DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Tuesday, February 3, 2004

9:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

P. Joan Chesney, M.D., Chair
Thomas H. Perez, MPH, Executive Secretary

SGE CONSULTANTS (VOTING):

Mark Hudak, M.D.
David Danford, M.D.
Richard Gorman, M.D., FAAP
Robert Nelson, M.D., Ph.D.
Susan Fuchs, M.D.
Robert Fink, M.D.
Victor Santana, M.D.
Norman Fost, M.D., MPH
Judith O'Fallon, Ph.D.
Ralph D'Agostino, Ph.D.
Mark Fogel, M.D.
Tal Geva, M.D.
Craig Sable, M.D.
Vasken Dilsizian, M.D.
Marilyn Siegel, M.D.
Phillip Moore, M.D.

MEMBERS (VOTING):

Mary Glode, M.D.
Steven Ebert, Pharm.D. (Consumer Representative)

FEDERAL EMPLOYEE (VOTING):

Mario Stylianou, Ph.D.

INDUSTRY REPRESENTATIVE:

Samuel Maldonado, M.D.

FDA:

Shirley Murphy, M.D.
Solomon Iyasu, M.D.
Hari Sachs, M.D.
Julie Beitz, M.D.
Sally Loewke, M.D.
Shavhree Buckley, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. CHESNEY: Good morning and welcome to what should be a very fascinating day and a half. I would like to start by saying that there is the potential for us to finish our work today if we stay very focused and very attentive to the specific issues that the FDA is asking us to address. But first we need to have the introductions and I think maybe we could start with Dr. Maldonado and go around this way, please.

DR. MALDONADO: Samuel Maldonado, from Johnson & Johnson.

DR. MOORE: Phillip Moore, from the University of California San Francisco, pediatric cardiology.

DR. SIEGEL: Marilyn Siegel, from Washington University in St. Louis, pediatric radiologist.

DR. DILSIZIAN: Vasken Dilsizian, University of Maryland, Director of Nuclear Cardiology, both adult and cardiology and nuclear medicine.

DR. SABLE: Craig Sable, Children's National Medical Center in Washington, Director of

Echocardiography.

DR. GEVA: Tel Geva, Department of Cardiology at Children's Hospital in Boston.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, statistician.

DR. FOGEL: Mark Fogel, pediatric cardiology, Children's Hospital, Philadelphia.

DR. SANTANA: Victor Santana, pediatric hematologist, oncologist at St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. GORMAN: Rich Gorman, pediatrician, private practice, Ellicott City, Maryland.

DR. EBERT: Steve Ebert, infectious disease pharmacist, Meriter Hospital, Professor of Pharmacy, University of Wisconsin, Madison.

MR. PEREZ: Tom Perez, executive secretary to this meeting.

DR. CHESNEY: Joan Chesney, Professor of Pediatrics at the University of Tennessee in Memphis and also at St. Jude's Children's Research Hospital.

DR. FOST: Norm Fost, Professor of Pediatrics and Director of the Beioethics Program at the University of Wisconsin, Madison.

DR. NELSON: Robert Nelson, Critical Care

Medicine, Children's Hospital, Philadelphia.

DR. FINK: Bob Fink, pediatric pulmanology, Professor of Pediatrics, Children's Medical Center, Dayton, Ohio.

DR. O'FALLON: Judith O'Fallon, biostatistician, recently retired from the Mayo Clinic.

DR. FUCHS: Susan Fuchs, pediatric emergency medicine, Children's Memorial Hospital, Chicago.

DR. DANFORD: Dave Danford, Professor of Pediatrics, Section of Cardiology, University of Nebraska Medical Center and Crayton University in Omaha.

DR. GLODE: Mimi Glode, pediatric infectious disease at Children's Hospital, University of Colorado in Denver.

DR. HUDAK: Mark Hudak, Professor of Pediatrics and Neonatology, University of Florida, Jacksonville.

DR. SACHS: Hari Sachs, Professor of Pediatrics and medical officer at FDA.

DR. IYASU: Solomon Iyasu. I am team leader at the FDA.

DR. S. MURPHY: Shirley Murphy, the "other

Murphy." I am the Director of the Division of Pediatric Drug Development and I am going to be sitting here today because the "other Murphy" may have to deal with counterterrorism.

DR. CHESNEY: Thank you and we particularly welcome our cardiology and imaging consultants so that we have some expertise on the committee. We are going to be very dependent on you to talk to us about degrading nuclear particles and so on in the major session for this morning. But next we would like Tom to give us the meeting statement, please.

Meeting Statement

MR. PEREZ: Thank you. The following announcement addresses the issue of conflict of interest with respect to Section 17, Best Pharmaceuticals for Children Act Adverse Event Reporting, and is made a part of the record to preclude even the appearance of such at this meeting.

This morning you will hear from Dr. Solomon Iyasu, lead medical officer with the Division of Pediatric Development. As mandated in the Best Pharmaceuticals for Children Act, Dr. Iyasu will report on adverse events for the

following drugs that were granted market exclusivity under 505(a) under the Federal Food, Drug and Cosmetic Act, Paxil, paroxetine; Celexa, citalopram; Pravachol, pravastatin and Navebjne, vinorelbine.

Because the agency is not seeking advice or recommendations from the subcommittee with respect to these products there is no potential for an actual or apparent conflict of interest.

The following announcement addresses the issue of conflict of interest with respect to the use of imaging drugs in conjunction with cardiac imaging procedures in the pediatric population and is made a part of the record to preclude even the appearance of such at this meeting. Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular firm's product is discussed, issues of broader applicability involve many sponsors and their products. All subcommittee participants have been screened for their financial interests as they may apply to products and companies that could be affected by the subcommittee's discussions of imaging drugs used in conjunction with cardiac

imaging procedures in pediatric populations.

To determine if any conflicts of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. Based on this review, it has been determined that there is no potential for an actual or apparent conflict of interest at this meeting.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Samuel Maldonado is participating in this meeting as an industry representative acting on behalf of regulated industry. Dr. Maldonado is employed by Johnson & Johnson.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's involvement and exclusion will be noted for the record.

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

Ted Treves is Chief of the Division of

Nuclear Medicine at Children's Hospital, Harvard, who was an invited speaker for today, will not be able to attend.

DR. CHESNEY: Thank you. Our first speaker this morning will be Dr. Rosemary Roberts, who is going to offer a welcome on behalf of the Office of Counteterrorism and Pediatric Drug Development.

Welcome

DR. ROBERTS: Good morning. I would like to take this opportunity to thank you all for coming today. I would also like to thank the "Murphys" for allowing me to come up and speak. I rarely get to do it; you know, I am sort of the guy in the middle. I know some of you had to experience much worse weather than we have here today in order to get here so we certainly appreciate all of your dedication in coming.

Our office, as you know, has two high priority areas, counterterrorism which we might be dealing with today unfortunately, and also pediatric drug development, and we are certainly happy that we have this program today.

We are excited about learning more about cardiac imaging and having this opportunity to

discuss it and have such a distinguished group of people here to help us see how to move forward in this area. So, thank you very much for coming. I hope that you have a good day and we appreciate all the advice that you can give us.

One other thing, as you know because Diane Murphy mentioned it yesterday, with the recent legislation, the Pediatric Research Equity Act, we now have a full pediatric advisory committee. We are working on that charter and hope to have something going on with that in the next couple of months and then we will be setting up that advisory committee. Thank you.

DR. CHESNEY: Thank you, Dr. Roberts. Our next speaker is Dr. Solomon Iyasu who is going to bring us up to date on the adverse event reports as required by the BPCA.

Adverse Event Reports per Section 17 of BPCA

DR. IYASU: Good morning. Yesterday I presented adverse event reports for paroxetine and citalopram pertaining to psychiatric adverse events. Today I will be presenting on adverse events reported for paroxetine and citalopram and then, subsequently, I will report on adverse events for vinorelbine and pravastatin.

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First I would like to acknowledge the contributions of these individuals.

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First I will speak about paroxetine and citalopram and then vinorelbine and pravastatin.

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The data source for the adverse events is from the FDA's Adverse Event Reporting System which is a spontaneous and voluntary system. This system has several limitations which I wanted to bring to your attention. The under-reporting is a very significant problem. There are reporting biases that may be associated with either media publicity or depending on how long the drug has been on the market. The quality of the reports is variable, often very scanty. And, this database only includes the numerator data, therefore, it is very difficult to estimate the true incidence rate of events or exposure risk.

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Since I will be talking about the use of these medications in the pediatric population, I would like to also tell you a little bit about this database that FDA has. The first is IMS Health,

National Prescription Audit Plus which measures prescriptions dispensed from retail pharmacies, but the disadvantage is that it does not provide demographic information or prescription use. So, it only gives you total prescriptions dispensed.

The other database is the National Disease and Therapeutic Index, which is a survey based on a sample size of about 2,000 to 3,000 office-based physicians. The small sample size can make these data projections unstable, particularly when use is not very prevalent as in the case of the pediatric population.

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Another database available to FDA is based on a large prescription claims database but, again, these data cannot be projected nationally. There is no methodology developed for that.

Premier is another database which contains inpatient drug use from about 400 acute, short-stay, non-federal hospitals. There is national projection methodology available for this data, but accurate national estimates are selectively available. Drug use cannot be linked to diagnosis or procedures, and the treatments administered at hospital outpatient clinics are not

included in this database.

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There is one more inpatient database, which is the Child Health Corporation of American Pediatric Health Information System which captures information from about 26 free-standing children's hospitals with charge level drug utilization data. Again, although this is very pediatric specific, the data are from a limited number of hospitals and, therefore, cannot be projected nationally.

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Now coming to the drugs that I will be talking about today, there is some background about Paxil which I mentioned in yesterday's presentation. It is an antidepressant which is marketed by GlaxoSmithKline, first approved in December, 1992. Its adult indications are several psychiatric conditions--major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder and generalized anxiety disorder, post-traumatic stress disorder. There are no approved pediatric indications. Exclusivity for this drug was granted on June 27, 2002.

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The relevant safety information on the

label as it currently exists refers to pregnancy category C, which means that the drug has not been studied in pregnant women and, therefore, when using it in pregnant women the risks and the benefits have to be weighed.

I talked about precautions specifically pertaining to psychiatric events yesterday. Today I have listed them here but what is specifically important here are the seizures and the adverse reactions with abrupt discontinuation of this medication, and in patients with a history of seizures caution should be exercised with the use of this medication.

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Additionally, there is information in the adverse event section of the label pertaining to pre-marketing reports and that includes hypertension, diabetes, dysphagia and nausea and vomiting.

In post-marketing reports there are reports of serotonin syndrome, hepatic dysfunction and anaphylaxis, and also in the overdose section of the label about dangerous hepatic dysfunction.

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Coming to the use data for this

medication, it is the second most commonly used SSRI in children. For some of you who were here yesterday at the other meeting this is a repetition but, for the benefit of the others who were not at that meeting I am repeating this information. Both pediatric and adult prescriptions have increased steadily in recent years. Pediatric diagnoses most often linked with use of this medication include depression, anxiety and obsessive-compulsive disorders. And, pediatric patients account for approximately 3.5 percent of total U.S. prescriptions of Paxil between July, 2002 and June, 2003.

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When we looked at the one-year post-exclusivity determination period, there was a total of 127 pediatric adverse event reports. After my review and excluding all the duplicates, these are the unique reports for pediatrics in one year. We categorized them into different categories and psychiatric adverse events accounted for about 68. The rest of them are discontinuation syndrome, about 7 patients. Maternal exposure was about 33; neurologic about 8; accidental ingestion in 2 and then others were 9. So, today we will be

talking mostly about the non-psychiatric which includes the 5 categories that I have here which are on this slide.

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First I will talk about the adverse events pertaining to pediatric deaths. There were about 10 deaths involving direct pediatric exposures; 9 completed suicides, which I discussed yesterday; and 1 case of Stevens-Johnson syndrome. That patient was also receiving valproic acid, with a known association with Stevens-Johnson syndrome.

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There were 3 deaths among patients with pediatric exposure. The pediatric exposures included congenital heart disease and 36 premature infants who died after 75 days postnatally. The second case was a 53-day old infant who was also getting OxyContin and immediate-release oxycodone and Paxil exposure prenatally--not the kid. Autopsy was done and it was determined to be a SIDS death by the medical examiner. The third case was a multiple congenital anomaly, possibly a genetic syndrome. This was an aborted fetus and it was a fetal death.

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Going into detail about the 33 in utero exposures or breast feeding exposures, there was a possible withdrawal syndrome reported in 11 patients, one of the fatalities previously described; and congenital anomalies in 5 patients and seizures in about 4 patients; developmental delay or abnormality in 4 and murmur or congenital heart disease in about 3; and insufficient weight gain in 2 patients; and there were others that included various events that could not be classified.

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Focusing on the direct exposures, there were 8 patients with neurologic events. Among these, 3 patients had extrapyramidal or movement disorders. Two of these involved other medications as well that are listed here, which are known drugs associated with this kind of syndrome. Seizures were reported in 3 patients. Two of these patients had existing seizure disorders and were also receiving Paxil.

There was one patient where there was a loss of consciousness and hallucinations. The patient was also on amphetamine-dextro-amphetamine at the same time. Then, there was one patient

where serotonin syndrome was reported as an adverse event.

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Continuing with the pediatric adverse events, there were also reports of accidental ingestion. One was a 2-year old who ingested 6 tablets of paroxetine and recovered without sequelae. A 2-year old was a comatose patient with ingestion of multiple medications including paroxetine who recovered after an ICU course. There were a number of medications that were involved as concomitant medications, including other psychotropic agents, theophylline, amytriptyline--there were several of them so this was a very complicated polypharmacy case. Other events--there were 9 single occurrences and the majority were labeled.

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In closing, most of the events were labeled or related to labeled events. Unlabeled events involved maternal exposures. And, the safety of paroxetine will continue to be monitored in the future. We could not determine causality of any of these medications because of the multiple medications and also the scant histories in some of

the case reports. Nevertheless, we will continue to monitor adverse events for paroxetine in the Adverse Events Reporting System.

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Now I will talk a little bit about Celexa, citalopram which is also an antidepressant, marketed by Forest Pharmaceuticals. Its only adult indication is for major depressive disorder and the typical adult dose is about 20-40 mg/day. Again, there are no approved pediatric indications. This was first marketed in July, 1998 and pediatric exclusivity was granted in July, 2002.

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Again just mentioning some of the relevant safety labeling associated with this drug, it is again a pregnancy category C drug. It is also excreted in breast milk so caution should be exercised when used in nursing mothers.

In the precautions section there are precautions regarding impairment of intellectual or psychomotor functions with the use of citalopram. Also, there is danger of seizures, especially in ones who have history of seizure, and citalopram should be used with care. In the post-marketing reports and overdose section of the label, there

are adverse events pertaining to QTc prolongation.

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Summarizing some of the use data for citalopram, it is the fourth most commonly used SSRI in children. Both pediatric and adult prescriptions have, again, increased steadily in recent years. Pediatric patients account for approximately 3.3 percent of the total U.S. prescriptions of Celexa. Pediatric diagnosis is often linked with its use in depressive disorders, obsessive-compulsive disorder and attention deficit disorder.

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For the one-year period of review, which includes the post-exclusivity period, there were 42 unduplicated pediatric reports after this review was undertaken, and 16 out of the 42 were in utero exposures and mostly resulted in unlabeled events and one death that I will discuss later; 26 children involved direct exposure and 8 resulted in unlabeled events and no deaths. As I mentioned yesterday, there were 16 serious adverse events, 10 hospitalizations and about 4 life-threatening and 2 with disability.

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Going to the gender and age distribution of these adverse events, they were both in females in both direct and in utero exposure. As expected, the in utero exposures were reported in 4 patients who were less than 2 years. The majority of them were actually less than 1. In the direct exposure they were mostly in the older patients, 9 from 6-11 years and 15 patients in 12-16.

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Looking at the reasons for exposure to citalopram in these reports, as I mentioned, 16 of them were in utero and included 13 patients who were receiving citalopram for the treatment of depression. Two involved ingestion of another person's prescription and then other events which are post-traumatic syndrome and GAD and RDD and also anxiety, aggression and one was ADHD, just one single occurrence of those conditions. Then, in 6 patients it was unknown why they were receiving citalopram.

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Focusing on the known adverse events, of the 16, as I mentioned, there was one death. There was an autopsy done and there was no cause of death identified by the medical officer. It was signed

out as a SIDS death in a 4-month old. There were congenital anomalies in 7 patients. Three were unrelated kidney malformations; 1 eye malformation; 1 cardiac defect; 1 cleft lip and 1 congenital megacolon. Then, there were 5 patients where potentially there was a neonatal withdrawal syndrome, and then there were 3 other patients with myoclonus and otitis in 1 patient and delayed head control at 1-month in 1 patient. In the last patient there was a report of fetal asphyxia.

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Among the direct exposure group there were 21 patients, excluding the 5 psychiatric events that I reported on yesterday. There were 4 patients in which cardiovascular events were reported. One was a supraventricular tachycardia in an 8-year old with a prior history of similar episodes. It resolved after Celexa was discontinued. There were 2 patients with prolonged QTc. One involved syncope and seizure in a 13-year old who was also taking other medications concomitantly, albuterol, cetirizine and montelukast. There was also a patient where an overdose of citalopram was involved in a 14-year old. Whether this was an intentional overdose or

accidental was not reported so we cannot give you additional details on that. There was 1 patient where arrhythmia was reported in an 8-year old with overdose of citalopram.

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In the group where there were reports of neurological or special senses adverse events, there were 8 patients. One involved demyelinating spinal lesion in a 13-year old who was also on methylphenidate and multivitamins. There was a patient with a visual field cut in a 15-year old who was also on Depo Provera and who improved after discontinuation of Depo. There was one patient with a cataract, a 10-year old, also on risperidone, and 5 patients with seizures.

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Among other events that were reported there were 2 patients where serotonin syndrome was predominantly given but also, as part of the syndrome, seizures occurred in both of these cases. Then, there was 1 where only syncope was reported with the use of Celexa.

There was one curious report of a false-positive drug screen for cocaine on crushed tablet. We tried to get additional information on

this and from the chemistry point of view there is no relationship between these two structurally or chemically. It may have been a problem of adulteration of the patient's medicine. We do not have any details but this involved a police test that tested a crushed tablet found on a person found to be positive for cocaine. There were others. Five patients involved concomitant medications and/or complicated underlying disease which could not be categorized into a specific category.

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In summary, unlabeled events included in the non-psychiatric adverse events are the ones that I mentioned involving in utero exposure and the case where demyelinating spinal cord lesion was reported for one patient; visual field cut in one patient and the supraventricular tachycardia in another patient. These are single occurrences. Supraventricular tachycardia is not specifically labeled but tachycardia and sinus tachycardia are in the label.

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In conclusion, we will continue to monitor these adverse events but I wanted to bring to your

attention that there will be updates that will be provided in the future meetings regarding three issues that are under review, neonatal withdrawal, ophthalmologic malformation and then the QTc prolongations. We will be reporting on this in future meetings.

So, I am done with paroxetine and citalopram and if there are questions about this section I will entertain any questions. There are more details that are needed but Dr. Hari Sachs will work very closely with me on these issues and we will have some details about the cases if there are any questions. Yes?

DR. CHESNEY: Yes, Dr. Nelson?

DR. NELSON: Remind me, given our discussion yesterday, can you tell from the data or, if you can't is it worth finding out what the timing of the suicide events on paroxetine is in respect to when the drug was started? In other words, within a week, the first two weeks of exposure to the drug?

DR. IYASU: It varied. It varied from patient to patient. There was no clear pattern. Most of them were on therapy at the time that the suicide events occurred. It varied from about 14

days to about a year in terms of how long they had been on therapy. The events that were reported varied also. But there was not much detail so that we can make a clear, distinct pattern as to when. Some of them were early; some of them were later. It was very difficult, as I mentioned yesterday, to try to pin it down because of the scanty descriptions that were provided in the case reports but most of them were on therapy. There were a few that were post-therapy and during the withdrawal period.

DR. CHESNEY: Dr. Ebert?

DR. EBERT: Of the 33 maternal exposures you noted with paroxetine, do you know what proportion of those were in utero versus breast feeding?

DR. IYASU: Out of the 33, about 6 of them involved also breast feeding exposure.

DR. EBERT: I noticed there was no caution regarding breast feeding, or you didn't mention one specifically with that product in the labeling.

