stable economy. It's all
20 of that stuff. That works best for your outcomes, the
21 same with surgery, too.

22 So there is an extraordinary need, as

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1 you've just pointed out, for stratification and for
2 many different parameters. And certainly race is one
3 of them.

4 CHAIRMAN NELSON: I see hands going up,
5 and I am going to write them down. But I just want
6 people to think. We have been at this now nine and a
7 half hours today. And the last thing I want you to do
8 is start talking about tomorrow's question. All
9 right? So to the extent that we want the wisdom of
10 the current speaker, I think that is important. But
11 we don't need to start talking about the questions
12 that we're going to deal with tomorrow, which we
13 started this slide into a little bit.

14 I'm going to go to Dr. Botkin. Then I'm
15 going to look around the room and get the names of the
16 people that have their hands up and hopefully everyone
17 will consider the risk and benefit continued.

18 (Laughter.)

19 CHAIRMAN NELSON: So, Jeff, it's to you.
20 And then we'll --

21 DR. BOTKIN: If you have a 15 or
22 16-year-old who had failed conventional approaches and

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1 you were wanting to discuss a surgical procedure with
2 an adolescent in the family, would you consider each
3 of these to be on the table for discussion or do you
4 have a clear preference or sequence?

5 And, sort of in parallel with that, if one
6 were to do a LAP-BAND, is there a contraindication
7 later or any experience with later going to one of the
8 more invasive procedures?

9 DR. GARCIA: You know, I'll answer that
10 question with some trepidation because I stand here in
11 the company of adult bariatric surgeons who taught me
12 and certainly have done orders of magnitude more
13 procedures than I have.

14 Having said that, I do present the three
15 procedures that I alluded to as the more common ones
16 to the patients that I have. I tell them in very
17 concrete terms, both the patient and the parent, about
18 the risk-benefit ratio of a LAP-BAND as well as the
19 roux-en-y gastric bypass. I also tell them that there
20 is another procedure.

21 And, again, most of our patients are super
22 obese. And in that patient population, the biliary

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1 pancreatic duodenal switch, they would be considered
2 candidates for that because they were enjoying I think
3 a better success.

4 So I mention that that is yet another
5 operation. And the advantage of that operation is
6 that they won't have the limitations in how much they
7 need. They will have some, but they won't have it to
8 the same extent as they will with the restrictive
9 procedure. I really asked them to think about that.

10 With that as my practice, I will tell you
11 that I have had not one patient recommend or at least
12 agree to have the LAP-BAND, even though I try to push
13 them to have the LAP.

14 I think it's not that they don't
15 appreciate the safety and the efficacy of it. They
16 want that weight off. They come so desperate. At
17 that BMI, they are so desperate they want the weight
18 off yesterday.

19 So I draw up for them what the profile is
20 as far as the weight loss, that yes, it will be slower
21 with the LAP-BAND, but eventually you'll get up
22 comparable to a little bit closer to where you are

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1 with the roux-en-y gastric bypass. They want it.
2 They want it off yesterday. And that is fascinating.

3 CHAIRMAN NELSON: The list I am working
4 with right now is Hudson, Choban, Ward. And, Richard,
5 was that your hand up there?

6 DR. BOTKIN: Skip, let me finish up with
7 that same question. I think a quick answer, if you
8 had a LAP-BAND first, would there be any
9 contraindication later if you weren't satisfied with
10 going ahead with the other bariatric procedures?

11 DR. GARCIA: I mean, I can comment on what
12 more experienced surgeons have told me. I have not
13 been that experienced. Dr. Pories can share with you
14 what his thoughts are on that.

15 I will tell you that the individuals who
16 have taught me who have done literally three to four
17 thousand procedures, some LAP-BANDS, there is
18 technical difficulty that those who would say that,
19 oh, if you have a LAP-BAND, you could just pull it out
20 and just simply go ahead and do a roux-en-y gastric
21 bypass and it's no selecting a walk in the park.
22 That's not what the experienced bariatric surgeons

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1 will tell you. Those who have been in the fray, in
2 the battle, in the trenches, they will say that it is
3 technically more difficult.

4 Dr. Pories?

5 CHAIRMAN NELSON: Do you agree with that
6 characterization?

7 DR. PORIES: You can convert them. It's
8 difficult. There are a fair number of adhesions. It
9 will probably increase the mortality of the operation,
10 maybe twofold or threefold. It's probably something
11 like two or three percent.