DR. IYASU: Yes, I think I may not have mentioned it but there is also in the label information about nursing mothers.

DR. CHESNEY: Dr. Glode?

DR. GLODE: I just want to clarify, as part of the pediatric exclusivity there is no requirement for the sponsor to do any sort of random sample or active surveillance for safety issues or adverse events? They just also use this passive reporting system? Is that right?

DR. IYASU: Well, as part of the BPCA, it is my understanding that the manufacturers are required, just by FDA regulations, to report all adverse events that come to them to the FDA. But this is for the passive surveillance system. Unless there are specific sorts of adverse events that are agreed upon in the pediatric studies for follow-up, they do not have to report on follow-up. Diane can add to this.

DR. D. MURPHY: The only thing I wanted to add is that we have asked for specific post-studies, you know, completion of study surveillance for certain products. But it has to be asked for in the written request. Outside of exclusivity there are Phase IV commitments that could be asked for. But, in general, what you heard is what usually happens--studies are completed and unless there is a specific requirement they revert to the passive reporting

system unless a company notices a signal that they then bring to the attention of FDA.

DR. S. MURPHY: Joan, I just wanted to add for our guests that are here from imaging that this is mandatory one-year reporting required under the Best Pharmaceuticals for Children's Act in which a drug gets pediatric exclusivity, which you will learn about in a little while from Susan's talk. Then we are required by law to report to this committee publicly the adverse events that occur forward for one year. So, that is why you are seeing reporting on these drugs. They have triggered a time point for the committee to hear about the reports.

DR. CHESNEY: Could I ask a question, please? Could you clarify this--Dr. O'Fallon mentioned in the van this morning reading about this neonatal withdrawal syndrome and it didn't come up yesterday. I notice with paroxetine you commented that these are unlabeled events involving maternal exposure. What exactly is the withdrawal syndrome, and is this something that should be in the label? Could you elaborate a little?

DR. IYASU: These are issues that are under review right now, but to give you sort of

additional information on what the concern is I have some notes here. It is usually associated with reports that involve nervous or neuromuscular effects after birth when the mother is exposed to some of these SSRIs, including citalopram or Paxil. This may include symptoms like irritable or agitated crying, hyperreflexia, hypertonia, seizures or seizure-like movements, and also include some breathing difficulties as well as feeding difficulties. So, this is sort of a syndrome that is increasingly being recognized with babies who have been exposed prenatally to some of these drugs. It is still under continued review right now to see whether this is information that needs either to be communicated to the public or be put in the label. I can't give you more details except that we are looking at it very closely.

DR. CHESNEY: Presumably, these were serious enough to cause somebody to make a report which is impressive to me. This is quite an impressive number for just voluntary reporting. Do you have any more information about whether they needed to be managed? I assume if they had seizures they had to have some specific management issues.

DR. IYASU: I don't have additional information right now about what specific measures will be taken regarding this, except to say I think this is something that we are concerned about and specific recommendations as to what would happen as follow-up are still open.

DR. CHESNEY: Maybe I can ask some of the FDA folk, is there anything that we can do to help move this along? This seems like it might be a significant issue.

DR. S. MURPHY: I think just what you have done is expressing your concern and we will take that back to the Division. I think that it is under review right now and I think that is why Solomon can't say more.

DR. IYASU: Yes.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: Are you aware of the Canadian literature surrounding this withdrawal syndrome from the unit in Toronto that looks at maternal-fetal exposure rate and has noted an increased transfer to NICUs for babies born with these agents?

DR. IYASU: Yes, I am and it is good that you are pointing that out, and the Division is also

aware of the data.

DR. CHESNEY: I have one other question relative, I guess, to yesterday's discussion, the paroxetine 68 psychiatric adverse events in children, were those along the lines of what we were talking about yesterday, which is activation of stimulant syndrome, or do you have any further breakdown of those?

DR. IYASU: Actually, we were talking about this with Hari. Hari, do you want to comment on that?

DR. SACHS: You know, as Solomon pointed out yesterday, there are the 9 completed suicides and 17 suicide attempts. I went back and just checked the case reports to see how many of them were associated with agitation. I picked up 8, 2 of which have resulted in completed suicide, 2 with suicidal ideation, 2 with suicide attempts and 2 with self-mutilation. Interestingly enough, for 4 of them the kids' reasons for treatment were not major depression; they were OCD and anxiety; 4 of them were for depression and it was pretty split, half female, half male, and half of them were on concomitant medications, including other psychotropics or having a history of substance

abuse. So, it is definitely a very mixed bag.

DR. CHESNEY: If we subtract out the suicidal issues, that still leaves a significant number of other children. What were their adverse events?

DR. S. MURPHY: The other psychiatric adverse events, as I said, the totals were the 9 completed suicides, 17 suicide attempts, several cases of suicidal ideation and 10 of self-injury. Then, the rest of them were kind of emergence of other psychiatric symptoms such as mania. So, it depends I guess on what you look at but what I was thinking was that the agitation was picked up, or at least the other suicidality issue was picked up as well as the agitation. It wasn't that agitation looked, you know, linked to anything else at least in these 68 reports.

DR. IYASU: Yes, I think just looking at these case reports there was tremendous variability also. But you can find some agitation in some of the case reports and no mention of it in others. So, it was hard to sort of see which one is predominant there; there is a mixture.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I realize this suggestion may

be naive from a resource point of view but, given the discussion, does it make sense to do a more in-depth case ascertainment both for the cases you have got and to see if there are other cases, and to see if someone could do a case study design approach to see if they could ascertain that this--you know, similar to what happened with the rotaviral vaccine--might be a hint relative to the timing and to this issue of agitation? I mean, that might be one way to try to sort this out?

DR. IYASU: I think that is a good suggestion. These kind of studies always require additional resources that the Office of Drug Safety may not have available, but theoretically I think you can go back and try to ascertain some of these cases. But one thing that we have to be careful about is that the cases that come to our attention are a selected few and we don't know what they actually represent because, you know, it is really a small percentage of an unknown group of adverse events. So, it requires I think careful assessment of what the cases actually represent. Do they represent other cases that are occurring in the population? But it is a good suggestion.

DR. CHESNEY: Dr. Glode?

DR. GLODE: I would just like to emphasize, and I think this came up for many people yesterday, that with a database of between 3,000 and 4,000 children with regard to safety issues, it is a very inadequate number for safety. So, there needs to be some mechanism I think, other than this passive surveillance reporting, for doing additional safety studies whether that is by Phase IV studies from the sponsor, or whatever, but there needs to be more safety data beyond 3,000 to 4,000 I think for children for these drugs.

DR. IYASU: I think your point is well taken.

DR. CHESNEY: Thank you.

DR. IYASU: All right, thank you.

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Now I will report on two other medications that have received exclusivity. The first drug is vinorelbine which is an anti-tumor drug marketed by GlaxoSmithKline. The indications which are approved are in adults as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced non-small cell lung cancer. Again, there are no approved pediatric indications for this

medication. Exclusivity was granted on August 15, 2002.

[Slide]

Summarizing the use data, there wasn't much in terms of our databases that revealed a lot of use for this medication in the pediatric population.

In CHCA, which is a children's hospital corporation database which is 26 children's hospitals that I mentioned before, which is a discharge-based database, there were 5 discharges in 2001 and about 21 discharges in 2002 that indicated that this medication may have been used. The diagnoses that were closely linked with its use were put under the category of chemotherapy and most of them were Hodgkin's disease.

[Slide]

Looking at the adverse event reports for vinorelbine, the total raw number of adult and pediatric reports that were received were about 495, and 181 of them were domestic and 314 were international reports. These are not adjusted for duplicates so this includes duplicates also.

Looking at the pediatric reports for the one year, there were 3 unduplicated pediatric

reports and 1 was U.S. and 2 were foreign. All were reported as having serious outcomes but there were no deaths with the use of this medication in the one-year period that was evaluated. Five of the 16 adverse events that were reported were considered unlabeled. The diagnosis or the reason its use was for the treatment of rhabdomyosarcoma in 2 of the patients and 1 of the patients had neuroblastoma and the drug was being given for that treatment.

[Slide]

I am just summarizing the 3 patients who were reported to us with adverse events. The first one is a 14-year old with rhabdomyosarcoma who developed neutropenia, a labeled event, and was successfully treated with Nupogen.

The second patient was a 2-year old with rhabdomyosarcoma who developed life-threatening adverse events including unlabeled events that included epidermolysis, muscle inflammation, somnolence and tachypnea. This patient was also on cytoxan. The patient was hospitalized for about 16 days and eventually recovered and was discharged.

A 6-year old was diagnosed neuroblastoma and developed adverse events including one of the

unlabeled events, the muscle spasm, but the adverse events that reported for this patient resolved after lowering the dose of vinorelbine.

[Slide]

So, it was a small number of reports that we got for the labeled and unlabeled adverse events were reported, as I mentioned before. The unlabeled events have also been reported in adults and are not unique to pediatrics. The FDA will continue its routine monitoring of additional data on adverse events in all populations, including pediatrics, to follow-up on the significance of any of these events.

[Slide]

The last drug I will be presenting on is pravastatin, which is one of the statins. It is marketed by Bristol-Myers Squibb. In adults it is indicated for the prevention of coronary and cardiovascular events and hyperlipidemia. In children it is approved for 8 years and older for the treatment of heterozygous familial hypercholesterolemia. Pediatric exclusivity was granted on July 10, 2002.

[Slide]

Drug use databases indicate that the total

dispensed prescriptions have increased by about 17.5 percent between September, 1999 and August, 2003. That is, from 13.4 to 15.8 million per year for pravastatin and that is adults and pediatrics. This is total dispensed prescriptions. Pediatricians wrote about 47,000 or about 0.4 percent of the total of the 15.8 million pravastatin prescriptions during that period.

[Slide]

Looking at the proportion of pediatric prescriptions, an estimated 7,900 prescriptions were dispensed nationwide to pediatric patients aged 1-16 years. This is based on a calculation of the proportions that were obtained from advanced PCS, which is a database that I mentioned before which has demographic information, and applying it to the total dispensed prescriptions. It is a small number but this has to be interpreted with caution because really this is an estimate.

[Slide]

There was a total number of adult reports, about 993 reports during the exclusivity period and 691 were U.S. and 302 were international reports. There were no pediatric adverse event reports that were mentioned in the one-year exclusivity period.

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Therefore, I don't have any additional comments on pravastatin in the pediatric population, except to say that we will continue to monitor the database and see if there are any adverse events that emerge. Thank you very much.

DR. CHESNEY: Thank you. Are there any questions? Yes, Dr. D'Agostino?

DR. D'AGOSTINO: Could you tell me or us what the physicians do with the statins in terms of muscle, liver and so forth in the pediatric population? Do they do anything routinely in terms of the side effects? I mean, what do you do with a child with muscle problems? The children are growing and so forth so how do you recognize that that is happening?

DR. IYASU: Well, from the adverse event reports there is no way to tell, or there is no information as to what actually is being done to treat that, except in the cases that were presented today where they were admitted but what actual treatment was given was not clearly specified.

DR. D'AGOSTINO: Do we know if there is withdrawal of the drug in the children where things like that might be happening? That is not an

adverse event necessarily but if the children are complaining about muscle pains and so forth.

DR. IYASU: I can't tell you because the narratives that were provided to us were very scanty. So, what treatment was given to these individual patients is not clearly stated in those narrative reports, except that there was an ICU course for one of them where it was considered to be serious enough that the patient was admitted. In terms of the complaints, they were elicited and reported by a health professional. Whether these were based on clinical records or medical records or whether they were just clinical encounters, I couldn't tell from the narrative.

DR. CHESNEY: Dr. Santana?

DR. SANTANA: Can you clarify for me a process issue? My understanding is that when an agent is granted exclusivity there is a commitment to do a number of studies and those studies may occur in different time lines. When does that data from those studies surface in adverse event reporting to this committee? Because it seems to me that what we are seeing are reports that are coming from different sources, more public kind of usage sources, but the data from the actual studies

that are being done or have been done under the exclusivity--when does that surface for us to see in these reports?

What made me think about that question is that for a lot of the oncology drugs that may be granted exclusivity, and I think this one is a good example, those studies will occur in a semi-closed system either through the cooperative group mechanism or through large oncology institutions, and those data may not necessarily show up in these other databases. For the oncology drugs, why don't you go to the NCI and request their adverse event reporting for the pediatric patients that are participating in those studies under drugs that have been granted exclusivity? That would be a more enriched data set than using this other system. Can you comment, please?

DR. IYASU: My comment is that the adverse events are reported to FDA, again, through this passive system. The exclusivity is granted on a specific data and then, if there is a change in labeling for example, it may not happen for several months after exclusivity is granted. So, in theory, what you would expect is that there would have been a change in the label and then there

would be increased usage of the medication and then we have to monitor or would pick up if there are any adverse events that emerge as use expands. But with many of these drugs maybe the indication is not approved and, secondly, there is a time lag between the use and the period that we are looking at because this is immediately the one-year after.

Now, we depend on adverse event reporting with the system that we have. We don't have any other system. But an active surveillance mechanism is where we actually go to do case finding and querying other databases is something that is a good idea. But, again, as I said before, that system is not in place to go after that.

DR. SANTANA: So, the data that is being collected by the sponsors for the studies that may be related to exclusivity, when does that data surface for us to see?

DR. IYASU: Oh, that is a question that--

DR. S. MURPHY: Yes, the medical officers' reviews have to be posted on the web 180 days after exclusivity is granted. I think you bring up an excellent point. I think what we are trying to do is interpret the law and figure out the best way to report to you, and that is one of the things I was

going to ask you, if this is the best information. What we are doing now is going to the AERS passive system and picking up all the reports for a year after exclusivity. We are not going into the trials and pulling those out.

DR. SANTANA: Yes, what highlighted my comment was the oncology example.

DR. S. MURPHY: That is a very good example.

DR. SANTANA: You would not pick up a lot of the oncology adverse event reports through these databases. You would have to go to a very enriched data set that already exists.

DR. IYASU: I agree.

DR. SANTANA: There is a lot of under-reporting here.

DR. S. MURPHY: Yes, there is a lot of under-reporting.

DR. SANTANA: This drug is an example but I suspect if we continue that practice with oncology drugs we will see a lot of under-reporting that will not come out until years later when the drugs are being used in a different way.

DR. S. MURPHY: Well, I agree with you. I think that the reporting of a lot of this, you

know, can be enhanced and we have sort of taken a year now to report this way. I think we also realize that the label is going to get out there for six months at least. So, is there really, after exclusivity, a big peak in pediatric use, or does the use come later, or was it used off-label before?

DR. D. MURPHY: I think the question is really good but it gets to a different process and I think it is an important process for this committee to think about because it has huge ramifications. What the law mandates we do is, as has been noted, to report on the adverse event reporting after exclusivity. At some period in that exclusivity the product will be approved and labeled.

The issue is that the BPCA has said that this information will be posted. The studies will be posted on the web and theoretically in the medical review information on the oncology product--I mean, the information that came out during the studies should be up on the web at that point.

Now, I think the other issue though that people are pointing out, and that I think this

committee is now very familiar with is that if you have a new label and that label is supposed to reflect the adverse events that were defined in those studies, then that is the way of communicating to the public what those adverse events were that were found in that better process, which is controlled studies, versus this passive adverse event reporting. That label sometimes is not available except up on the web site somewhere for different periods of time depending on how many labels are out there already, etc. So, it will vary.

So, I think you are bringing forth a very important question which is access to this information, which we talked about yesterday quite a bit. Second is the issue--and I really think the committee needs to think about this for a long time--are you asking us to review every study that is approved under exclusivity? There have been over a hundred determinations and over 60, 70 labels. That would be 60 meetings literally to go over each of the studies. So, I think that is a different question. I just want to make sure that we define when the information will be available.

DR. CHESNEY: Dr. O'Fallon had her hand up

next.

DR. O'FALLON: I have another process issue. I was curious because in looking at pravastatin, or whatever it is, there are two different estimates of the size of the prescription to the pediatric population. On one slide it says pediatricians wrote 47,000 of the total prescriptions during that year and the other one says an estimated 7,900 prescriptions were dispensed. Now, I realize you are working off two different sets but the difference between 8,000 and 47,000 is big in my mind and I am wondering is that sort of a very high upper bound and a very low lower bound, or what. You are trying to get at what is the piece of the pie that goes for prescriptions to this age group.

DR. IYASU: Yes, I think that is an important point. There is obviously a big discrepancy between the two estimates. One is referring to dispensed prescriptions written by different specialties. The other one is getting proportions out of a database that is not nationally representative and applying the demographic percentage to the national database. So, we are trying to get sort of two estimates but

they are giving us different estimates and we don't know how to sort of marry the two. But we thought that we would give these databases and explain what the limitations of both of these databases are, which I mentioned before. So, that is a good point. It is something that we have to work on to try to get better databases that could give us better estimates and not miss significant portions of dispensed prescriptions. That is a good point. Thanks.

DR. CHESNEY: Dr. Gorman and then Dr. D'Agostino.

DR. GORMAN: I can explain four of those pravastatin prescriptions, I wrote them for my mother.

[Laughter]

So, a pediatrician wrote them but it didn't go to a pediatric patient. So, that is four and you only have 47,000 more to go. So.

The other issue that I think is a little bit more global is that I think I hear a different theme emerging from our discussion which is that we have listened to the AERS data reporting system and its weaknesses and we have listened to the concerns that there are safety signals we will not meet

during the controlled clinical trials for efficacy. I think the AERS system grew up in a totally different generation of information collection and distribution and perhaps there needs to be a more active system looking for safety signals than we presently have. I think I heard Dr. Glode say that and I have heard other people say that with active case finding there is a more active searching, and I am not sure that is inside the charge of the FDA but I am sure that that is something that would enhance the safety of these agents. Rather than demanding of sponsors that the clinical trials get larger and larger and larger, look for clinical safety signals and perhaps there can be another mechanism that allows us to look for safety signals for the rare events after post-marketing.

DR. CHESNEY: Dr. D'Agostino?

DR. D'AGOSTINO: My comment is similar to that. I mean, in some fields like cardiology with the statins we have an idea, we have a very good idea of what some of the problems are and there are lots of different companies and lots of different trials, but it is quite quick in some cases to put together how many problems are developing. Instead of each study being reported separately, I know

with the OTCs and things that we do in some of the cardiology we can quickly find out how many muscle problems are developing, how many liver problems are developing without having a list of each study being laid out but these companies are constantly surveying. They know what some of the problems are and they have active ways of getting at them. Are we doing the same here? I mean, I presume we are and the question is how do we get that information to the committee here and how you are actually pulling that data together because, as we said, the AERS is not really going to do it.

DR. D. MURPHY: The companies are required to report this to us so it is coming into AERS. If the company knows about it, it is coming in to us.

DR. D'AGOSTINO: What I was saying is some of these are doing active registries, surveillances and so forth so they are actively looking. They are not just waiting for a passive.

DR. D. MURPHY: I think what Dr. Gorman and you all are trying to say is that you have heard the limitations, and we have sort of pounded you with it multiple times, and that there needs to be a better way but that we can't power safety studies for rare events. That just won't go

forward; it is not feasible.

I was just trying to see if somebody from our ODS Office was here because it would be good for them to hear your concerns and we will relay those back to them, how can we improve the process? Can we target--I think one of the questions is can we target areas, which it sounds like others have, where we think there needs to be an active surveillance system? Certainly, as I mentioned earlier, we have done that in a few cases where we know what the safety signal is. If you know what the safety signal is, then it is a lot easier to design that kind of surveillance system. So, you know, it gets back to that kind of focused system versus finding in kids unexpected results which I don't know that we are able to do yet.

DR. CHESNEY: Dr. Danford?

DR. DANFORD: To briefly address Dr. D'Agostino's earlier question about what would the response of a pediatric cardiologist be to muscle pains, myalgias or muscle problems we might encounter in starting these medicines in children, I think that we would be pretty quick to withdraw the medicines under those circumstances. I don't think, watching the people who handle our childhood

lipid problems in our town--I don't think that the discovery of that or any of the other relatively well-known complications discovered by our adult colleagues would necessarily trigger a report that would show up in AERS. You know, we know about these things; we stop the medicines and we don't think about it. It highlights once again the inadequacies of this approach and our need to look for other ways.

DR. IYASU: I think these are all very good comments and, in terms of the limitations of the AERS database, I think everybody recognizes that it has very limited utility in terms of picking up adverse events. It is useful to sort of maybe generate some potential signals, especially rare events that have not been picked up in clinical trials, but to confirm the existence of an event in association with a particular drug it is terribly inadequate and I understand and I hear what you are saying in terms of are there any better ways of looking at adverse events and monitoring them that would be a step forward. But there are also limitations in terms of whether you do it for specific adverse events for a specific drug or whether you do it for all the medications

that are regulated by FDA. As Diane said, it has been done for certain specific events of concern but when you try to do it to capture all potential adverse events, that is a big undertaking and we look forward to having some specific recommendations from the committee. Thank you very much.

DR. CHESNEY: Thank you. Just thinking out loud, Dr. Danford raises a very interesting point which is that if there were a difference in the incidence of a labeled adverse event in children we would never pick that up because we would just say, well, yes, we know that happens but if it were more common in children than adults we wouldn't pick that up. Does that make sense?

DR. IYASU: Well, we look at sort of the pediatrics and compare whether it is more common in pediatrics for a specific event than in adults. But it is always very difficult also to sort of have a relative rate of the event in the two populations because of the different use patterns and different frequencies of use in the different populations. So, a sort of head-to-head comparison sometimes doesn't work but it gives us some idea in terms of whether there is a potential signal that

we need to look further into.

DR. CHESNEY: Right, but a lot of these wouldn't be reported to AERS because, "well, this is something that we know happens" and unless it may be happening much more often in pediatrics it wouldn't be reported because it is a labeled adverse event.

DR. IYASU: Absolutely. Under-reporting is one of the big issues in AERS. Thank you.

DR. CHESNEY: Thank you very much. I think we have one new person at the table, Dr. Stylianou, would you mind introducing yourself, please?

DR. STYLIANOU: Mario Stylianou, statistician from NIH. I do some work with pediatric clinical trials at the National Heart, Lung and Blood Institute.

DR. CHESNEY: Thank you. There is nobody scheduled to speak at the open public hearing but let me ask if there is anybody not scheduled who would like to come to the microphone. Apparently not. We are scheduled for a 15-minute break. Given the small room and small number of people and potential to move ahead today, maybe we could take 10 minutes and, according to this clock, be back

between 10:20 and 10:25 to begin our discussion of the cardiac imaging drugs. Thank you.

[Brief recess]

DR. CHESNEY: Let's get started if everybody could find their seats, please. We do have some new people at the table so I thought we might take this opportunity to let them introduce themselves and start over here.

DR. BEITZ: I am Julie Beitz. I am the Deputy Director of the Office of Drug Evaluation III.

DR. LOEWKE: I am Sally Loewke. I am the Acting Division Director of the Division of Medical Imaging and Radiopharmaceutical Drug Products.

DR. BUCKLEY: Hi, I am Shavhree Buckley. I am a medical officer in the Division of Pediatric Drug Development, and a pediatrician.

DR. CHESNEY: Thank you. Just one technical or business detail, it was brought to my attention that some people would be willing to either forego lunch or make it a brief 15-minute lunch in order to keep on going. So, please keep that in mind and we will raise it again at the end of this morning's session as to whether you want to do that.

The rest of our session very briefly, as I understand it--and this will be repeated to us a number of times but for the committee's benefit and for me thinking out loud, our challenge is to help the FDA determine what cardiac imaging drugs, not devices or procedures but what cardiac imaging drugs do we need pediatric labeling for. Very few of these imaging agents or drugs currently have pediatric labeling, and how many need it and for how many could the use simply be extrapolated from adult labeling? Specifically, they are interested in what imaging drug classes need further study. Secondly, what patient populations would be available to receive these drugs. Along that line, utilization information is particularly important. In other words, how many children would undergo a procedure involving the agent such that there would be enough to do a study with the agent?

So with that, I am pleased to introduce Dr. Susan Cummins who is the lead medical officer in the Division of Pediatric Development. I understand that in addition to introducing this session, she may have some comments for us about the previous issue of adverse drug reporting.

Use of Imaging Drugs in Conjunction with

Cardiac Imaging Procedures in the Pediatric Population Pediatric Regulatory Update

DR. CUMMINS: Good morning. First, just to comment on the adverse drug reporting feedback that you gave us, I wanted to let you know that we kibitzed over the break and what we will do for our next meeting and into the future is provide you with the medical officers' summaries for the drugs that are granted exclusivity. We will also provide you with the labeling changes, as well as the AERS summary that you get now in the summary that is provided to you in your packets.

Diane Murphy has already shared your concerns with the Office of Drug Safety who, themselves, are always interested in strengthening drug safety reporting to the FDA and we will be talking with them about your concerns and see how to go forward with them.

[Slide]

I want to welcome you all here. There are a lot of new faces at the table. I am Susan Cummins. I am a medical team leader in the Division of Pediatric Drug Development and Shirley Murphy asked me to tell you a little bit about myself so here is a 30-second story.

I came to the Division from the National Academy of Sciences a little over a year ago where I was the Director of the Board on Children, Youth and Families. This board was a joint board with both the Institute of Medicine and the National Research Council.

I also brought along a long experience with environmental health, especially in childhood lead poisoning. For many years I managed the childhood lead poisoning prevention program for the State of California. In that role we used meetings such as this one, advisory committees, extensively. We were actually mandated by state law to use advisory committees to help us with complex issues of science, medicine, public health and policy. So, I have a lot of experience with meeting processes both at the National Academy of Sciences and in California, and I love meetings like this. I think your input is just so valuable and really helps us be able to move forward.

I want to thank you in advance for all your time and wisdom, and at the end of the day for the advice that you are going to give us. Many of you, in addition to coming today, participated in a series of scoping interviews that we conducted to

plan this meeting and to help us define the issues that we needed to address. That was just unbelievably helpful. I don't know that we could have moved forward in planning this meeting without the input that you have given us already. We also look forward to a very stimulating and productive day so I want to thank you already for all that you have done.

[Slide]

What I am going to do today is give you a brief overview of the last decade of pediatric drug development efforts at the FDA. I am also pleased to report that the agency is fully engaged in efforts to strengthen labeling of products for use in the pediatric populations.

Today I am going to talk about the issues listed here. First I am going to review pediatric issues, especially pediatric safety issues which have long influenced the evolution of FDA law, regulation and policy. That said, today I am going to focus on recent milestones, those of the last decade.

I will also briefly review the written request process, discuss current pediatric labeling and exclusivity statistics, the big goals of these

efforts and pediatric resources that are available at the FDA Internet web site. For the standing committee members this will be yet another review and I apologize for that, though I appreciate Joan Chesney's gracious comments yesterday that no review could be too many. However, many of you are new, as I just mentioned and have just come for this meeting and this topic is intended to provide you with a quick primer on how these issues have unfolded at the FDA.

[Slide]

As in every field, we at the FDA conduct our work with many acronym shortcuts. You have your MRI, your PET, your SPECT, your XR, and we have our FDAMA, BPCA, PREA and WR. The acronyms I will use for my talk are listed here. The first three refer to recent laws. FDAMA is the Food, Drug and Cosmetic Modernization Act. BPCA is the Best Pharmaceuticals for Children Act. PREA is the Pediatric Research Equity Act. WR refers to a written request and PPSR refers to a proposed pediatric study request. I will describe all of these throughout the course of my talk.

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In 1994 FDA issued pediatric regulations

that required data review for pediatric labeling. This rule required sponsors to review both their existing data as well as available published literature to see if enough data was available to support pediatric labeling. No clinical studies were required by this rule. Importantly, this rule introduced the concept of extrapolation of efficacy data from adults to children when that extrapolation seemed scientifically appropriate.

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In 1997 FDAMA was passed by Congress. FDAMA actually brought the FDA law up to date. It was a big law that modernized the Food, Drug and Cosmetic Act. Included in this law were several pediatric provisions, most importantly the exclusivity incentive, which is a big carrot based on compliance with terms of a written request issued by the FDA to drug sponsors. Before the passage of FDAMA the pediatric market, with the exception of perhaps antibiotics and a few other product classes, was too small to support a drug development program so pediatric studies were not done. Pediatric exclusivity changed all of that, as you will see in a minute. The pediatric exclusivity provisions of FDAMA sunsetted on

January 1, 2002.

[Slide]

Now, what is pediatric exclusivity? Pediatric exclusivity is an additional 6-month period during which a sponsor retains exclusive marketing control of all forms of a drug product line. It requires either an existing patent or exclusivity and is not a patent extension. FDA doesn't have the authority to grant a patent extension; only the Patent Office can do that. Pediatric exclusivity attaches to an existing patent or to other exclusivities which have been granted by the FDA.

This is a very powerful economic incentive for pediatric drug development because it confers to the entire drug moiety and every product that contains that active drug product. It delays for 6 months the introduction of generic products. As soon as the generic product is introduced the sale of the branded product declines dramatically.

For example, consider the steroid fluticasone. When exclusivity was granted to fluticaszone it attached to Flovent, the inhaled product; to Flonase, the nasal spray; to Cutivate, the topical product; and to Advair, the combined

fluticasone and salmeterol product. Imagine, for example, a product with 2 billion dollars annually in sales. Exclusivity translates to an additional 1 billion dollars in sales. So, this is a very, very powerful economic incentive for pediatric studies, and this was the carrot that made pediatric studies economically feasible.

[Slide]

I want to touch on one part of FDAMA about which there has been some confusion on the part of industry, the FDAMA priority list. The priority list consisted of several hundred drugs that were prioritized for pediatric studies by the FDA. If a drug was on the priority list it did not require FDA to issue a written request. Issuance of a written request if a drug was on the priority list was optional. But important for now, this list has sunsetted. Its sunset was on January 1, 2002. So, it sunsetted when the pediatric provisions of FDAMA sunsetted so now this list is a piece of history; it really no longer exists.

[Slide]

The next advance I want to mention is the Best Pharmaceuticals for Children Act, the BPCA, which became law on January 4, 2002. The BPCA

re-authorized the exclusivity provisions of FDAMA for on-patent drugs. In addition, it also includes an additional mechanism for obtaining information on the safe and efficacious use of off-patent drugs in the pediatric populations.

There is a slide missing so I am going to tell you what it says. The Best Pharmaceuticals for Children Act--as I just mentioned, BPCA establishes mechanisms for study of both on-patent and off-patent products. It requires in addition the FDA to collaborate with NIH on these studies. For off-patent products that is the major focus of the work of our Office and for on-patent products that industry does not want to study. So, if industry does not want to study an on-patent product we have a mechanism through BPCA to get studies done aon that product for pediatric labeling, as well as mechanisms for doing studies of off-patent products. For both on-patent and off-patent products industry has the right of first refusal to conduct studies that are requested through the written request process.

[Slide]

There are two paths to a written request. First, FDA can itself issue a written request and

this happens when the agency determines that there is a public health need for the studies that are being requested. The definition of a public health need can vary on many factors, such as whether there is substantial off-label use; if the proposed use is a significant pediatric issue; and whether there are other treatment options available. Having a disease be prevalent is not the only factor that we fold into a decision about the public health need. Pediatric studies for drugs to treat rare diseases may also have a high priority, especially when no other treatment options are available.

The other path is when industry submits a PPSR to the FDA. In that circumstance the FDA may accept the proposal as it is and issue a written request. It may modify the proposal and issue a modified written request, or it may not accept the proposal at all and the factors that we just described fold into the decision-making process. In that case, if the FDA decides not to issue a written request then it will issue an inadequate letter.

[Slide]

Now, what is a written request? A written

request is a legal document that provides a detailed outline of the studies needed by the FDA to adequately label the product for us in the pediatric population. It is an outline, a detailed outline that does not have the kind of detail you usually see in a protocol. Once a study is moving forward based on a written request, then a protocol is developed. The written request specifies all the study needs to label the product, including indication, population, types of studies, PK, safety and efficacy studies for example, safety parameters that need to be monitored, whether there is a need for long-term follow-up and what that might be and the time frame for response. In the next few slides I am going to review the written request process.

[Slide]

These slides focus on the on-patent process. The off-patent process is fairly similar. In this example the industry sponsor submits the proposed pediatric study request to the agency and the FDA reviews the PPSR to determine whether there is a public health benefit to the proposed studies. Again, the public health benefit issue here is important. The agency only issues a written

request if it determines that there is a public health benefit to the studies. If so, it issues a written request and, again, if not, it issues an inadequate letter.

[Slide]

Once the FDA has issued its written request, the industry has 180 days to respond to that request. If it declines the request, then the WR may be referred to the National Institutes of Health Foundation for funding of the requested studies. I would add though that currently there are very limited funds available within the NIH Foundation to conduct studies of on-patent products.

[Slide]

I am not going to talk about this slide. I want to move on and talk a little bit more about the on-patent drug exclusivity process because that has been somewhat of a mystery, what happens at the FDA in this on-patent written request review issuance, and then review studies once they come in to the FDA.

[Slide]

This slide addresses all of that and I want you to focus on the right side of the diagram,

this column right here. Prior to issuing a written request the agency does background research on the drug product and the issues at hand and conducts a literature review. That literature review is used to inform the drafting of a written request. The draft request is then reviewed by PdIT, the pediatric implementation team which is a cross-functional team that meets regularly within the agency to discuss draft written requests.

Once the draft is reviewed, has been discussed, has been revised and finally approved, it is issued to industry by the review division. The studies are completed by the sponsor, if the sponsor agrees to perform them, and the results are submitted to the agency. So, we are right here.

Once the FDA receives the submitted study reports a time clock starts. It has 60-90 days to review the reports and make an exclusivity determination. The submission is reviewed eventually by the exclusivity board which is a cross-CDER team. It is a very formal meeting and the team is chaired by Dr. John Jenkins. The review focuses not on whether efficacy has been demonstrated but, rather, on whether the sponsor has fairly met the terms of the written request.

That is the legal standard that we must meet. This is determined by making a very careful comparison of the submission that we have received from the sponsor compared to the written request that was issued.

If, for example, the written request asks that 10 children between the ages of 6 and 10 be included in the study population, then the review carefully checks to see if, in fact, 6 [sic] children were included in the study population in the submission. If exclusivity is granted, then that notice is posted on the pediatric page and on the web. Other actions to the label follow within a few months.

[Slide]

This incentive has really been a tremendous success. Please note here, this slide reports on industry response to the written request process as of January, 2004. Your handout may say 2003. It is one of those last minute errors you see after looking at a slide a dozen times. To date we have received over 300 proposals from industry. We have issued nearly 300 written requests. We have made exclusivity determinations for 101 cases and granted exclusivity in 91 of

those cases. This effort has led to 63 new labels.

The significance of these new labels really cannot be underestimated. It isn't just data; the labeling changes determine how we use these drugs and provide new information on how to use these drugs safely in the pediatric population on issues such as dose, unanticipated adverse events and the like.

[Slide]

I want to move forward to the present. On December 3, 2003 the President signed the Pediatric Research Equity Act, PREA, into law. PREA mimics the Pediatric Rule which was overturned by the courts in 2002, and this form provides the stick that balances the carrot that I talked about earlier. PREA is retroactive for applications back to April 1, 1999.

[Slide]

PREA requires pediatric studies of certain drugs and biologics for the issues listed here: if there is a new indication; if there is a new dosage form; a new route; a new dosing regimen; or a new active ingredient. Biologics are included because biologics have not been eligible for exclusivity in the past because they don't have patents.

The Act also establishes, as was mentioned earlier, a formal pediatric advisory committee and this committee will be seated at the Commissioner's level so it will advise the agency on pediatric issues for most of the FDA centers--for drugs, biologics, foods and devices, probably not veterinary medicine. Its range of issues will be even broader than that of the current subcommittee which has tackled a number of issues. The range of issues we have tackled since I have been here is just extraordinary. Implementation of the Act is still under discussion within the agency. The FDA is currently in the process of developing a guidance to advise on how we plan on implementing the Act.

[Slide]

This is our goal for all of these efforts, to add new pediatric information to the labels of drug products that are commonly used in children. Before pediatrics came to the FDA drugs were commonly used off-label, as I know you all know, and in that circumstance each child was an N of 1. Little was learned from any of these individual treatment experiments and we already have gathered a lot of very valuable information since this

effort has started.

[Slide]

I want to close by mentioning just a couple of resources that are available on the FDA Internet. If you go to the FDA home page, which is shown here, at www.fda.gov and you look at the lower right corner--this little arrow right here, there is a little link to the pediatrics web home page.

[Slide]

Then if you go to the pediatric home page there is a lot of valuable information--statistics, guidances, information about pediatric advisory subcommittee meetings and much, much more.

That concludes my comments. I want to thank you for your attention and I will turn the podium over to Sally Loewke.

DR. CHESNEY: Just in advance of Dr. Loewke, I wonder if all of the speakers who follow her, and including her, could tell us just very briefly, 30 seconds, about your background, please.

FDA Perspective

DR. LOEWKE: Good morning and welcome all.

[Slide]

My name is Sally Loewke. I am the Acting

Division Director for the Division of Medical Imaging and Radiopharmaceutical Drug Products. I am a nuclear medicine physician and I am going to note some bias here. I am a mother of twins with a son who has had some cardiac problems, who has actually had to have cardiac catheterization and some cardiac procedures. So, I am going to throw that out just so you know.

[Slide]

Dr. Chesney and panel members, I really want to thank you very much for coming here today and taking time out of your busy schedules to talk about this very important topic, the use of imaging drugs in conjunction with cardiac imaging procedures in the pediatric population. As you know, cardiac imaging plays an important role in the management of patients with cardiac disease and to date we have very few drugs that are approved for cardiac indications in the pediatric population.

We are here today to get needed input from you about the use of these products in the pediatric population. The information that you will bring forward will be invaluable to the agency as we proceed in our efforts to provide safe and

effective drugs for the pediatric population.

[Slide]

These are several areas that I will be addressing over the course of this presentation this morning.

[Slide]

The FDA is a regulatory agency. It is made up of 6 centers. The center that is responsible for review of drugs for human use is the Center for Drug Evaluation Research. We are also known as CDER. An important piece of information to also take away from this slide is that the devices are regulated by a different center within the FDA, CDRH, Center for Devices and Radiologic Health.

[Slide]

CDER's mission is to assure that safe and effective drugs are made available to the American people.

[Slide]

The Division of Medical Imaging and Radiopharmaceutical Drug Products is one of 18 divisions that makes up the Office of New Drugs within CDER. The Division is responsible for the review of drugs that are utilized for diagnostic

imaging including some radiotherapeutic products as well. The medical imaging drugs have been broken down into two categories, the contrast agents and the radiopharmaceuticals. The definitions you are about to see come from the FDA draft guidance which is in your packet.

[Slide]

A contrast agent is a medical imaging agent used to improve the visualization of tissues, organs and physiologic processes by increasing the relative difference of imaging signal intensities in adjacent regions of the body. Some common examples of these types of agents include iodinated contrast, gadolinium and microspheres.

[Slide]

A diagnostic radiopharmaceutical is an article that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons, or any radioactive reagent kit or nuclide generator that is intended to be used in the preparation of such an article. One of the common radioactive tags that is used in nuclear medicine imaging, including nuclear cardiac

imaging, would be technetium 99-M.

[Slide]

As an aid to your understanding of the Division and its thinking about the development of medical imaging drugs, you were provided with the draft guidance for developing clinical imaging drug and biologic products in your preparatory package. This document provides information on important areas that need to be discussed during the course of drug development. I refer you to the guidance for specifics, however, I will briefly touch upon the types of indications that could be sought for both the pediatric and adult indications.

Structure delineation--an imaging agent is able to locate and outline normal anatomic structures and, in doing so, can clarify the spatial relationship of that structure with respect to other body parts or regions.

Disease or pathology detection--an agent is able to detect and locate specific disease or pathological states.

Functional, physiological or biochemical assessment--an agent is able to evaluate function, physiology of biochemistry of a tissue, organ system or body region. This type of indication

could apply to an agent that is used to detect either a decrease or an increase of a normal function or physiological or biochemical process.

Diagnostic or therapeutic patient management--a medical imaging agent would improve patient management decisions or improved patient outcomes, including predicting survival or patient response to specific therapies.

[Slide]

To provide you with a framework of the types of information we routinely see when new drug applications come into the agency, I have this one slide. It is not all-inclusive for the clinical assessment and it is not all-inclusive for the information that we seek in a new drug application but it highlights a couple of points I wanted to discuss further. For efficacy, obviously, we review the data and review the studies to make sure an appropriate dose has been selected that is going to give you a useful image. We look at the pharmacokinetics and make sure they are well defined.