12 So yes, it can be done. It is difficult.
13 I would imagine in the near future, as we get more
14 experience doing it, we'll find more mortality as
15 well.

16 CHAIRMAN NELSON: Dr. Hudson?

17 MEMBER HUDSON: You alluded to the
18 experience of other chronic disease and long-term
19 follow-up and that from that experience, we know that
20 it's important to get to follow children into
21 adulthood to assess some late treatment complications
22 of these procedures.

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1 Well, in fact, I'm monitoring a very
2 vulnerable population. And it's increasingly
3 challenging because they're mobile, they don't want to
4 come back, and the institution in various places that
5 not support that type of medical follow-up. How do
6 you accomplish this or how have other surgeons
7 accomplished this?

8 For us, long-term follow-up in oncology is
9 beyond five years. So will the centers of excellence
10 have this mechanism? Are there registries that are
11 developed to monitor morbidity and all of these
12 problems long term? How are you guys doing it now?

13 DR. GARCIA: Tom? We're not doing as good
14 a job as I think we should. And we're still trying to
15 get our hands on that because, unfortunately, there is
16 not funding, then, to sort of do that robust analysis
17 and follow-up. We're not doing as good a job as we
18 should.

19 I come back, then, to my contention. It's
20 my own contention that I think we in looking at these
21 adolescents can learn lessons from our business
22 colleagues of how they can come back again and again.

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1 And we've got to think outside of the
2 medical model and look at the life skills, look at how
3 you can enjoy life. I mean, one of my consultants
4 whom I sort of banty back and forth with, you can
5 build this room and we would have computers that would
6 be operated by people dancing on the floor.

7 And, again, there is this expertise where
8 you can actually design areas so that, instead of that
9 analyst going to the club, he wants to come to your
10 hospital. Maybe it's not in the hospital setting but
11 come to your facility because we have made it
12 attractive, we have made it fun.

13 And I think to me the strategy is thinking
14 outside. When he comes in or she comes in, everyone
15 talks about protein and design. You know, we're doing
16 our exercise. They could be doing protein and
17 exercise and may not even realize it.

18 MEMBER HUDSON: But, see, you're still
19 talking short-term follow-up because the long-term
20 follow-up that tells us what the impact is on
21 morbidity or even some of these shorter-term
22 parameters, they're adults at that point. So you have

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1 to change from engaging your adolescents to keeping
2 the adults engaged. So is it a registry?

3 DR. GARCIA: Yes, yes. And, actually, Tom
4 has such a registry to do that follow-up. One of the
5 questions that we don't have that no one is asking yet
6 is, we are a children's hospital. How do you follow
7 these as adults? What are you doing as far as
8 transitioning into health care?

9 DR. INGE: I also think that this brief
10 comment, that it's important to consider the
11 differences between cohort management in the study and
12 cohort management, which is incredibly difficult, no
13 matter what disease process or treatment program you
14 look at in an adolescent population, an adolescent
15 population distinguishes itself in multiple studies,
16 but including the transplant literature, where the
17 grafts are viable, is demonstrably worse for the
18 adolescent than the younger school-aged children or in
19 the adult population as directly compared head to
20 head.

21 So I think that we do have an extremely
22 significant challenge ahead of us for the clinical

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1 treatment, but I do think that in regard to what the
2 panel will be looking at; that is, you know, trial
3 design, that there will be ways to ensure a valid
4 scientific interpretation of data via standard trial
5 cohort management techniques.

6 DR. GARCIA: But on that point, as far as
7 the transplant literature and the graft laws, I think
8 that there are some differences there because if you
9 have a child who is taking steroids and wants to get
10 off his steroids or has steroids because she wants an
11 improved basis for the -- I think it's very different
12 for a child who has lost weight and has a new figure
13 and, yet, is still not able to compel them to --

14 CHAIRMAN NELSON: Dr. Choban?

15 DR. CHOBAN: Yes, but one of the things we
16 were charged or that was described yesterday as part
17 of our panel and what industry gets held to and what
18 kind of studies is we talk about things being the
19 least burdensome. Yet, we have talked about things
20 like multiple failures of diets and multiple failures
21 of drugs and things like that before.