The pivotal Phase III trials are the trials where we get most of our efficacy information and what we like to see is a trial

design that includes clinically relevant endpoints, relevant patient populations and an appropriate standard of truth.

The question is what does all that mean? I am going to give you an example to help illustrate my point here. It is not a cardiac example but I still think it makes the point effectively. If you are developing a medical imaging agent that you felt could distinguish between benign versus malignant lesions, having an agent that could identify a malignant lesion obviously has clinical utility. Physicians will know what to do with that information and it is very useful. So, you would then pursue study of that agent in a patient population who would present with a tumor or a lesion that needed further evaluation. Ultimately, how do you validate the performance of the new drug? You would do so in this case by getting biopsy and confirming the pathology of those lesions.

From a safety perspective, we identify any major toxicities that might have come about during the course of drug development and we put together an adverse event profile that, if the drug is approved, generally is put into drug labeling.

So, overall our review and action on a drug, whether it be approval or non-approval, is based on a risk/benefit assessment. In this case risk can mean a safety hazard or risk. It could also mean hazard could be occurring from a misdiagnosis as a result of the imaging drug.

[Slide]

The Division has several drugs in which cardiac indications are approved. This slide lists drug classes and some of the general indications that are approved in both the adult and pediatric populations. The iodinated contrast drug class is the only drug class that has a cardiac indication approval in both the adult and pediatric populations, that being for conventional angiography. The pediatric approval goes down to the age of 1.

The gadolinium drug products are not approved in either the adult or pediatric populations for a cardiac indication, however they do have other indications that are approved in both populations.

The radiopharmaceuticals--we have approval for myocardial perfusion identifying cardiac ischemia and other myocardial functional

assessments such as ejection fraction, wall motion and viability. Again, those are studied and approved in the adult population.

Microspheres are one of our most recent drugs that have been on the market. They have been approved for left ventricular opacification and endocardial border delineation but have only been approved in the adult population.

[Slide]

Historically, children were felt to be considered like little adults and we could dose on a milligram/kilogram basis and, therefore, research in children really wasn't necessary. However, in the 1970s there was a change in that thinking where people actually felt it was unethical not to study drugs in the pediatric population as many new drugs were flooding the market and were being used in this population.

Today, as Susan has mentioned, we have the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act which are congressionally mandated, and Congress has clearly stated that children deserve the same level of evidence as that provided for the adult approvals.

[Slide]

The agency has tried to foster pediatric drug development and, in doing so, has made comments about the potential use of extrapolation from efficacy data from adults to the pediatric population. Therefore, if the course of disease and the effects of the drug are similar in adults and pediatric patients, then the FDA may conclude that pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in the pediatric population such as pharmacokinetic and safety studies.

[Slide]

When may it not be appropriate to extrapolate? When the disease is different in etiology, pathophysiology or in its manifestations; when the response to therapy is different; when the pathophysiology may be comparable but the response unpredictable; or when pharmacokinetic parameters are not well-defined in the adult population.

[Slide]

We know that there are differences in pathophysiology of cardiac disease between the pediatric and adult populations. Pediatric population presents with congenital heart disease

and the adults with atherosclerotic heart disease, and most of our drug approvals for cardiac indications in adults have revolved around patient populations that have signs and symptoms of atherosclerotic disease. So, the question to ponder later today is do differences in the etiology and pathophysiology affect imaging drug performance?

[Slide]

We have had great difficulty in getting accurate use data of these products. In an effort to try to give you some perspective, we looked at the Child Health Corporation of America's Pediatric Health Information System database. Currently, this is inpatient data from 31 free-standing children's hospitals with charge level drug utilization information. It is our first access to pediatric inpatient drug use and, since many children's hospitals are the sites of research trials, we feel that we probably get great information on potential off-label use of these products.

This database, however, has a lot of limitations to it. You cannot nationally project. The FDA only has access to data dating back to

1999. There is no direct link between drug and diagnosis procedure. It does not capture outpatient use and free-standing image center use. And, the contrast media radiopharmaceuticals are usually bundled together with the imaging procedure and cannot be specifically separated out.

[Slide]

So, this is the result of our database search and this is specifically from 26 free-standing children's hospitals at the time this was done. These are drug mentions in the pediatric population for the years 2001 and 2002 out of the total discharges that you see at the bottom of the slide. The iodinated contrast agents have the most drug mentions for both 2001 and 2002, followed by the gadolinium contrasts, radiopharmaceuticals and the microspheres.

[Slide]

Since most of our products are not approved in pediatrics we have little knowledge about their safety. I just want to step back for one second to make one more comment about that database information on use. We are fully aware that it is not an accurate representation of the use of these products because we know many imaging

procedures are performed on an outpatient basis and are performed at free-standing imaging centers. So, we hope that the discussions later today and the presentations from our experts will help enhance our knowledge of the frequency of use of these products.

[Slide]

Unfortunately, we have a limited knowledge base for pediatric safety data as well since we have few approvals. So, in an attempt again to give you some kind of flavor of what we do know, we did a data search of the Adverse Event Reporting System, also known as the AERS database. It is a spontaneous and voluntary reporting system and it too has many limitations which you heard about earlier today. There is under-reporting; reporting bias; the quality of the reports is very limited; and you cannot estimate the true incidence rate of events or exposure risk.

[Slide]

I just want to go over the methodology briefly of our search. We did not want this whole meeting to revolve around any one specific drug but, rather, the drug classes so in an attempt to keep that theme with the search of this database we

selected two drugs per drug class which we thought were relative market leaders and did a search of the database in both the adult and pediatric population.

Once we got those results, we then combined them and, as you will see, the slides that will be forthcoming are combined data for the drug class per se. We report out the most common adverse events reported in 10 percent of the total or greater. We report out the deaths and the search time frames were variable depending on the specific drug product that we used and their original approval dates. Again, be warned that this database has its limitations and cannot be construed as an accurate representation of the adverse event profiles for these drug classes.

[Slide]

This is the data we generated for the iodinated contrast agents. As you can see here, there were 2,997 reports in the adult population versus 68 in the pediatric population. The common event types were pruritus, dermatitis and urticaria in the adults and urticaria, dyspnea and facial edema in pediatrics. There was a total of 274 deaths in the adults and 2 reported in the

pediatric population.

Those 2 deaths in the pediatric population included a 9-year old male having an abdominal CT who had an anaphylactic reaction and died. This patient was noted to have a history of asthma. The other patient was a 7-month old with multiple cardiac anomalies who died approximately 6 hours after a cardiac cath procedure. As you can note, these common events are really a hypersensitivity type reaction and these are very common for iodinated contrast agents.

[Slide]

This slide represents the gadolinium drug class. There is a total of 5,163 reports in the adult population versus 233 in the pediatric population. Common events in adults include urticaria, vomiting, nausea, dyspnea and pruritus, and in children vomiting, nausea and urticaria. There was a total of 108 deaths in the adult population and 3 in the pediatric population.

Those 3 deaths were as follows, a 7-month old with gastroenteritis had an MRI to exclude meningitis. The patient had spina bifida and the patient died 2 hours after the procedure from septic shock.

A 12-year old female died from complications of brain stem glioma and a 5-year old male with meningeal toxemia died approximately 8 hours after an MRI from complications of hemorrhagic stroke. Again, as I stated earlier, the gadolinium drug class does not have a cardiac indication approval in either population.

[Slide]

The radiopharmaceutical drug class--a total of 334 reports in the adult population versus no reports in the pediatric population. Common events in adults include dermatitis, pruritus, urticaria, nausea, cough, headache and dyspnea and a total of 16 deaths were reported.

[Slide]

The microsphere drug class--a total of 107 reports in the adult population, no reports in the pediatric population. Common events in adults are back pain and headache and no deaths reported.

[Slide]

Overall, to date we have few approvals of cardiac imaging drugs in the pediatric population. We have limited use data and limited safety data, and we have the question to ponder whether the differences between cardiac disease processes in

adults and kids can actually allow us to extrapolate the efficacy data.

[Slide]

These are basically the questions for the panel that will be coming up either later today or tomorrow. I just flash them on the screen for the benefit of the audience so you can understand as you listen to the speakers talk later.

The first question basically revolves around extrapolation. Is it possible? If so, when? The second question is a series of questions that we would like addressed per drug class category, asking whether there is needed study for the drug class and, if so, what patient populations, what disease states, etc.

[Slide]

The third and last question is the relevance of new drug developments in the field of adult cardiac imaging and whether they are applicable to the pediatric population.

[Slide]

So, we would really like today's focus to be on the imaging drugs. I know it is hard to separate the imaging procedure and the device but I ask that people try. We also know that there are

many ethical issues in pediatric research. Again, we would like today's discussion to focus on the science and trial design issues. Do we need additional drug labeling, and for what classes, and what do we need to know? How are these products being used and for what purpose and what population? And, how do they alter your management decisions, the information that you gather? The bottom line, do you feel that extrapolation is potentially possible?

[Slide]

I want to thank you very much for attending today. As Susan had alluded to, we counted on many people on this panel and others who are not present to help organize this meeting and your help has been very invaluable and I thank you very much.

DR. CHESNEY: Thank you, Dr. Loewke. We will have time for questions and answers of the speakers after the next two presentations. The next presentation is by Dr. John Ring, representing the American Academy of Pediatrics, to give their perspective on the issues Dr. Loewke just outlined.

American Academy of Pediatrics Perspective

DR. RING: One of the advantages of

becoming middle aged is that you get a bit farsighted over time so I am thinking that this will probably work.

[Slide]

Apropos Joan's request to identify oneself, I have found, now that I am clearly unequivocally middle aged, that it is important for me to start each day by orienting myself to a person, place and time--

[Laughter]

--so, this is who I am. This is where we are and this is who you are, in case any of you require this type of orientation as well.

The five physicians sitting to my right along this part of the table will offer detailed information this afternoon regarding the application of intravascular contrast agents and radiopharmaceuticals to various pediatric cardiac diagnostic modalities. My assignment is more general. It is to present the position of the American Academy of Pediatrics as to whether these agents should be studied at all. I believe I have been selected for this role because I have practiced pediatric cardiology for over 20 years with extensive experience in the cardiac

catheterization lab and because I am also a member of the national AAP Committee on Drugs. My two sons, Jack and Patrick who are sitting in the audience feel that I was selected for this presentation today so that they could miss three days of school.

[Laughter]

[Slide]

The four points which I am about to summarize represent what we know for sure about the use of intravenous contrast agents and radiopharmaceuticals in pediatric cardiology. These points are that congenital and acquired heart disease is common in children and of considerable clinical importance; that accurate diagnosis is central in order to effect a good clinical outcome; that the diagnostic use of intravascular contrast agents and probably radiopharmaceuticals is likely to increase in the target patient population; and, finally, that our current use of these agents is guided really by good intentions rather than by data.

Taken together, these points identify a clinical problem that is of major clinical significance in children. They indicate that there

is a trend toward increased utilization of these diagnostic units and they highlight what the Academy feels is a glaring deficiency in our knowledge base regarding their use.

[Slide]

As a good academician I did a literature search. I did a literature search in large part because the American Academy of Pediatrics has not given these agents focused consideration and, thus, there are no official AAP policies, technical reports or practice guidelines that speak to their use. Regardless, the AAP recognizes that in general children's health care needs are unique, that these needs commonly vary with the patient's age, and that optimal pediatric therapy, regardless of type, is predicated on the performance of appropriate scientific studies performed in children.

[Slide]

Put very simply, knowledge is good and children are not little adults. I spoke a minute ago in regards to a literature search in order to see what guidance we had there. With the help of three research librarians at two institutions, the University of Tennessee and St. Jude Children's

Research Hospital, we searched key words such as intravascular contrast agents and radiopharmaceuticals. We focused the search on children rather than adults. We specified that we were most interested in cardiac disease and we had a particular interest in identifying complications.

[Slide]

The databases searched are those that are listed and the time frame for the search is a particularly long one. Unfortunately, but not to much to my surprise, what we found is that there is virtually no information extant in the literature which speaks to the contemporaneous usage of contrast agents in pediatric cardiology or, by extension, radiopharmaceuticals.

Something has happened to my script. Well, let's go back to the four things that we actually know for sure.

[Slide]

What in particular is the scope of the problem? The reported frequency of congenital heart disease in the population is 2.03 to 8.56 per 1,000 live births, with a median figure of 5.93. The figure that is generally quoted for the quiz is the higher of these. Even when one requires more

firm diagnostic criteria, for example cardiac catheterization, intraoperative inspection or postmortem examination, the figure is still substantial, up to 4.3 per 1,000 live births.

We have a population of children with congenital heart disease which is aging. An article from The American Journal of Cardiology, in 1982, so a relatively dated reference, indicated that there were at that time approximately 8,500 children with operated congenital heart disease reaching adulthood each year. Thanks to advances in diagnosis and therapy that number is actually increasing. In addition, those patients constitute an aging population, the natural history for which is entirely unclear. So, we are obviously on a voyage of discovery.

As far as inflammatory cardiac disease is concerned, the first two points indicate that the incidence and prevalence of Kawasaki syndrome and acute rheumatic fever are substantial in the pediatric population. As far as myocarditis is concerned, more frequent myocardial biopsy in children coupled with better diagnostic modalities, for example PCR analysis, are beginning to extend the scope and define the specificity of this

diagnosis which to date has been largely descriptive.

[Slide]

One of the ways in which pediatrics differs from adult medicine is with its focus on the future. The mission statement of the American Academy of Pediatrics is very clear on this point: The AAP is committed to the attainment of optimal physical, mental and social health and well being for all infants, children, adolescents and young adults. Balance this against the fact that congenital anomalies are the fifth ranked cause of premature mortality in the United States. That is taken from a reference in Morbidity and Mortality weekly reports in 1998. Of interest for this group's deliberations, structural congenital heart diseases account for 6 of the 15 most lethal congenital malformations in this group.

[Slide]

Optimal interventions in pediatric cardiology really do depend, in large part, on good imaging. A good picture is worth a thousand words. Pediatric cardiologists and cardiovascular surgeons are visually oriented practitioners. We cannot treat effectively what we cannot see well. This

applies both to surgical and catheterization laboratory interventions.

Our patient population today is undergoing higher risk interventions both in the cath lab and in the operating room. These interventions reduce what we consider to be the acceptable margin of diagnostic error. Our patients are usually younger, sometimes much older--for example, adults with grown up congenital heart disease--and usually sicker. They have a limited tolerance for long, stressful procedures. Accurate imaging then provides the road map to reach our therapeutic destination in a timely fashion. Just as the children's oncologist can now choose the safest, most effective treatment for his or her patients with leukemia through use of genetic subtyping, so the pediatric cardiologist can choose, at least to a degree, the safest, most effective dilation balloon or closure device provided that he or she has a detailed and accurate image with which to work.

Finally, different imaging modalities are complementary rather than competitive. The echocardiogram, for example, will certainly satisfactorily define the basic anatomy of

tetralogy of flow. Angiography, however, is necessary to dilate and stent the focal pulmonary artery stenoses that often complicate this lesion and affect its clinical outcome.

[Slide]

The use of these agents is likely to increase. The volume, for example, of interventional cardiac procedures performed in children is increasing rapidly and in most centers interventional procedures take place in a third to two-thirds of cardiac catheterizations. These interventional procedures oftentimes require more angiograms, though of a different type or programs, and smaller but more frequent injections.

The number of adult patients with congenital heart disease is increasing as well. Thus, the assessment of myocardial function and blood flow becomes clinically of greater significance. This may be particularly true in those structural cardiac lesions which involve abnormalities of coronary arteries, for example transposition of the great arteries or anomalous origin of the left coronary artery from the pulmonary artery. This may apply particularly to children who survive acute Kawasaki disease but may

go on to be at cardiac risk for myocardial ischemia.

Our colleagues in interventional radiology apply procedures to non-cardiac areas in pediatric practice as well. For example embolization of venous malformations in the central nervous system and catheter-directed thrombolysis have implications for the use of these agents as well.

[Slide]

Young people search extensive databases on the web. Older people, like myself, pick up the telephone and call respected colleagues at big programs. So, what I did to prepare for this meeting was to query the cardiac cath lab directors at five programs throughout the United States. Four of these five programs are university affiliated. One is a respected adult in a pediatric multi-specialty clinic that does a large volume of pediatric cardiac disease. These five centers do a total of approximately 3,000 pediatric cardiac catheterizations in a year's time. The number of children they catheterize who are under one year of age is 30-50 percent and in some programs somewhat greater. The number of interventional procedures performed during these

cardiac catheterizations at present are upwards of 50 percent of these cases. Each of the programs did a handful, in one case approaching 5 percent of their cath lab volume, of immediate postoperative catheterizations. All of the centers had an increasing population of adults with congenital heart disease, 10-15 percent and in some cases larger.

What do these inquiring pediatric cardiologists want to know? the first thing they want to know is are nonionic contrast agents really that safe or have they just been lucky or good in their practice? The type of complications that we are talking about do not really reference nausea and vomiting; they reflect the sort of complications which are meaningful to this gun-slinging subgroup of pediatricians. That would be death, shock, anaphylaxis, life-threatening respiratory distress, gross hematuria, acute renal failure and so on.

Their experience is that with the development of nonionic contrast agents those complications, all of which were seen previously in frighteningly high numbers, have now disappeared almost completely. But there still is a question

in the mind of the practitioners as to what is safe. That is important particularly when we consider whether there is a maximum volume of contrast that I can inject safely. Most pediatric centers will limit contrast injection to a total of somewhere between 5-7 cc/kg of body weight during the course of a single cardiac catheterization. Some centers have hinted that as they approach that contrast wall they will forego indicated diagnostic procedures till another day for safety-related reasons. Is that a good practice? Nobody really knows.

So, cardiologists would like to know how safe these contrast agents are and does that safety factor vary with age, vary with lesion, vary with co-morbidities, or vary with the program of injection? Are a couple of great, big angiograms like we used to do better or worse for the patient than a whole bunch of small angiograms that might guide an intervention during a dilation and stenting? The data is simply not there.

Finally, is there an agent that will give adequate opacification at lower volumes of contrast administered in large patients? This is particularly apropos to that increasing patient

population, the adult with congenital heart disease.

The final question is one that many pediatric cardiologists ask themselves at the end of the day, especially if their day is ending in the middle of the night, how can I earn as much as my colleagues in internal medicine do? I know that is beyond the scope of this committee to answer.

[Slide]

Why wouldn't you study these agents? That is the question that I came to ask myself as I tried to prepare these comments. There may be philosophical considerations at work here. Some feel that data-driven decision-making is of no particular value. Others may feel that children are unable for some reason to receive the benefits that accrue to the adult patient through scientific study. Evidence-based medicine has refuted, I think quite effectively, both of these contentions and Congress has mandated that the benefits of study should be available to children as well as to adults. There may be some who believe that clinical resources do not exist to study this problem effectively in children.

Each of the institutions I have surveyed

indicated that they would be pleased to participate in studies to answer some of the questions that were raised. That doesn't represent written in stone commitment but it certainly does indicate interest and, coupled both with the incidence and prevalence factors that I spoke of initially, indicates that I think there is a patient population there readily available for study.

Finally, there may be some hard-core skeptics who are either unfamiliar with or frankly doubtful that important practice improvements have been made as the result of the fruits of FDAMA.

[Slide]

Dr. Cummins pointed you toward the FDA web site which, much to my surprise, I was actually able to access in a user-friendly fashion. That is a comment on me; that is not a comment on you. What I found is that the FDA has so far issued approximately 300 written requests and that, as a result of the studies requested, there have been over 90 changes in labeling. I can say as a pediatrician that fully 15 of those 90 changes are changes that impact my practice, five of which very directly and I am a niche practitioner--studies on midazolam, studies on fentanyl, studies on all of

the statins, studies on all of the prils have been important to me as a practicing pediatric cardiologist. As the Carpenters would say, we have only just begun to gather this information.

[Slide]

If you look at the exclusivity statistics you will see that some divisions have been very active in requesting studies in pediatric patients, and one particular division has not, the Division of--what do you call yourselves?--Medical Imaging and Radiopharmaceutical Drug Products. We single this out because it is the subject of today's discussion. We feel clearly, as pediatricians, that this area deserves study as well.

[Slide]

So, what are the recommendations of the American Academy of Pediatrics? We feel that the FDA should exercise its authority to require that appropriate studies be performed regarding the use of intravascular contrast agents and radiopharmaceuticals in children cardiac disease.

We feel that those contrast studies should focus on dosing considerations, balancing safety concerns with imaging effectiveness. As an aside, there is a question in the mind at least of all the

practitioners as to whether the new nonionic contrasts achieve a comparable level of opacification and, therefore, diagnostic information. Inadequate data or erroneous data can be as damaging as no data at all. So, clearly, that has to be balanced against the safety consideration.

Finally, we wonder, and this is just a question, whether a different regulatory posture may be needed on the part of the FDA in order to study these agents as effectively as others have been studied. It is our understanding that currently intravascular contrast agents and radiopharmaceuticals are regulated or studied under the auspices of a device rather than a drug, and we are not certain, if that is the case, whether this is the most effective way to pursue that. Regardless of whether it is a drug or whether it is a device, whether it is done through this division or that division, we feel there is a substantial problem to address a large pediatric population which can potentially benefit from an informed consideration of these agents. Thank you.

DR. CHESNEY: Thank you, Dr. Ring. Because of how these meetings are run, since Dr.

Ring is not at the table this is our only opportunity to ask him questions that the committee may have. Once our next speaker begins we can no longer ask him questions. Are there any questions for Dr. Ring?

[No response]

Thank you very much.

DR. LOEWKE: Excuse me, I just wanted to clarify that the contrast agents and radiopharmaceuticals are approved at the Center for Drugs.

DR. CHESNEY: Our next speaker is Dr. Geva, from the Children's Hospital Boston. Please, do give us a few seconds of your background.

Cardiologist Perspective

[Slide]

DR. GEVA: My name is Tel Geva and I am from the Children's Hospital in Boston. Just give me a second here to set this up. I spend the majority of my time--I divide my time between taking care of children with congenital heart disease and imaging. With regard to imaging, I divide my time between the cardiovascular MRI program in Children's Hospital in Boston, which I direct, and the echocardiography laboratory.

[Slide]

My task this morning is to give you an overview of progress in the field of pediatric cardiology. This is, of course, a mammoth task but what I will focus on are the following areas, first the scope of congenital heart disease; trends in congenital heart disease outcomes; trends in management; trends in imaging of pediatric and adult congenital heart disease; and, finally, I will try to identify some of the gaps in knowledge as they pertain to imaging.

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As the previous speaker has alluded to, the incidence of congenital heart disease as widely quoted is approximately 8 per 1,000 live births. This comes from the American Heart Association. With approximately 40,000 patients born every year with some form of congenital heart disease there are presently approximately a million Americans currently living with congenital heart disease.

An extensive review by Hoffman and Kaplan, published in The Journal of the American College of Cardiology in 2002, analyzed 62 studies on the incidence of congenital heart disease published since 1955. They found an incidence ranging from

4-50 per 1,000 live births. It turned out that the variations between those studies had mostly to do with the inclusion of small ventricular septal defects and it has to do with what kind of imaging or diagnostic modality was used to identify those ventricular septal defects.

However, moderate and severe congenital heart disease--the incidence of those is approximately 6 per 1,000. Those are patients that require some active management of their heart disease, and the incidence of 6 per 1,000 relates to the population of patients without excluding bicuspid aortic valve. If you include bicuspid aortic valve, then the incidence increases to approximately 19 per 1,000 live births.

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Here is a rundown of the types of congenital heart disease, and that is taken from that paper published in JACC and the numbers here are the median incidence per one million live births excluding non-stenotic bicuspid aortic valves and silent PDAs. Also excluded are tiny ventricular septal defects. Still, VSD or ventricular septal defect is the most common form of congenital heart disease, followed by several

acyanotic congenital heart diseases. Tetralogy of flow is the most common form of cyanotic congenital heart disease, followed by transposition of the great arteries. If you look down here, at the bottom, all cyanotic congenital heart diseases account for approximately 1,270 per million of live births; all congenital heart disease, approximately 7,600, which is close to the 8 per 1,000; and then bicuspid aortic valve being the commonest form of congenital heart disease. However it manifests clinically oftentimes later in life.

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Moving on to outcomes of congenital heart disease first looking at mortality, mortality has consistently decreased over the years. This is a paper that originated here from the CDC, published in Circulation in 2001, showing the deaths per 100,000, age adjusted, and showing a trend of declining overall mortality from congenital heart disease from 1979 through 1993.

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When you look at age at death, then it turns out that 51 percent of the deaths occur in infants; additional 7 percent between 1-4 years of age. So, the majority of deaths occur early in

life and then it plateaus for several decades until it starts to pick up again in the elderly. There are some racial differences with approximately 19 percent higher mortality in Blacks compared with Whites, as found in that paper, and slight gender variations, as you can see from this graph.

[Slide]

This is data from Children's Hospital in Boston looking at the cardiac intensive care unit admissions--the blue bars here, from 1992 through 2003. Here, in red, is the overall mortality from all causes in cardiac patients. This does not capture all deaths from congenital heart disease, nevertheless, the majority do occur in the cardiac intensive care unit and that is a relatively accurate representation of mortality in a large tertiary care acute care referral facility. If you look at the numbers, about 14 years ago overall mortality was approximately 6 percent and that has decreased quite consistently in the last several years to somewhere between 2.5 and 2.8 percent for overall mortality.

[Slide]

Still, despite the overall decrease in mortality there are some pockets of resistance and

there are certain types of lesions that are still at a high level of mortality. I am just bringing as an example pulmonary vein stenosis which is nearly universally a fatal condition. There are fortunately not too many similar conditions, nevertheless, there are some challenges in the field of pediatric cardiology even when it comes to mortality.

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However, the majority of patients with congenital heart disease survive and the majority of the therapeutic interventions--surgeries, interventional catheterization, medical therapy--do not lead to cure. Residual anatomical and functional abnormalities are very common in our patients. Neurodevelopmental issues are of substantial interest, as well as social and insurability issues.

[Slide]

As survival of patients with congenital heart disease improved attention shifted from getting these patients alive out of the hospital to improving their functional, psychological and social outcomes. These are just a few slides showing some of the work that has been done in that

field. This is from the circulatory arrest versus low flow cardiopulmonary bypass trial where patients with transposition of the great arteries were randomized into circulatory arrest versus low flow cardiopulmonary bypass, and this is the 8-year full-scale IQ results showing that in patients transposition in ventricular septum--their full-scale IQ is nearly normal as a group, whereas patients with transposition in ventricular septal defect who were randomized to the circulatory arrest arm actually as a group,had lower overall IQ.

[Slide]

There is similar data on patients after the Fontan operation, again showing full-scale IQ verbal and performance tests, and showing that overall these patients are doing nearly as well as the normal population.

[Slide]

Here is a group that doesn't do as well, albeit a small group of patients with interrupted aortic arch. Their performance is sub-normal in all levels of tests.

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It is interesting to compare patients with

congenital heart disease to other pediatric patients with different problems. This is what this work did, published in Circulation in 2001, comparing physical health summary and psychosocial summary in patients with transposition, asthma, juvenile rheumatoid arthritis and attention deficit disorder and you can see the comparison in this slide. Patients with congenital heart disease don't do particularly worse than some other common forms of pediatric illnesses.

[Slide]

I mentioned earlier that patients with congenital heart disease, despite the excellent survival, overall have residual anatomical and functional abnormalities. This is an example of a 22-year old woman who had coarctation repair in infancy so even when we think that our treatment leads to cure, these are some of the complications or residuals that could develop--a huge aneurism. You can see part of the dissection right here in a patient about 20 years after repair of congenital heart disease.

[Slide]

This is an example of a common problem in a fairly large and rapidly growing population of

patients, survivors of TOF repair. Most of them survive and they reach adulthood. However, most of them have significant pulmonary regurgitation. It is essentially part of the operation to repair the tetralogy and they have free pulmonary regurgitation which you can see here on this image. Here is a 4-chamber view showing the markedly dilated right ventricle and right ventricular dysfunction. So, these types of functional abnormalities are quite common in our patient populations.

[Slide]

Let me switch gears to trends in management of congenital heart disease. Many variables account for the dramatic progress in treatments of congenital heart disease: Better understanding of the anatomy, embryology, molecular genetics, pathophysiology and natural history and improved diagnosis and I will come back to that as this is the focus of this meeting. Support technology has improved dramatically, including cardiorespiratory support and monitoring technology in the intensive care unit, operating room and the like, development of extracorporeal membrane oxygenators, mechanical assist devices. Those are

some examples of improved support technology; pharmacotherapy such as pressors, ACE inhibitors, beta-blockers and the like. Surgical techniques have improved and transcatheter therapy is playing a major role in management of congenital heart disease.

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Let me briefly touch on the overall progress in our surgery for congenital heart disease. There has been a revolution in surgical management of congenital heart disease with early emphasis on a staged palliative approach, with emphasis on treatment of symptoms. Examples include aortic pulmonary shunts to treat cyanosis in patients with reduced pulmonary blood flow, or placement of a pulmonary artery band to control pulmonary over-circulation. That was then.

Nowadays there is a growing emphasis on early anatomical repair, with emphasis on restoration of normal physiology with complete repair of complex anomalies done soon after birth in patients that are as small as 1.8 kg, with or without the use of cardiopulmonary bypass.

Other areas of improvement include protection of vital organs. Areas of research

include circulatory versus low-flow bypass that I have mentioned earlier; improved myocardial protection; improved oxygen delivery; and then development of minimally invasive surgeries such as video-assisted thoracoscopic surgery and robotic surgery as an example.

[Slide]

This is the Da Vinci robotic surgery. For the purpose of this presentation, this is in fact a pig with a coarctation model and the surgeon, in fact, sits right here and this is the robot. The surgeon controls the robotic arms, which you can see here, from a distance. In this case he sits next to the operating table. In fact, it is possible to do that from thousands of miles away. Here is an example of coarctation surgery. This is practice coarctation surgery using robotic surgery. This particular experiment was done by Dr. Pedro De Lido from our hospital. You can see that the robotic arms are essentially doing pretty much everything that the human arm can do. What Pedro is telling me is that the degree of accuracy and control is far superior with this type of approach. In the interest of time, I will stop here but essentially all of these surgeries can be

accomplished robotically.

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Moving on to another area where there has been tremendous progress, this is transcatheter therapy of congenital heart disease. The interventionalists are able to treat a growing number of conditions without the need for a thoracotomy or full cardiopulmonary bypass, valve and vessel stenosis using balloon stents, radio frequency energy, occlusion procedures for atrial and ventricular septal defects, collateral vessels, fistulae and the like. There is a variety of occluding devices and coils available. Arrhythmia therapy and fetal interventions are only some of the excellent work that is done in the catheterization laboratory.

[Slide]

There has been a trend in the catheterization laboratory. This is the annual case volume in the cath laboratories in Boston from 1990 through 2003. I would just like to turn your attention to two things. Number one, the overall case load has gone up and down a little bit but hasn't changed dramatically. What has changed is the proportion of cases, in pink, of purely

diagnostic procedures. Not only did they go down in absolute terms, but even more so in relative terms. So, the percentage of non-interventional procedures, in fact, has gone down to less than 25 percent. That is, more than 75 percent of cases are, in fact, interventional.

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Moving on to a different area, that is, improved diagnosis which is the focus of this discussion, there has been obviously an evolution in introduction, development and use of various imaging modalities in the field of pediatric cardiology. Cardiac catheterization with the use of X-ray angiography has been the first, dating back to the late 1930s. I am not exactly sure when nuclear radioactive tracers were first introduced but I am told that goes many, many years back. However, the modern use of radionuclear cardiology, if you will, is not as old.

Echocardiography came into the clinical arena sometime in the late 1970s. Use of ultrasound in medicine goes back several years earlier than that but echo has truly revolutionized the way that pediatric cardiologists practice. I will not spend time on that. Needless to say, that

technology has evolved dramatically and is the primary imaging tool used in the field of pediatric cardiology.

CT came to the clinical arena sometime in the mid-1970s and is continuously improving in terms of resolutions and its role in imaging patients with congenital heart disease certainly has a place.

MRI is the newest kid on the block and is of particular interest to me. The success of MRI in congenital heart disease has to do with the transition from being primarily an anatomical imaging modality to being a much more diverse tool that allows for a comprehensive evaluation of the cardiovascular system including anatomy, function, flow analysis, effusion viability and so on and so forth. Dr. Fogel, I am sure, will get into that into more detail.

[Slide]

Just to give you a perspective with regard to the use of these imaging tools in congenital heart disease, here is the breakdown of use of imaging techniques. I didn't include CT simply because we don't really have an identifying code for cardiac CT as opposed to chest CT for various

lung diseases. So, we don't really know how many CTs we perform. Nevertheless, you can see here that echo by far has exceeded every other imaging modality.

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So, the excellent overall survival of patients with congenital heart disease and the associated high rate of residual anatomic and functional cardiovascular impairments in these patients result in a rapidly growing population of individuals with a life-long need for surveillance that includes cardiac imaging. In other words, the patient population that we will be asked to image is rapidly growing.

[Slide]

Here is some of the evidence for that. Here is the annual case load in echocardiography at our hospital. I can tell you that this is not because of improved marketing or because we have changed dramatically our capture of the local market. This is based on analysis of the data and mostly has to do with simply the growing population. This is a reflection of improved survival and the fact that these patients come back again and again and again because they are not

cured and they need to have continued imaging.

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Similarly, in the cardiovascular MRI program, albeit there are much smaller numbers, this not only reflects evolution of the technology but also the fact that the same patients come back again and again, and it gives you a flavor as to how these imaging modalities are used in clinical practice.

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The last issue I would like to touch on are safety issues in pediatric cardiac imaging. There are many safety issues that are worthy of in-depth discussion. Not all of them directly relate to this committee or the other committee or this body of the Food and Drug Administration. I am listing as many as I could think about.

The issue that is unique to pediatrics or nearly unique has to do with sedation. Young children cannot cooperate with many imaging tests and the more involved the imaging procedure is, the greater the need for sedation for the patient to stay still, calm, to alleviate anxiety, etc.

There are inherent risks of invasive diagnostic procedures that I will not go into but

they have to be taken into account. So, when you have a choice of making a diagnosis or getting information by a non-invasive technique or an invasive technique, the inherent risks of invasive techniques must be taken into consideration.

Ionizing radiation exposure--I will come back to that briefly. Contrast agents is the focus of this discussion so I will not discuss those. Radiopharmaceuticals, the same. Auditory trauma is something that is relevant to magnetic resonance imaging. Pharmacological testing--I am not sure if Mark will touch on that but we are doing a growing number of pharmacological testing in the MRI suite with children. Just to give you an example, children with Kawasaki disease who have large coronary aneurysms are being sent to us for assessment of myocardial ischemia and viability. So, we are doing adenosine stress, gadolinium perfusion and viability exams in those children.

Lastly, improper use of imaging technology, including an unfavorable risk/benefit ratio--this is not an obvious safety issue but I think it is. I think if a patient is set for a test such as cardiac catheterization or CT with its risk of ionizing radiation and there is an

alternative at least as good non-invasive test without those risks, then that patient is exposed to an unnecessary risk.

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Let me finish off by touching on ionizing radiation exposure. Briefly, this is a paper that was published in 2001 in AJR. I am sure many of you are familiar with it and, if not, the reference is available. It looked at the estimated risk of radiation-induced fatal cancer from pediatric CT.

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This is a graph of pharmacokinetics from a subsequent article. This is the estimated lifetime attributable risk of fatal cancer in pediatric CT. On the X axis is age and on the Y axis is the percent risk. So, 0.1 means 1/1,000 will die from cancer related to radiation from CT examination. Notice the relation between age and risk. Here is a unique issue relevant to the pediatric population. As you get to the first decade of life, especially during the first 4 years of life, these patients are particularly susceptible to risk of ionizing radiation.

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Dr. Brenner estimated that above the dose

of 50-100 mSv protracted exposure or 10-50 mSv acute exposure there is direct epidemiologic evidence from human populations that demonstrate that exposure to ionizing radiation increases the risk of some cancer.

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It takes years to realize the risk from ionizing radiation, as it did for realizing the relationship between cigarette consumption and lung cancer. So, with regard to cardiac catheterization in the pediatric age group, this is the first direct evidence or the first paper that I was able to find that actually demonstrated that link. This is a paper published in the International Journal of Epidemiology in 2002. The reference is up on top. This group looked at 674 children who underwent cardiac catheterization between 1950 and 1970 in Israel, and 28.6 had more than one catheterization. The mean age at cath was just about 9 years. Mean age at follow-up was 37.5 years. They compared the data to a national database and the expected number of malignancies was 4.75 whereas the observed number of malignancies was 11, yielding a standardized incidence ratio of 2.3 and you can see the 95

percent confidence intervals. Of the 11 malignancies, 4 were lymphomas and 3 were melanomas.

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In summary, advances in diagnosis and management of congenital heart disease have led to a dramatic decline in overall mortality to less than 3 percent. With the rapidly expanding population of patients with congenital heart disease, currently estimated between 1-2 million in the United States and growing, patients are rarely cured. Frequent anatomic and hemodynamic abnormalities require surveillance, that is, imaging. And, there is an increasing use of transcatheter and minimally invasive surgical interventions that also are based on imaging.

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Consequently, the number of cardiovascular imaging procedures in patients with congenital heart disease will continue to increase, and there is an urgent need for research in pediatric cardiac imaging with regard to safety and efficacy of radiopharmaceuticals; the cost and risk/benefit ratio of various imaging strategies; and minimizing exposure to ionizing radiation. Thank you.

DR. CHESNEY: Thank you very much. Your graphics were wonderful. We now can take questions for Dr. Cummins, Dr. Loewke and Dr. Geva. Dr. Fost?

Q&A for Speakers

DR. FOST: I doubt that you have numbers on this but I am interested in how commonly you get adventitious findings with the expanded use of these various imaging procedures. You mentioned one study showing 50/1,000 congenital heart disease picking up some clinically insignificant lesions but I am wondering if there were wider use of various imaging procedures how common do you think it would be that clinically insignificant findings would be picked up which could lead to both medical risks, that is, impulsion to do further studies and possibly even unneeded therapeutic studies but more invasive diagnostic studies, and psychosocial issues, stigmatization, confusion, parents thinking their child had some severe cardiac disease? How common is that and how do cardiologists handle that now?

DR. GEVA: No, I don't have numbers but, in the spirit of an overview, I think that overall the problem is not widespread. I don't think it is

a major problem. Perhaps I have a skewed view residing in a tertiary referral center. There are some issues with identification and proper diagnosis of congenital heart disease that have to do with some of these imaging tests performed by non-experts or by people who don't do that for a living. There has been, for example, an excellent paper published from UCSF where they looked at accuracy of diagnoses, accuracy of identifying congenital heart disease by echocardiography comparing pediatric echocardiography laboratory to adults and showing significant differences with either misdiagnoses or wrong diagnoses when echo was done in non-expert hands. Certainly from anecdotal experience, that is true for other diagnostic testing in congenital heart disease.

DR. FOST: I was more interested in the issue of over-diagnosis rather than under-diagnosis, but I am also interested in adventitious findings of extracardiac lesions. That is, you do scans of various types and you pick up lesions that you weren't even concerned about which are in the body, in the kidney, brain and so on, some of which may be clinically significant and variable but many and probably most which will be

of very uncertain clinical significance. Is that a common phenomenon? Do you have any thoughts about the expanded discovery of such adventitious things with the standard use of imaging, particularly in following up children over the years, and so on?

DR. GEVA: It happens. I don't know how common it is. I simply don't have data that I can provide you with. In the course of either an echocardiographic examination or cardiac MRI examination we have discovered all sorts of non-cardiac abnormalities, anywhere from thyroid cancer in young patients who get an MRI for congenital heart disease to bronchial cyst picked up on echocardiogram, and so on. This is anecdotal. I am not aware of a systematic data set that, in fact, looks at it, that I am aware of.

DR. CHESNEY: Yes, Dr. Santana?

DR. SANTANA: As a non-cardiologist, can you help me understand how these modalities are used in different historical time points for the patient? Do you always get an echo, a diagnostic cath or MRI diagnosis and then after that you say I am going to use this modality from now on or I am going to complement it with something else? That is one question, if you could clarify it for me.

The second is you obviously come from a large center where you have done a lot of cardiac caths historically. Have you looked at your data set in terms of second malignancies in relation to radiation exposure, and how do you quantify the radiation experience for patients receiving all this imaging?