22 These adolescents we have also talked

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1 about have difficulty running the gauntlet can get
2 access to roux-en-y gastric bypass is sort of what we
3 have talked about. We are trying to think of a more
4 generic scope.

5 So I guess as you look at LAP-BANDs versus
6 the stimulators, there are some of the things that
7 have less risk and do -- I guess do we trade selecting
8 for success by taking only those adolescents who can
9 run the gauntlet versus okay, we're going to give them
10 a try with it since we don't have good selection
11 criteria, if it's a fairly low-risk procedure, is that
12 a reasonable balance? If you think it's lower-risk,
13 it's almost like we're willing to accept a little
14 higher failure rate in terms of weight loss if we're
15 not buying more problems with it.

16 So is that a reasonable thing in this
17 adolescent population who is having trouble running
18 the gauntlet versus is that not a reasonable
19 assumption if we're thinking of them as sort of
20 vulnerable?

21 DR. GARCIA: Let me sort of address that
22 from two perspectives. Number one is that I don't

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1 think that we're anywhere close. At least in our
2 experience, there are individuals who come from a very
3 sort of nuclear family who have done well. And there
4 are those who have come from a very nuclear family and
5 they have not done well. There are those who have
6 really -- they have a single parent and they are a
7 lower socioeconomic group and they are a minority.
8 Some have done well, and some have not done well. And
9 we sit in our meetings and say, "Well, who would have
10 thought?" So to say run the gauntlet, I don't know
11 that we have that particular skill. I don't think we
12 have that in our material.

13 My concern as far as going with a lesser
14 procedure that has a lower risk is that if we take,
15 then, the experience of a Paul O'Brien, who would
16 suggest that they are eating faster and they are
17 eating more, that that may then result in a higher
18 incidence of prolapse, that that so-called low risk
19 may not really stand a test of time unless we do
20 something as far as getting them to be better
21 compliant.

22 DR. CHOBAN: GPS trackers in the band?

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1 CHAIRMAN NELSON: Dr. Arslanian, do you
2 want to talk on this point or --

3 DR. ARSLANIAN: Yes. Just to give an
4 example about adolescent being different from adults,
5 the diabetes control and complications trial, which
6 was an intervention with 21 centers in the U.S., North
7 America, where the group of type I diabetics were
8 divided into receiving intensive diabetes management
9 versus conventional and every center included
10 adolescents as well as adults.

11 So it was the same team providing the care
12 to these people, these patients. And at the end of
13 the trial, whether the adolescents were in the
14 intensive or in the conventional, the HBA1C level was
15 by one percent higher in the adolescents. So there is
16 no question that with the same team. And, plus, there
17 was a very intense selection process that went on at
18 the beginning.

19 So here this is a landmark study with very
20 intense selection process that was applicable to
21 adolescents and adults, the same team providing the
22 care to these people. And, yet, adolescents had one

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1 percent higher HBA1C level pointing again that no
2 matter what approach you have, there is a difference
3 in how they receive and perceive your intervention.

4 So I think we have to keep that in mind as
5 we approach any intervention with adolescent age
6 group.

7 DR. GARCIA: This is very soft, but I
8 stand before you as I think having a unique experience
9 in dealing with adolescents, first during my time at
10 West Point as a battalion commander in charge of
11 adolescents, then as a military officer in the Army
12 for 20 years, again charged with adolescents.

13 What I come away with is that the way you
14 motivate adolescents to do things as even run up the
15 hill and face a fire is not what seems to be obvious
16 to the casual observer. That's the blue ocean
17 strategy that I really challenge you to sort of
18 explore to think outside the box, outside of the usual
19 medical approach in dealing with an ill patient, to
20 get them to comply.

21 The consequences are almost unbearable to
22 think of with the sort of prodigious epidemic that we

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1 have as far as obesity, the public health crisis that
2 this represents, that for that small but, yet,
3 significant segment of the population that weight
4 management or conventional therapy is not going to
5 work, that the only hope that they have is surgical
6 weight loss.

7 CHAIRMAN NELSON: Just two more names on
8 the list. It's Ward and Gorman. We're getting to the
9 point where we'll end up stopping at 6:00 unless we
10 get exhausted sooner. So Dr. Ward?