DR. GEVA: Let me answer the second one while it is still fresh in my mind. We have not looked at the relationship between cardiac catheterization, ionizing radiation exposure and cancer in our center, and that would be an important study to do. We certainly have the patient population, both in terms of how long the cath laboratory in Boston has been active as well as sheer numbers. But that study, to my knowledge, is not under way.

We do have the standard--whatever is mandated by the regulatory bodies--elements in place to monitor radiation but then I have to say that as I started looking into radiation exposure I discovered that this is not as simple as meets the eye. There are various standards and measures and what is often measured and recorded is not necessarily what is biologically important. My

suspicion is that you would have to go in and prospectively set up a system to, in fact, evaluate the amount of radiation that patients are exposed to that is biologically relevant. Again, I don't think that we or other places do that.

With regard to your first question, I would say that echocardiography is being used widely almost as an extension of the stethoscope. When a question about congenital heart disease comes up based on clinical suspicion, it almost automatically triggers an echocardiogram. Other tests or other diagnostic imaging testing that comes after that varies quite substantially across the field, even within a center from cardiologist to cardiologist whether to catheterize, when to catheterize. Use of cardiac MRI as a widely available clinical tool is in its infancy. I suspect that is the case for the high quality cardiac CT technology and similarly radionuclear.

DR. CHESNEY: Dr. Fink?

DR. FINK: Just a quick question, you presented the spectrum for CT for head and abdomen. Where would cardiac CT fit in that in terms of radiation exposure?

DR. GEVA: Closer to abdomen, number one,

but what I did not mention is the fact that these analyses were performed from standard CT examinations. The modern CT angiography studies using multidetector CTs, in fact, expose patients to much higher doses of radiation.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: Two comments, one is addressing the incidental findings in imaging. I can address that from a CT standpoint. Cardiac CT in children is still a relatively young tool but in our experience we have really not found incidental lesions I think in anyone in that population. In adults it is different because there are more risk factors. So, in adults we are going to see those pulmonary nodules and it is a problem--is it inflammatory or is it tumor? In children that has not been the case so far in, again, relatively early experience.

The other thing, which I will address in some of my presentation, is the radiation risk with CT. In adults, if you do coronary CT you are using a limited area and you can get some high radiation. In children, when we do cardiac CT we are really examining the entire chest. I will show you that some of the doses are lower now with the techniques

that we are using.

DR. CHESNEY: Yes, Dr. Maldonado?

DR. MALDONADO: This question is for Dr. Cummins. Before I ask the question I just want to make the comment that I fully agree with her that this carrot that the BPCA has created is really significant, except that not all the drugs are block-buster drugs like fluticasone or Viagra, and I am sure you know that Viagra has a written request for pediatrics in the FDA. It had better be for a different indication.

[Laughter]

By saying that, I am not trying to minimize the importance even for all the other drugs that are not block-buster drugs. For me, working in the pharmaceutical industry, it is a very good tool and it is a good tool that helps us to balance the fears and the disincentives that have been in place for years, like the liability issues that are very big in the minds of the leaders in the pharmaceutical industry.

But there is another element that I should mention, and that is that the fact that the government has created two laws for pediatric drug development by itself makes a strong statement

that, indeed, you mean business and it is better to respond to that. Indeed, even when the economic incentive may not be significant, it is significant--those two statements that the government has made.

That leads me to the following question, as chair of the pediatric working group in PhRMA, with all the other members of that group we do an extensive advocacy because we are not just trying to use these tools but also advocacy. I went to the FDA web site in pediatrics--and by the way, as Dr. Ring said it is a very good, user-friendly web site--trying to look for the list of the sponsors who have not responded either because we have refused or basically have not responded to a written request, and I know that the list of non-responders was supposed to be made public and maybe I am looking in the wrong place or may have missed altogether that list of drug companies that have not responded. Why I wanted that list is because if I can identify those, I can do advocacy--not me personally but through all the members of the pharmaceutical industry--to find out why they are not responding and maybe correct that problem. But maybe I am looking in the wrong place

and I don't know where that list is.

DR. CUMMINS: I am going to defer to my senior management on that one.

DR. D. MURPHY: Dr. Maldonado, I think what you are referring to is the process where if we issue a written request and it is turned down by industry and we send it forward to NIH or to the Foundation, then it becomes public. But if we issue a written request to a sponsor for an on-patent product and they decline it and we do not forward it for some reason, such as additional information has occurred and maybe somebody else's study is done in some other way and we are not going to forward it, then we would not make that information public. So, what you are asking for is really the list of off-patent plus those that are referred to the Foundation. Is that correct?

DR. MALDONADO: Not the off-patent, the on-patent drugs that have minimal response from industry to forward to the Foundation. Some people actually questioned that in the law, saying are you trying just to embarrass those companies by making it public. That is fine, they can be embarrassed if you need to embarrass them but, at the other end, I would like to have that information to see

if, through the PhRMA pediatric working group we can do some advocacy for them to respond.

DR. D. MURPHY: I guess one thing I am just not completely sure is once we send it to NIH or to the Foundation whether at that point it becomes completely public knowledge. I mean, after we get the response from the industry that it is no and we refer it to the Foundation, it is when that process becomes public that we need to follow-up on with you. Okay? Because we do have a couple that we are referring to the Foundation. We will be glad to get those to you as soon as we can.

DR. CHESNEY: Dr. Fink?

DR. FINK: This is a question for FDA. From a regulatory standpoint, are there any obstacles or hurdles you would face in doing pediatric studies for some of these indications when the adult studies for similar--well, different indications but the same adult studies of cardiac use of these compounds have not been performed?

DR. D. MURPHY: You say this would be a new indication for the drug altogether?

DR. FINK: No, most of the FDA regulations seem to be based on the assumption that adult studies have already been performed and pediatric

studies then follow on. In some of these places we would actually potentially be jumping pediatrics ahead of adults because there is not an approved adult indication. Is that a regulatory problem at all?

DR. D. MURPHY: Susan?

DR. LOEWKE: I don't believe so. No, if there is a patient population for which there would be benefit to study this product we would pursue it. Obviously, we like to rely on a database of information from adults. That makes us much more comfortable when we move into pediatrics.

DR. CHESNEY: Dr. Glode?

DR. GLODE: I also have just a quick question for Dr. Cummins. If, by virtue of a written request or a proposed pediatric study request, exclusivity is granted and the company does three studies in children and all three show no efficacy, is then automatically the label of the drug changed to say studies have been done in the pediatric population which demonstrated no efficacy or what happens?

DR. D. MURPHY: If they do three studies and they are all negative, and they came in after BPCA was enacted and after they had gotten the

letter from us saying they were now under BPCA, all of those will go up on the web. Those studies will go up on the web. The controversy really now is the label. The divisions have had different approaches to this depending on the risk of putting the information in and having that information actually lead to improper use versus putting that information in and thinking that they are able to qualify it or modify it in a way so people understand the context. So, the bottom line is that sometimes they do put that in the label, that a negative study has been conducted, because they think that, unlike neuropharm where you may get 10 or 12 studies, you know, usually you get positive studies fairly rapidly if they are well designed and they think it is important to say, and we have had that happen where they put that information in the label.

One of the problems we have found is that if you put information in the label, and particularly if you describe the studies and the dosing that occurred in the study, it is taken as a de facto indication even when you say that that study didn't show efficacy. So, there is a balance in trying to provide information in the label that

describes the context of that information. In other words, this is three studies out of three really good studies, and they try to tell you how many patients and whatever, and they were negative, or these are three small studies and we don't think that they were able to tell us that much. That is the quandary because the label, as you know, is what allows marketing. So, that is why we have to be careful what we put in it, even if it negative. So, it is a balance of trying to put very few sentences in that would describe those negative studies and put them in context and that is why you get some of them not put in the label.

DR. CHESNEY: Yes, Dr. O'Fallon?

DR. O'FALLON: A follow-up on that then, say pediatricians are needing something, this is an indication that is real in the pediatric population, and they got three negative studies, that is, negative for efficacy but they collected a whole ton of adverse events data, what happens? Does the adverse event data information get into the label?

DR. D. MURPHY: The answer is sometimes. It would depend on is it already labeled. In other words, does the adult indication have the same

adverse event? And, there might be a statement in there and they may not say anything additional. However, if there are unique adverse events that are considered important and significant to be put in there, yes, they would put that in there. From yesterday's discussion you can see where that cut might vary but the answer is if they are unique adverse events that are safety issues that the division agrees are solid data, then it would go in there. But I think propyphol is one of those examples where there was a great concern about what it meant. You had one positive, one negative. There was a lot of discussion as to one center driving that data; lots of controversy. Yet, it was felt that we could find a way to state in the label in a limited way what the problem was so that safety data did go in.

DR. O'FALLON: Because yesterday we did see examples in which the statement was made that the adverse events pattern was similar to that of the adults and, yet, it really wasn't. When you looked at it the same things were showing up but in rather significantly different frequencies of occurrence. So, you know, they say "ah, yeah, they are seeing seizures." Well, they are seeing

seizures in half of one percent in adults and five percent of children. Now, is that similar? That type of thing.

DR. D. MURPHY: That gets to be a discussion within the division.

DR. CHESNEY: Dr. Fink, you have another question?

DR. FINK: This is I guess also for Diane. It sounded like your implication was that, let's say, you took a dermatologic topical that had not shown efficacy in young children but the safety data was okay, if you put that in the label the company could potentially then advertise that the product was safe to use for children down to age two even though efficacy hadn't been shown between, let's say, in age two and five.

DR. D. MURPHY: No, they couldn't market it as being proven to be efficacious. I guess what I would say is that if you got something in the package insert which says it has been studied and there were no adverse events, that might be utilized in a way that wouldn't be optimal.

[Laughter]

DR. CHESNEY: Yes, another question?

DR. FOGEL: Yes, this is a question about

the exclusivity rule. It just wasn't clear from the presentation how many times can industry actually use it? In other words, if they come out with one indication and they get the exclusivity rule and then they come up with a second indication does the exclusivity rule go into effect so they have a year's worth of exclusivity? Or, can it only be used once?

DR. ROBERTS: They can actually have two exclusivities. The first exclusivity is the one that Susan described in her talk where that six additional months of marketing attaches to the entire moiety or the entire product where they have existing exclusivity or patent to attach to. The second period of exclusivity is much more limited and has not seemed to be of big interest to industry. We have only had maybe three to five times where they have actually attempted to get the second period of exclusivity. For the second period it will attach only to the indication that they receive. Therefore, unlike the first period of exclusivity, they actually have to submit a supplement that gets approved and then they can get the six months of additional exclusivity on the three years of Hatch-Waxman exclusivity that they

would get with the approved indication. That has always been available to industry; that is not new, except for the six months of additional pediatric exclusivity. They have always had the ability to get the three years of Hatch-Waxman. So, we don't see that there has been much interest in that.

DR. CHESNEY: I think maybe we have exhausted all the questions. We are scheduled to begin again at 1:15. Unless I hear a significant outcry for making it 15 minutes instead of half an hour, I think maybe we will stick with the 1:15. Does the committee have any strong feelings about cutting off 15 minutes?

[No response]

So, we will reconvene at 1:15. Thank you.

[Whereupon, at 12:45 p.m., the proceedings were recessed for lunch, to resume at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. CHESNEY: We are still looking at the possibility of finishing up today. One suggestion that has been brought to my attention is that we could stay as late as 6:00 or 7:00 this evening if that would significantly affect people's travel plans. If everybody is planning to stay over tonight regardless of when we finish, then maybe it is not quite so urgent to finish. Does the committee have any feelings about whether we push on till later or shall we wait until after the break to make that decision? The question is are we having cocktails at 5:00?

[Laughter]

Well, we will wait until we see how the afternoon progresses and at the break we will make a final decision, and the FDA has offered to help with getting people tickets out this evening if that is our decision.

Our first speaker for this afternoon is Dr. Mark Fogel who will discuss contrast enhanced cardiac magnetic resonance imaging.

Contrast Enhanced Cardiac Magnetic Resonance Imaging

DR. FOGEL: While we are waiting, my name

is Mark Fogel. I am Associate Professor of Pediatrics and Radiology at Children's Hospital of Philadelphia. I am a director of cardiac MRI. I also spend a good portion of my time in the echo lab as well. I have been doing cardiac MRI since 1990 so I have seen a decade's worth, at least a decade's worth of development of the field. I did take a three-year hiatus to run large-scale clinical drug trials for a pharmaceutical company so I have the unique experience of being able to see drug development from both sides.

[Slide]

Today I am going to be talking with you about contrast enhanced pediatric cardiac magnetic resonance imaging. Although MRI is a multi-faceted technique, what I am going to concentrate on is just the contrast enhanced version of it. What I am going to talk to you today about--and this is the order in which the talk is arranged--is the description and properties of the most commonly used contrast agents, in particular gadolinium; how it is used, for what purpose; the dosing and administration; and then just a brief slide about the future.

[Slide]

I first want to take 30 seconds and step back a little bit for how MRI generates an image. That is important because you need to know where some of the contrast agents act. MRI can differentiate tissue by its magnetic properties. You will see on the screen the four major ways of how cardiac MRI does that: The hydrogen and proton density of the tissue; the T1 recovery rates, and T1 is also called the longitudinal vertical or spin-lattice relaxation; the T2 recovery rate, which is also called the horizontal/transverse/spin-spin recovery rates; and, finally, the motion/flow properties of the various tissues.

Gadolinium, the major contrast agent in MRI, works mostly in T1, right over here at this portion. Gadolinium itself is, as I said, the most common contract agent that is used by cardiologists for contrast enhanced MRI. It has 7 unpaired electrons in its outer shell. It is paramagentic, meaning that it generates a large magnetic moment when placed in a magnetic field. It is toxic. It is a heavy metal. So, the way we have gotten around that is that it is bound to a chelator. The most common one, and I will probably pronounce this

wrong, is diethylenetriamine pentaacetic acid, abbreviated DTPA. There are other ways in which gadolinium can be bound to large molecules, like albumin which doesn't diffuse through the capillary membranes, making it a blood pool agent. However, that has yet to be FDA approved.

[Slide]

It is an extracellular agent. It has rapid vascular equilibration and extravasation into the extravascular tissue. The mechanism of action, the way it works is that it increases the relaxation rate of the surrounding protons when it is injected in a dose-dependent fashion. As I mentioned before, it does affect T1 mostly and that is the major effect of gadolinium. It decreases the T1 constant and, therefore, increases the signal intensity of the image. For your reference, T1 of blood is 1,200 measure and it decreases it down to 100 measure at 1.5 tesla. The formula you see on the bottom basically is the way people calculate the relaxivities of the various gadolinium agents, R being the relaxivity constant and the Gd with the brackets around it is the concentration of gadolinium.

It does also affect T2 but that is a very

minor component of it. It increases the rate of decay of that and what tissues benefit the most from gadolinium targeting. That is, if the target tissue, the T1 value is similar to the background but, yet, the target tissue takes up the gadolinium, such as blood, and the rest of the background does not, that is the tissues that benefit the most from gadolinium enhancement. As such, because it affects T1 the most, sequences that have short repetition times, shown here as TR, moderately short echo times, or TE, as well as high flip angle studies are the ones that we use gadolinium with the most.

[Slide]

Pharmacokinetics is what makes this thing work. You will see why in a second. Free gadolinium, as you know, is a heavy metal and is toxic, as I mentioned. Its half-life is actually several weeks. The way we get around it is chelation, but chelation is a tradeoff. Chelation decreases the efficiency of increasing the T1 relaxation rate and, therefore, increasing the signal intensity. At the same time, chelation allows the toxicity to be much, much less. It decreases the toxicity because it allows for the

excretion of the gadolinium very quickly. When it is chelated there is a 500 time increase in the rate of renal excretion relative to pre-chelation. When it is chelated its half-life is about an hour and a half.

There are two ways in theory that gadolinium can become more toxic. One is that increased association from the chelated agent will increase the toxicity. You may see it in the literature called transmetallation. What happens is there are competing moieties, for example copper and zinc, that displace gadolinium from its chelator and, therefore, allows you to have free gadolinium in the body and, therefore, makes it a little bit more toxic. Of course, increasing the time of gadolinium in the body also increases its toxicity.

[Slide]

The median lethal dose for gadolinium DTPA is 10 mmo/kg. To put that in a reference frame for you, it is 60-300 times the diagnostic dose. The LD50 for two of the more common types of gadolinium preparations is highest Omniscan and lowest Magnevist.

Its safety profile is better than

conventional iodinated contrast agents. There are a number of studies. I just picked these three examples that you see here. There are few reported fatalities that were temporally related to gadolinium administration, and all those reports seem to question the association of the gadolinium administration with the fatality. As far as I could tell, there are no known contraindications.

[Slide]

If you look through the literature, adverse events are very low. Idiosyncratic reactions are rare. There is a good review article by Runge in The Journal of Magnetic Resonance Imaging, in 2000, which I believe is in your packet, that reviews that. In most of the studies the AEs that are related to gadolinium are approximately less than 5 percent, with the vast majority being minor, and there is a whole host of transient headache, nausea, vomiting, local burning, cool sensation, hives, temporal increase in bilirubin and a temporary increase in iron.

Anaphylactoid reaction is estimated between 1/200,000 and 1/400,000 doses. And, it is safe in renal patients even at doses of 0.3 mmo/kg, the normal dose being 0.1 mmo/kg. It has been

studied in numerous papers with patients with renal failure, dialysis, renal A stenosis and renal tumors. There are numerous reports, although I have to say that the reports that I could pick up were very small numbers, and here are examples of some of the reports.

[Slide]

There are multiple safety studies for use in children without danger. This is not for cardiac but it is for other indications so not in patients with congenital heart disease. There are five papers which I have listed here. The top one for example by Marti Bonmati, in investigative radiology, looked for example at lab values or vital sign abnormalities. There were 51 percent in the contrast group with an N of 39 and 80 percent in the non-contrast group with an N of 20.

If you take all these five studies together and you lump them together, they encompass doses of 0.1-0.2 mmo/kg, 1,368 children ranging in age from 15 days to 21 years of age. The AEs vary between 2 to 5 percent, none of which were serious.

[Slide]

This is the latest I could find in terms of the approved MRI contrast agents. The top seven

are gadolinium based. The one right below the purple box is a manganese ion. The last two are superparamagnetic iron agents. These two we don't use, we haven't used at all in cardiac. If you look at some of the gadolinium agents you can see that there are some differences between them, and I will go into that in a second but since I have the table up here, the highest ones in terms of osmolality are Magnevist and MultiHance and the lowest one is Gadovist. The osmolality is important because in case of extravasation of the gadolinium agent you can get pain at the site as well as sloughing so that is an important consideration.

[Slide]

There are similarities between the gadolinium agents, in particular reporting of adverse events in terms of their frequency being less than 5 percent and the types are all similar between the marketed products. The dose in general for all the marketed products is around 1.1 mmo/kg. The packaging is all the same. A 0.1 mmo/kg dose in a 0.5 mmo solution gives you a dose of 0.2 cc/kg.

The relaxivity, which is the amount of T1

and T2 relaxation with a given field strength and concentration, meaning how much it increases the signal intensity in the image, is the same throughout. Therefore, you really can't tell the difference between the gadolinium agents when you are examining the images. The nephrotoxicity for all the marketed products is none.

[Slide]

There are differences, as I mentioned. Magnevist has been on the market four years longer, at least four years longer than some of the others. Magnevist was approved in 1988, ProHance and Omniscan in 1992 and 1993 respectively. Some of the products are ionic. Magnevist has a charge of minus 2, and some of them are nonionic like ProHance, Omniscan and OptiMark. Their osmolality, as I mentioned, is different between the different marketed products. The upper dosage of Omniscan and ProHance has been approved for up to 0.3 mmo/kg. Magnevist, for example, is only 0.1 mmo/kg.

[Slide]

Now that we have talked about the different types and how gadolinium works, when we administer the gadolinium how do we monitor

patients during the study? The personnel that are available are cardiologists and radiologists, a sedation nurse and MRI technician. The monitoring equipment that we use is direct visualization via video link, direct audio feed from the scanner, ECG, pulse oximetry and when a patient is sedated we use end tidal CO2 as well as blood pressure monitoring.

[Slide]

In terms of the frequency of use, it really depends on the institution. At Children's Hospital Philadelphia we use gadolinium in a vast majority of cardiovascular cases and I would say that would be approximately 70-90 percent of the clinical cases that we do. Out of approximately 400 cases in the 2003-2004 academic year we will do approximately 330 cases with gadolinium. The notable exceptions are, of course, patients who we do an MRI on and they are normal; patients in whom we are just looking at RV dysplasia, although there is one paper I believe in the literature that has actually looked at gadolinium and RV dysplasia. And, when we are strictly looking at ventricular dysfunction without perfusion we won't use gadolinium.

The uses of gadolinium break down into three basic categories, anatomy, blood flow and tissue characterization, and we will go into those in detail in a second.

[Slide]

There have been multiple studies in congenital heart disease for anatomy, for efficacy. I just picked two examples here, one published in 2001 which took 73 patients looking at pulmonary artery size anatomy with and without breath hold. Then, one that was published in 2000 that took 38 patients with various types of congenital heart disease.

Studies investigating blood flow and perfusion and tissue characterization are still underway in the pediatric age group. The imaging itself you can divide up into two categories, first pass, meaning that the gadolinium is injected and we take the images during the first pass of the gadolinium through the circulatory system, or delayed enhancement, which means we will let the gadolinium circulate for 5-10 minutes and then do the study itself. The first pass technique, in and of itself, can be divided up into two different kinds. One is the time resolved where we are

actually watching the gadolinium enter the body and watching it circulate throughout the circulatory system. One is freeze frame where we will actually try and get all the pictures in one image and we are not following it through the body but we are going to get a static image that has all the gadolinium in it in the area of interest.

[Slide]

This is meant as an overview. These next three slides are going to be overview slides of the various uses for gadolinium in congenital heart disease. We will go over them in detail in a second.

This is specifically for anatomy. This is a gadolinium enhanced MRI looking at a patient with a coarctation which you can see right here. We are basically marching through the body from right to left in very thin cuts. There are maximum intensity projections which give you a much more three-dimensional picture of the cardiovascular system. This is actually a patient with a right aortic arch with a coarctation. There is a shaded surface display where we take the gadolinium volume data set and make a shaded surface display. This is a patient with an isolated subclavian artery

which you can see right here. Those two were freeze framed.

[Slide]

This is a dynamic injection, a time resolved injection, if you will, where you can also see the anatomy. This is during an angiography in the cath lab. This is a patient who had a stenting procedure and you can see the upper and lower limbs of the pathway right here.

[Slide]

In terms of blood flow, which is the second of the three uses, again you can see blood flow to the lungs and you can actually qualitatively see the perfusion in this time resolved injection.

[Slide]

Then, of course, there is myocardial perfusion where you can actually look at how well the myocardium is perfused. The cavities first light up and then the myocardial tissue itself lights up afterwards.

[Slide]

Finally, there is tissue characterization which is the third use. One can identify scarred myocardium, also called delayed enhancement. You

can see the arrows here. This is actually a patient after tetralogy flow repair and you can see the bright tissue here of the ventriculotomy. You can actually identify scarred or infarcted myocardium, as well as that different tumors of the heart take up gadolinium in different ways and you can actually characterize a tumor with whether or not it takes up gadolinium.

[Slide]

Now that you know the uses, let's see how they help us when we want see a patient with congenital heart disease. This is that patient whom we saw earlier who has a right aortic arch with a coarctation. It is actually a circumflex aortic arch where the aortic arch passes over the right, comes across and goes down the left side of the spine. So, these are the two-dimensional images that we would normally get. These are axial images so this is anterior, posterior, and that is right and left. You can see the aortic arch right over here. If we move a little bit lower down you can see the ascending aorta, part of the aortic arch here and then another circle here which is actually the descending aorta. If we go down a little bit further you can see the aorta crossing

over to that descending aorta on the left and then, finally, if you move down further you can see the descending aorta right here.

Although you are cutting at the picture, you would like to maybe see it a little bit better than to have to go through cuts. Basically what gadolinium does for anatomy is that it gives a three-dimensional nature to the picture.

[Slide]

So, you can look at those straight cuts or you can look at a maximum intensity projection and see the squiggly cardiovascular structure that is the aorta, right here, much better than you can visualize it as you are just going through a two-dimensional cut.

[Slide]

So, not only can we make it a three-dimensional image and twirl it around any which way we want, we can actually make very, very thin cuts and we can make them parallel to each other or we can make them rotate. For example, this is a rotation as if you were sitting on the top of the descending aorta and turning yourself over from posterior to anterior. If you follow it here you will see it again as it starts in the

middle. One branch comes out to the descending aorta and the other branch comes to the ascending aorta. So, it gives you a lot of flexibility in terms of visualization and getting a three-dimensional picture in your mind.

[Slide]

Not only can we do straight cuts, we can also do curved cuts. This is a patient actually after an arterial switch procedure for transposition of the great arteries and with left pulmonary artery stenosis which you can visualize right here in this axial view. What we asked the computer to do is to take this axial view and to cut it in this curved cut and show us what it would look like if we cut it in this particular plane. This is the resulting image. The computer basically displays it and you can see the stenosis of the pulmonary artery here very nicely. This is the left pulmonary artery, the right pulmonary artery and the main pulmonary artery right here.

[Slide]

Of course, if you don't like looking at any one of those, you can also go to a shaded surface display, again, made from the three-dimensional gadolinium images. This is

another patient with transposition after arterial switch and you can see how the pulmonary arteries drape over the aorta as the surgeon typically does a LeConte maneuver for that kind of repair.

[Slide]

Finally, time resolved gadolinium injection can also help. This injection was done to rule out a clot in the superior vena cava. You can see here is the gadolinium going in, first lighting up the right side and then lighting up the left side. You can see here is the superior vena cava and you can see that there is no clot or filling defect in this blood vessel.

[Slide]

What are the kind of patients we use gadolinium for anatomy? Well, we use it for patients with coarctation to get a three-dimensional picture of the coarct; patients with supravalvular aortic stenosis to get a three-dimensional picture of that for example in William's syndrome; a dilated aorta for patients for example with Marfan's. This three-dimensional image down here, maximal intensity projection, has both the dilated aorta right here, as well as two areas of coarctation right up here, in the

transverse arch and over here as we start going into the abdominal aortic arch; aortic aneurysms and dissection as well as vascular rings. This is a shaded surface display of a double aortic arch. You can see why it is called a double aortic arch. Right here are the two limbs of the aortic arch. We can turn it over the lateral dimension, basically fly over it, and you can see the circle there which creates the vascular ring. That is why it is called the double aortic arch.

[Slide]

So, you can see that there is a whole host of aortic anomalies, anomalies of the aortic branches like the isolated left subclavian which I repeated again down here that you can see so well; the relationship of the aorta to the pulmonary arteries which we saw earlier, like in transposition after arterial switch; collaterals from the aorta, for example in patients with tetralogy flow with pulmonary atresia; aortic conduits for complex congenital heart disease; or reconstructed aortas such as aortic-pulmonary anastomosis.

This is a three-D shaded surface of the aortic-pulmonary anastomosis. You can see here is

the native aorta and here is the native pulmonary artery connecting to each other, right up here.

[Slide]

Not only do we use it for the aorta, we also use it for the pulmonary arteries as well. Patients with pulmonary stenosis, like in tetralogy of flow or pulmonary artery dilation like with tetralogy absent pulmonary valves which you can see right here how dilated the pulmonary arteries are; pulmonary origins, for example in patients with truncus or hemitruncus, or pulmonary artery conduits for patients with heterotaxia. This is actually a maximum intensity projection of a patient with a left ventricle to pulmonary artery conduit. The conduit starts here at the apex and goes out to the pulmonary arteries. Or, patients with reconstructed pulmonary arteries like in Fontan patients.

[Slide]

We also use it for pulmonary venous anomalies, anomalous pulmonary venous connections. In the lower left-hand corner here you can see that we are going to be marching through the body from anterior, posterior and back again. This is a patient with an anomalous right pulmonary vein that

is entering the right atrium. You can see it right over here as it comes down, entering into the right atrium right near the IVC close to a scimitar vein. Pulmonary vein stenosis or repaired pulmonary veins, or systemic venous anomalies like anomalous systemic venous connections.

This is that normal that you saw earlier as a comparison. You can see the right side lighting up first and then the left side. Now if you look at this one, this is actually a patient where all the systemic veins go straight into the left atrium, the right and left superior vena cava and hepatic veins, and you see as soon as the gadolinium hits everything lights up. You are not seeing the right side nicely and then the left side; everything lights up so you can basically confirm that, indeed, that is what the patient has, as well you can identify the left and right superior vena cava.

[Slide]

How does it help us? As I mentioned, it gives you a three-dimensional nature to the study. It helps surgeons and cardiologists visualize what the anatomy is. It also labels the blood so you can visualize the third to fifth generation

branching of blood vessels. You can identify small collaterals that can be used for coiling or for unifocalization procedure where we take the collaterals off the aorta and connect them back to the pulmonary arteries.

[Slide]

Moving on after anatomy to blood flow, remember, there are two kinds. One is myocardial perfusion and the other would be lung perfusion. For the myocardial perfusion what happens is that the gadolinium is injected and it is followed by time resolved imaging, watching the gadolinium enter the circulation. We image the myocardium in the region of interest that we want. So, what happens is that first the chamber lights up and then the myocardium lights up afterwards. Normally you should see uniform signal intensity around the entire myocardium. Of course, abnormal is that you have localized areas of decreased signal intensity when it should be uniform across the entire myocardium.

We can analyze this in a number of different ways: qualitatively, just basically eyeballing it; semi-quantitatively, looking at it with time intensity curves, looking at the

intensity as a function of time in a region of interest; finally, quantitatively, which would be mathematical modeling of the perfusion of the myocardium itself. The way imaging works is that the images at each slice position are taken at different parts of the cardiac cycle.

[Slide]

This is actually a patient after transposition of the great artery surgery after arterial switch procedure. You can see here that first the right ventricle cavity lights up and then the left ventricle and then the myocardium, and you can see uniform opacification of the myocardium. However, if you now look here towards the apex and look right down here, you can see how decreased signal intensity just remains even throughout the entire injection, meaning that there is some kind of decreased flow to that particular part of the myocardium near the apex. That doesn't necessarily translate into functional problems. Here you can see that even though there is some decreased signal intensity in this region, you can see that that region of the myocardium is actually contracting pretty well.

[Slide]

Moving from myocardial perfusion to lung perfusion, you get a qualitative sense during this time resolved injection about the perfusion to both lungs, right and left. Here you can see how symmetrical they are. Whereas here, in this patient with left pulmonary artery stenosis you can see, one, how dilated this pulmonary artery is and, secondly, look at the perfusion to the lungs through the generation branch, and how little you can see over here with the left pulmonary artery stenosis which is right over there.

[Slide]

The types of patients one uses this for, of course, the myocardial perfusion would be useful in patients with coronary artery diseases, like anomalous left coronary arteries from the pulmonary artery; patients with other coronary artery anomalies like the right coronary coming from the left cusp; hypertrophic coronary myopathy; or patients who are postoperative who have had coronary artery manipulation, like patients after arterial switch procedure or patients with a Ross procedure. Of course, for the lung perfusion one can use it for pulmonary artery or vein stenosis for example like in tetralogy.

How does that help us clinically? We can identify myocardium at risk and also for the lung perfusion it contributes to physiological information for the branch pulmonary artery stenosis and decrease in lung perfusion, basically confirming other types of imaging that we would do within MRI such as velocity mapping.

[Slide]

Finally, the third use of MRI is in tissue characterization, also called delayed enhancement. How does that work? We inject contrast right over here and the time clock starts. At approximately one minute or up until one minute is what we call the first pass technique. Then, greater than five minutes is the delayed enhancement technique. What happens is these curves represent the signal intensity or the contrast concentration within various types of myocardium. The normal, in white, rises during the first pass and then gets washed out by blood that didn't have gadolinium in it. Ischemic myocardium, in yellow, the same thing--it rises, not as high as the normal myocardium, and then gets washed out. But infarcted myocardium could do one of two things, in both of which after five minutes the infarcted myocardium or scarred

myocardium has much more contrast agent in it than does the ischemic myocardium because there is not that normal blood flow to wash it out. So, that is how that works.

The first pass, as I said, just comes by in the first minute and that is what we see. After five minutes is the delayed enhancement where we can actually identify scarred myocardial tissue that takes up the gadolinium, this infarcted region right over here.

[Slide]

How do we do this with MRI? This is the ECG, right up here. At the R wave we put in a trigger delay and then we do a non-selective 180 degree pulse, which means we flip all the protons negative so that nothing has any signal intensity at all. Then, as we watch them relax, what happens is the normal myocardium starts recovering and the infarcted myocardium starts recovering too but they recover at different rates. What we do is we try to aim for hitting it right here where the normal myocardium is just about to cross the zero line where it starts to give off signal, and that maximizes the difference between the contrast of normal myocardium and the contrast of the infarcted

myocardium.

[Slide]

This is an example of a patient after an endocardial cushion defect. You can see here that this brightness represents scar tissue, fibrous tissue that has accumulated over the ventricular septal defect patch. In short axis you can see it right here as well.

[Slide]

Not only can we look at scarred myocardium, myocardial tumors also take up gadolinium, different kinds of myocardial tumors take up gadolinium differently. This, for example, is a patient who had a right ventricular mass right over here, in the apex. This is a four-chamber view. We injected gadolinium and you can see in the four-chamber view how the outside gets more perfused than the inside. The short axis, unfortunately, didn't help us too much. But then when you look at the delayed enhancement images you can see that this is the gadolinium accumulating an incredible amount compared to the rest of the myocardium in the tumor itself in the apex of the right ventricle. That is in short axis and this is in the apical four-chamber view and you can see it

right here.

[Slide]

What kind of cardiac masses enhance or don't enhance? Hyperenhancement, tumors such as myomas, hemangiomas, angiosarcomas. Thrombus does not enhance. Then there are a couple that are non-specific as well as some that we haven't seen in published literature yet.

[Slide]

The types of patients we use tissue characterization for are, of course, those patients who have myocardial scarring; patients who have potential for that, patients with coronary artery disease or patients who are postop and, of course, as I mentioned, patients with myocardial tumors or masses.

So, how does it help? It identifies scarred myocardium and also can contribute to the prognosis in patients with tumors.

[Slide]

How do we dose gadolinium? The freeze frame people do it anywhere between a single or double dose. This reference that is right underneath is actually a reference from Journal of Magnetic Resonance Imaging in 1999 that actually

recommends double dose for all great artery injections of gadolinium. For the time resolved ones we can use anywhere between a quarter to half a dose as a minimum.

When it comes to blood flow, that is either the myocardial perfusion or the lung perfusion, we use about half a dose of gadolinium. Finally, with the tissue characterization we will just use a single dose of gadolinium. People do anything from power injectors to hand administration of the gadolinium itself.

[Slide]

What does the future hold for gadolinium enhanced cardiac MRI? Newer first pass agents that have a high relaxivity. A lot of them are higher concentrations instead of 0.5 mmo. It is 1.0 mmo solutions. Also, they can have a higher relaxivity for either one of two reasons, either increased protein interaction or an inherent increase in relaxivity depending on the chelator that one uses.

The blood pool agents, as I mentioned, remain in intravascular space and have more robust imaging of blood vessels and that could be useful in coronary imaging.

The superparamagnetic iron oxide agents,

which are not really used in cardiac but there are some studies that are being done, they do have an advantage of having a long intravascular half-life which would be useful for coronary imaging.

A now burgeoning field is molecular imaging where the gadolinium is tagged to antibodies or other agents that are directed against receptors and antigens. Now the 3T systems, the ones with the higher magnetic fields are now coming on line. They have improved signal to noise and better resolution types of sequences.

[Slide]

Whenever I talk about the future, I always temper that by quoting Yogi Berra who said "it's hard to make predictions, especially about the future." With that, the talk is over so thank you very much.

DR. CHESNEY: Thank you very much. We will have questions and answers for all the speakers at the end of this session. Our next speaker is Dr. Marilyn Siegel who is going to talk about contrast enhanced cardiac computed tomography.

Contrast Enhanced Cardiac Computed Tomography

DR. SIEGEL: While we are bringing this

up, I will just say who I am. I am from Mallinckrodt Institute of Radiology, which is the imaging department for Washington University School of Medicine. I am a pediatric radiologist. My areas of interest are cross-sectional imaging and particularly CT, MRI and ultrasound. I also do a little bit of work in adult imaging, particularly in chest and cardiac abnormalities.

[Slide]

This is the list of questions that we were sent by e-mail and I am going to address these individually but, before we do that, let's get a little background information on CT and cardiac imaging, the basic facts.

If you are doing this you really need a multidetector CT scanner. What does that mean? That means with each rotation of the tube we get multiple images. When we first started CT we were getting a single image, now we can get multiple images. That means that we have more data and we get better resolution and image quality. We get faster imaging times with multidetector CT. I can do a cardiac study in 20 seconds or less so we are moving patients through.

Faster imaging time means fewer artifacts

in children who can't hold their breath. We get better spatial resolution from 0.5 to 1.25 mm. We can get superb 3D images and we are getting better contrast enhancement and that is what we need to address, and the use of CT is increasing.

[Slide]

Contrast using cardiac CT--it is across the board 100 percent. If we can't get contrast we are not doing this study. There are problems in children which demand the use of contrast--small patient size. They have little fat which means we can't see structures as well and contrast helps us see those structures better. Then, intrinsically there is just poor differentiation of soft tissues on non-contrast enhanced CT. You can't see the various chambers and it is hard to see some of the vessels. So, we have to use contrast.

[Slide]

Let's start with the first question, the indications for cardiac CT in the pediatric population. Two-fold basically, first of all to make a diagnosis. Is there disease or pathology or is there not? Secondly, to aid in clinical decision-making. Is there a need for another diagnostic test? Should angiography be done?

Should MRI be done? Or, should there be some type of intervention? We do not use CT for defining normal anatomy. We don't use it for assessing function just yet. It can assess ventricular function and size and output but there is a problem currently with radiation dose. It increases when we look at the heart in different phases such as systole and diastole. It is not a screening tool. We have an issue of radiation, which has been brought up and which I will address later.

[Slide]

What can we use it for? We can divide this into a couple of categories, extracardiac great vessel anomalies, intracardiac shunt lesions and then some postoperative anatomy. In children CT is performed most often for congenital diseases; in adults it is usually for acquired disease, although we are seeing more of this use in adults for congenital diseases or living longer. We now have an adult cardiac clinic which has about 1,200 adults currently with congenital heart disease who have survived infancy. So, I think we will see more of that.

[Slide]

The extracardiac lesions--you have seen

them displayed quite well on MR. We see the same things--aortic arch anomalies, coarctations or narrowing, complete interruption of the arch, other anomalies such as a patent ductus arteriosus and pulmonary artery sling, these are the more common ones. There are other ones that aren't as common that I am not going to review now.

[Slide]

I just want to show you some examples. We are using more CT. The reason is that we can make many diagnoses and obviate angiography which is longer, needs more sedation and has a higher radiation dose. This is equal to MR but the advantage of CT is, again, the fast time. I can do this in 20 seconds or less. That means I don't have to use sedation. Sedation is required for MR. Of course, CT has the radiation risks so, as we have heard this morning, it really is a risk/benefit analysis. Some patients who are critically ill can't have MR and we need to do CT.

[Slide]

Just to give you a couple of examples, on the left-hand side we have a neonate with right arch. There was some widening on the chest X-ray. This clearly shows the right arch. We don't need

to go further.

This is an adolescent. We have a double arch. Here is the right arch, here is our left arch. This was an incidental finding. This patient doesn't need additional study.

[Slide]

Pulmonary sling is an anomaly where the left pulmonary artery arises from the right pulmonary artery. This is a neonate, not sedated. Here is the pulmonary artery. Here is the right pulmonary artery and here is the left pulmonary artery arising from the right, crossing behind the trachea to go to the left hilum.

[Slide]

I mentioned aortic coarctation. This is one of the lesions that we see--sorry, we will go to patent ductus arteriosus next. Patent ductus arteriosus is a communication between aorta and the pulmonary artery, short tubular structure connecting them. This is a 3D CT. Here is the aorta, pulmonary artery and this patent ductus in a very young patient. We can see similar findings on MR. So, we really are equivalent and can provide a diagnosis quickly.

[Slide]

The other indications for pediatric cardiac CT, diagnosis of shunts at the atrial level or the ventricular level, and then we are using it to evaluate some postoperative anatomy, usually in very complex cyanotic heart disease.