11 DR. WARD: I have a very simple question.
12 You describe the endoscopic partial gastrectomy as
13 having a complication figure of 9.5. How would you
14 rate the LAP-BAND placement endoscopically?

15 DR. GARCIA: I'm sorry? You meant
16 laparoscopically?

17 DR. WARD: Yes. Laparoscopically how
18 would you rate the difficulty of placement of the
19 LAP-BAND?

20 DR. GARCIA: I have never put in a
21 LAP-BAND. So I would have to defer that to someone
22 who has done a LAP-BAND.

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1 CHAIRMAN NELSON: The degree of difficulty
2 of the LAP-BAND is?

3 DR. GARCIA: The degree of difficulty is
4 what the experts would suggest to be on the order of
5 about five or six.

6 CHAIRMAN NELSON: Five or six. Five or
7 six? Does five or six sound right?

8 MR. VINCENT: Three or four.

9 DR. CHOBAN: Four or five.

10 CHAIRMAN NELSON: Three or four. Okay.

11 DR. CHOBAN: I think I would say four or
12 five. There's a learning curve on the LAP-BANDs, too.
13 But it's not as tight.

14 CHAIRMAN NELSON: Four to five. It sounds
15 as though that's a consensus.

16 DR. GARCIA: It's simpler than being a
17 roux-en-y gastric bypass.

18 DR. CHOBAN: Yes.

19 CHAIRMAN NELSON: Dr. Gorman?

20 MEMBER GORMAN: You were very eloquent in
21 your presentation about the need for earlier
22 intervention, not of the super obese but down to the

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1 NIH guidelines of 35, I think was their BMI, at which
2 they felt you could do surgical intervention.

3 Is there any data past that point that
4 would guide our discussion tomorrow for even earlier
5 intervention, which I think you implied you might be
6 interested in doing but stay within the safety of the
7 guidelines?

8 DR. GARCIA: Is there any data.

9 MEMBER GORMAN: On surgical intervention.

10 DR. GARCIA: On surgical intervention at a
11 much lower BMI.

12 MEMBER GORMAN: Correct.

13 DR. GARCIA: As far as having done them
14 successfully? Not that I am aware of.

15 MEMBER GORMAN: Thank you.

16 DR. INGE: Actually, in the packet in the
17 rec book, George Fielding's article, where he was a
18 senior author, Dolin was the first author, there was a
19 small handful of adolescents in that cohort that came
20 in with BMIs that caught my eye of less than 35.

21 DR. GARCIA: Oh, I'm sorry. I thought you
22 meant by age.

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1 DR. INGE: I meant by BMI.

2 DR. GARCIA: Oh, I'm sorry. I thought you
3 meant by age.

4 DR. INGE: But it's very sparse.

5 CHAIRMAN NELSON: Dr. Kral, do you want to
6 add to that information?

7 DR. KRAL: No. There are published
8 studies. Partly the SOS study itself had an inclusion
9 criterion which wasn't quite as strict. And they
10 reviewed that back in '97, their experience then.

11 But there are several series, one from
12 Italy on designing coworkers in a multi-center study.
13 And then there is the about-to-be-published study
14 from Melbourne from O'Brien, who actually has done in
15 adults BMI 30 to 35 against.

16 And he was prevailed upon to not use the
17 word "best" medical but optimum or state-of-the-art
18 medical treatment in the prospective randomized trial.
19 So there's data out there on 30 to 35 BMI.

20 DR. GARCIA: I misunderstood the question.
21 I thought you were talking about lower age.

22 CHAIRMAN NELSON: Since we seem to have

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1 transitioned away from questions to the speaker to
2 discussion among the panel, I think it's a good time
3 to say that we're going to have nine hours to do that
4 tomorrow, eight if you exclude lunch.

5 So I would like to thank Dr. Garcia for an
6 excellent presentation, remind people that we start at
7 8:00 a.m. tomorrow. And I don't think you could count
8 on this room being secured. So anything that you
9 think is eyeable, you should take with you. And I
10 think you could probably even just carry the papers
11 you've got because they may get cleaned up
12 inadvertently overnight.

13 So we'll see you at 8:00 o'clock tomorrow
14 morning.

15 (Whereupon, the foregoing matter was
16 recessed at 5:53 p.m., to be reconvened on Thursday,
17 November 17, 2005 at 8:00 a.m.)
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