[Slide]

This case is a one-year old, no sedation, about 10 multi-center of contrast. There is a communication between the right atrium and left atrium, atrial septal defect and, similarly, a ventricular septal defect. This patient had tricuspid atresia and has a graft in place, and they wanted to evaluate residual anatomic abnormalities.

[Slide]

This is another patient who had a murmur. They thought it was an atrial septal defect. We did a CT as a first examination--we were beginning to use CT more. We have contrast going between two atrial chambers. Here is the right ventricle, left ventricle. You can see normal tissue between the two. This is following repair, right atrium, left atrium and there is no contrast flow; there is no residual septal defect. By the say, you can see valvular anatomy quite well. There is the aortic

valve and you can see the three leaflets here.

[Slide]

Other postoperative evaluations, this is a patient who had tetralogy of flow, had bilateral Blalock shunts from subclavian artery to pulmonary artery. Here is one; here is the other. We can see that they are present and evaluate patency.

This is a patient with tricuspid atresia who had a graft from the right atrium to the pulmonary artery. That was the purpose of this study, to evaluate the graft.

I have only shown you selected cases, just to show you that we are able to do this study, do it quickly and do it without sedation in our younger population.

[Slide]

Next, the impact of CT then on diagnosis--we can make a diagnosis with CT. We can predict whether patients should undergo further invasive diagnostic testing, such as angiography, with CT. We can clarify equivocal angiographic finding, and we are using it to predict whether a patient might need additional surgery.

[Slide]

Just to give you a couple more examples,

this is a patient who had Mustard procedure for repair of transposition of the great vessels. This patient is about 19, comes in with some increasing cyanosis. Contrast is going in the superior vena cava, coming into the right atrium and going across the baffle Mustard into the left atrium and there is a leak here in the conduit which is abnormal and probably accounting for the cyanosis.

This patient had a coarctation repair. A stent was placed and you can see that a pseudoaneurysm has developed and has broken through the stent. So, we are using this again to make a decision whether we should go on to angiography or whether there should be a need for additional surgery or intervention.

[Slide]

Let's get to the contrast specific questions and look at how we do CT, some of the doses, some of the limitations and how we monitor safety.

[Slide]

Contrast dosing, the contrast volume is simply determined empirically based on patient weight. So, we are giving 2 mL/kg, maximum of 4 mL/kg or 125 mL. We are using nonionic contrast

medium. This is just standard now I think across the country in pediatric divisions, radiology divisions. We are using 280-320 mg of iodine concentration.

[Slide]

There are two ways of giving this contrast. One is by power injector, the other is simply pushing by hand. Power injector is really desired if it can be done, and it requires a catheter in the antecubital region. The flow rate depends on the size of the catheter in place. If it is a 22 gauge we are going to use a slower flow rate, about 1.5-2.0 mL/sec. If it is a 20 gauge we can use 2-3 mL/sec. I have even used higher rates of 4 mL/sec and in adults they will go up to 5 mL/sec. A 24 gauge central line can be injected. It is determined to be safe but you need to use a lower flow rate. If you have a catheter in the dorsum of the hand or the foot, you have to inject the contrast by hand or manually.

[Slide]

The limitations of contrast enhanced CT--the contrast-related ones are extravasation at the injection site and adverse contrast reactions. Then, there are some that are device related, and

the big one is radiation exposure.

[Slide]

Extravasation, a study by Kaste, in 1995, looked at extravasation with poorer injectors and manual injection, very small, 0.3 to 0.4 percent. With nonionic contrast, lower osmolar, this is not a problem. We have put a lot of contrast occasionally into a site where it shouldn't be because the catheter is not well positioned or it leaks and sometimes after 100 mL they may feel some fullness but there has been no really adverse sequelae. The contrast gets resorbed. There is no sloughing of the skin as there used to be with ionic agents.

[Slide]

Adverse contrast reactions--this is a new one that I added to the slide set. This was sort of a meta-analysis of low osmolar and nonionic contrast media. Looking at a number of institutions, overall the incidence of all reactions was 1-3 percent minor reactions, meaning no treatment necessary, maybe minimal rash or itching, or minimal vomiting--the incidence was near 1 percent. Major or severe, meaning intensive treatment necessary and maybe some life-threatening

issues such as hypotension or cardiac arrhythmia, is about 0.4 percent or 1/10,000. Most of these reactions occurred immediately at the time of injection. Five percent occurred late, after the time of injection and up to 24 hours. Mortality rate in series looked at since about 1980 with low osmolar contrast medium, 1/100,000. That is overall all-comers.

[Slide]

Now, if we look at children, and this is from a study in Finland and is one of the few I could find that has a larger number of patients and this was a questionnaire study so we have some limitation there. There was a 73 percent return rate. They used Omnipaque. Acute reactions, 1.9 percent, so in line with the larger meta-analysis I showed you, and all of them were minor or mild. They usually involved larger patients, older patients who weighed more than 24 kg.

Late reactions after the injection or up to 24 hours were about 6.2 percent of the population, again consistent with the larger series meta-analysis I showed you. These were mild. Some were intermediate. Intermediate means some treatment necessary but they are not

life-threatening. So more severe vomiting and large amount of urticaria is defined as intermediate. This affected the younger population.

[Slide]

There is one more series. This was one of the larger ones that had children and adults. They looked at the overall prevalence of adverse reactions. They found it was about 3 percent. Severe, 0.04 percent; deaths, 0.004 percent. Seventy percent of the reactions were within 5 minutes, the remainder later. They didn't quite define "later" but I guess 24 hours or maybe even later than 24 hours. But if we look by age again, for less than 10 years the overall prevalence was 0.4 percent; 10-19 years, 2.52 percent. Once you get to adults you get a higher prevalence and then over 50 years it decreases. So, that is just to give you a handle on how frequently adverse reactions to contrast occur.

[Slide]

This is the other issue. It is device related; it is technique related. It is radiation exposure. This is one of the headlines in 2001 and we are still dealing with this. There are a lot of

articles that have come out. There was another one that came out last week. This is an issue that we need to face when we do these studies.

[Slide]

So, CT accounts for about 10 percent of all our X-ray procedures but 65 percent of all the dose we give from diagnostic medical X-rays. Chest X-ray gives us about 0.1 mSv. A pediatric chest CT ranges between 1-10 mSv. With the current technology available we are able to do a scan and immediately know how much dose you are giving. This requires a 16-row detector. The first generation multidetector CTs were 4 rows. We were getting 4 images. Now, with 16 rows this is automatically on the scanner so you know what you are getting at that time. I have done neonates and I have gotten down as low as 1 mSv. I can get very low doses, as I will show you in a moment, by adjusting certain parameters. Adult chest CT, 7-15 mSv. Cardiac cath--this is something given to me by one of the cardiologists and there may be different numbers available but 20-30 mSv. So, if we can do multidetector CT well we can reduce this radiation dose if we can obviate cardiac catheterization.

[Slide]

The relative risks to the individual--this is something given to me by Jim Brink from Yale who looked at a number of articles out there and the lifetime risk of cancer is 20-25 percent or 1 person in 4 or 5. Added risk of CT, 0.05 percent, 1/2,000, not statistically significant. In the population as a whole, there will be about 600,000 pediatric CTs in the U.S. per year, and probably increasing. Without CT, 135,000 will die; with CT, 135,300 will die, again, not significant to the population but for each individual it is because you fear one of the children will get that cancer and that becomes a problem.

[Slide]

How do we monitor the safety? How can we have an impact on these risks? Well, obviously we don't want to overdose. We don't want to have too much contrast. That leads to a problem with renal failure, perhaps arrhythmias.

[Slide]

So, contrast is usually drawn up perhaps by a technologist at our place, but we always verify the dose prior to injection and contrast is administered by a radiologist or trained personnel.

Procedurally, we watch the catheter site. We actually feel the catheter site where the contrast is going in.

[Slide]

We try to identify patients at risk. Have they had prior moderate or severe contrast reaction? We are going to try to get another examination. Medically treated asthma is a risk. We heard about deaths this morning and if I am correct one of them did have asthma. Then, in patients who have had contrast reactions we may premedicate them with corticosteroids.

[Slide]

Again, the problem is the radiation dose. That is a harder one to deal with. The dose is directly proportional to several factors: Tube current, the amount of energy that is going into the patient; the voltage of the equipment; the scan time; the slice thickness; and the total number of slices. If we want to reduce dose we have to pay attention to each of these factors.

[Slide]

So, how do we do t? We reduce dose by optimizing those factors. We use a lower tube current. For quite a while, if you look at the

studies, 200 milliamperage was used in chest and abdominal CTs and in some places it still is. In pediatric radiology now, if we have an infant we decrease it to 25-30 milliamperage. In an adolescent we might use 80 milliamperage. So, by reducing that we can reduce the dose by half. We reduce the voltage. It is called kilo voltage. We used 120 for a long time now I am using 80 milliamperage or current. Reducing the kilo voltage will decrease the radiation dose by 30 percent.

Limited number of scans--in adult cardiac work and liver or pancreas we are using multiple phases, non-contrast, earlier arterial, later arterial, venous delayed. If you scan 4 or 5 times you are getting a lot of radiation. Our goal is to do it once and, hopefully, get it right and, therefore, minimize some of the radiation.

The newer equipment also has automatic dose reduction technology and they will tell you how low you can go. Of course, if there is another study that can be used and the patient is a candidate and can tolerate that study, then that ought to be used.

[Slide]

How successfully are we using CT? Well, as you heard this morning there are not a lot of studies out there that address that point. In adults we do have data related to CT angiography of the coronary arteries and we have dissection information available and aneurysms. In children there is overall paucity of data. There are some data available on aortic imaging. CT in children and in cardiac work really has just developed within the past two to three years so there are few studies out there. It also is difficult to get a prospective study because we are dealing with radiation issues. So, designing a study like that is going to be a little bit more difficult to do so a lot of what we are going to see is probably going to be retrospective analysis looking at series, meta-analysis. There are several review articles but, again, there is not any type of bench science looking at results.

[Slide]

In adults, to show you this one slide on coronary artery disease, it can be done quite well. I have compiled two studies, 95 percent sensitivity, 86 percent specificity detecting cyanosis greater than 50 percent. The key point

here is these are small vessels. We are seeing vessels and stenoses 2-4 mm in diameter. Given that, we ought to be able to do this in children and, from my experience, we can.

[Slide]

This is a series that we recently reported. It came out in The American Journal of Radiology. It was retrospective. We looked at 22 pediatric patients with some type of aortic anomaly, whether it was right arch, double arch, coarctation, patent ductus arteriosus. All of them did have some type of confirmatory study to confirm our findings. We were 96 percent correct and we could see stenotic vessels, areas of coarct, down to 2 mm. So, again, I think we can do it. It is going to be a little difficult to prove though at times.

[Slide]

Direction for CT as far as drug development or utilization of contrast agents, well, the goal of CT is to get the highest contrast enhancement with the least amount of contrast agent. So, when we do contrast enhanced CT we want a high level of contrast enhancement and a smaller amount of contrast agent. What affects contrast

enhancement? The flow rate and iodine concentration. Let me show you that.

[Slide]

If we look at different injection rates keeping everything else stable and we use a 5 mL flow rate, 3 mL and 1 mL, with faster flow rates we get higher enhancement, higher density, higher attenuation. Increasing the injection rate increases contrast enhancement. Theoretically, if we increase the contrast enhancement by increasing the injection rate we should be able to use a smaller volume of contrast. If it goes in quicker we get a higher contrast enhancement with smaller volume.

[Slide]

There is a problem in children. Because we have smaller catheters, sometimes we can't use that fast flow rate. In our adolescent population we can but not necessarily in our neonates.

[Slide]

The next thing we can look at is what about the concentration? In this model where they looked at different concentrations but keeping the iodine mass and flow rate constant, you can see that as the iodine concentration increased, 400 mg

of iodine, 350 mg and 300 mg, you got better contrast enhancement. So, perhaps we can get more iodine concentration in there and get better enhancement.

[Slide]

If we did that, we should be able to decrease the volume. Well, Becker looked at concentration and actually looked at flow rates and looked at left ventricular density in adults, and he used 300 mg iodine/mL and a flow rate of 2.5 mL/sec and he also used a higher concentration of 400 mg at 2.5 mL/sec. He found that if he used the low concentration and high flow rate he got the same result as a high concentration and a lower flow rate. So, higher concentrations work.

[Slide]

Implication in children--if we can use higher concentrations, as I mentioned, we may get smaller contrast volumes. This is the problem, the viscosity. Once you get out to 400 or more you can't push it through a smaller catheter. So, the challenge perhaps for manufacturers is can we get that high contrast or concentration out there and can we inject it?

[Slide]

What about future clinical utilization? I think we are going to see some ventricular function studies based on images in systole and diastole. As soon as we learn how to keep the radiation dose down that is a potential. But I think we will see more perfusion studies, pulmonary perfusion studies. Basically, what we are looking at here is measuring density or attenuation value, peak attenuation and time to peak attenuation.

[Slide]

Just one more example here. In this case we segment out part of the lung. By computer we are able to subtract the lung, remove the soft tissues and remove the heart because now we want to look at the perfusion going to the lungs. We can look at one lung. The right is in blue, the left in green. Or, we can look at both lungs and we can look at the densities of the whole lung, which I am showing you in this case. I can segment out and look at one lung. I can look at a part of a lung. I can do measurements or attenuation value on this. I can also apply color to this and look at perfusion to the lung.

This work has not been done in children yet. We are probably going to start this with some

of our lung transplants to look at perfusion to the lung. This has been done in adults. They have looked at perfusion in patients with pulmonary emboli but I think this has the potential to look at perfusion abnormalities associated with heart disease as well, how much blood supply is there really going to the lungs.

[Slide]

In summary, we are going to be seeing more CT. It is out there. It is being used more and it certainly can provide a diagnosis impact here. The challenge as far as the contrast medium goes is can we optimize contrast enhancement? We have discussed that. The other challenge for us is can we lower the radiation dose? At that point, I will stop and thank you.

DR. CHESNEY: Thank you. Our next speaker is Dr. Phillip Moore who is going to speak about contrast enhanced invasive cardiac imaging.

Contrast Enhanced Invasive Cardiac Imaging

DR. MOORE: While the computer is being switched over, I will introduce myself. I am an Associate Professor of Pediatrics at University of California San Francisco and I run the congenital cardiac catheterization laboratory there.

I was asked to give an overview of interventional catheterization and its current relationship to imaging modalities and some of the imaging agents. So, i will try to do that for you in the next little bit. Tom, I am either going to need your password or need your help, one or the other. I will take either. He chose the less interesting option, at least for us!

[Slide]

The role of interventional catheterization has changed over the years since the early '80s when it initially developed from basically blowing a balloon up into a clogged artery to a variety of things. With respect to congenital cardiology, if you look at the history surgery really developed in the 1940s with initiation of PDA ligation and BT shunt, with a huge explosion in the 1950s with the development of cardiopulmonary bypass, allowing application to complex disease. Then, in the '60s, '70s and into the '80s really the application of newer techniques and to younger and younger patients with congenital heart disease.

Surgery now has settled down a little bit in terms of its development, other than some of the newer issues that Tal mentioned. Interventional

catheterization, on the other hand, is tracking this to some degree but starting not until the late '50s, early '60s with initially balloon septostomy; then an attempt at PDA and ASD closure in the '70s that really got rolling in the '80s and the '90s. Now, in the 2000 decade we are starting to see application of some of these more simple procedures to more complex disease, such as hypoplastic left heart and the initiation of pulmonary valve and aortic valve implants.

[Slide]

The cath lab nowadays however still consists primarily of angiography and radiography and the contrast agents that go with it, although that is changing and I will take you through that a little bit. If you look at the impact of interventional catheterization on congenital heart disease, it is starting to become relatively significant. This is a slide that was shown earlier in the day, just looking at the incidence of different types of congenital heart disease lesions. You can see the common ones, VSD, PDA, ASD, pulmonary stenosis, coarctation. I have highlighted in yellow those that are now primarily treated in the interventional cath lab. Those in

red are lesions that are really shifting nowadays and we will have to see what happens over the next ten years, but from surgery to the cath lab. Even those more complex lesions, in green, often utilize interventional techniques in association with surgical treatment.

[Slide]

So, it is really becoming quite significant. This is the data from UCSF which is not unlike the data from Boston. We have had a steady increase in the number of patients we see a year in the cath lab, and some of that is significantly related to adult congenital heart disease. But you can see--in yellow is diagnostic and in red is interventional--that there really is a dramatic shift over the last ten years to treatment modalities in the cath lab rather than just diagnostic.

[Slide]

The impact, if you look at it globally, is quite significant. You have seen some of these numbers already and 32,000 to 40,000 infants a year are born in the U.S. with congenital heart disease. In fact, about 60 percent of those will require treatment at some point during their lifetime.

Right now about a third of those patients can be treated in the cath lab and with advancing modalities, both in interventional technique and imaging, as well as imaging drugs, the potential for up to two-thirds of these patients for treatment in the cath lab may be possible.

[Slide]

There are a variety of approved procedures already that are listed up here. They are not all that important to this discussion but they encompass a variety of different techniques and devices for a variety of different lesions that are currently performed.

[Slide]

There are some very interesting and exciting investigational procedures that are being developed, including valve stent implantation for both pulmonary insufficiency and aortic insufficiency, the latter of which might have quite a substantial impact on adult acquired disease; covered stent implantation in more complex lesions such as Fontan completion and shunt palliation in infants; internal vessel banding for hypoplastic left heart palliation; and intravascular suturing which is just really in its infancy but may have

some wide-reaching implications. All of these are going to require very, very specific improvements in imaging to take these to the next level in the interventional cath lab.

[Slide]

One of the difficulties, which you have already sort of touched on today, is that the range of patients is very huge, from premature infants down as low as 600 mg for valvular pulmonary stenosis in some institutions to adolescents, young adults and even nowadays some middle-aged adults with congenital heart disease. That obviously makes the application to imaging modalities and imaging drugs quite problematic.

[Slide]

Currently, in the cath lab by far and away radiography or fluoroscopy is the prime imaging modality that is used and nonionic contrast is the drug of choice that is used. In fact, this really has been studied quite a bit both in adults and pediatrics with regard to cardiac imaging and probably doesn't warrant a huge amount more issues.

We also use echocardiography, both surface, transesophageal and intracardiac imaging in the cath lab in interventional procedures

primarily. For contrast, it is agitated saline although some Optison type contrasts are currently being used.

[Slide]

This is just to give you an example of angiography. This is a lateral X-ray or angiogram of a patient who has had a tetralogy repair and has some compression of the repair site in between the right ventricle and the pulmonary arteries. We use that to define the anatomy, but you can see that you are quite limited here in terms of intravascular structures. You obviously don't see the myocardium; you don't see soft tissue structures around it.

Then, we also use this, including nonionic contrast, in some of the tools we use. This is a stent implantation to open that up. Then, afterwards again nonionic contrast angiography to look at the area where we have implanted the stent for improvement in the stenosis.

[Slide]

This is just an example of an ASD closure, using fluoroscopy here to define the delivery of the device. This little tube right here is actually intracardiac ultrasound. We are getting

ultrasound pictures while we are implanting. Then, using some nonionic contrast at the end of the procedure to confirm position of the device. But, again, you can see we are quite limited in terms of sort tissue definition here.

[Slide]

We pick up some of that in the cath lab with the use of echocardiography. This is an example of an intracardiac echocardiogram. So, the right atrial space is up here; the left atrial space is up here. We are evaluating the defect. This is a balloon that is passed through the wall here that has a hole in it. Now we are getting ready to deploy a device. This is a CardioSeal type device that has been opened in the left atrium and now we are bringing it back against the atrial septum. As I mentioned, we do occasionally use some contrast with regards to echo in the cath lab to assess position of devices. Again, this is the atrial septum hole; the device being positioned; the other side of the device has been deployed. Now the device has ben released and you can see we get much better soft tissue definition here. We will sometimes use, obviously, colored Doppler but you will see some injection of some agitated salien

contrast up here to look for any residual leak. But there are limitations to that technique in terms of some of the modalities we use.

[Slide]

How significant are complications or problems with currently used nonionic contrasts? They are really fairly limited. If you look at just all complications associated with catheterization in children, particularly interventional caths, you find that major complications are quite rare, less than 2 percent; minor complications less than 10 percent. In fact, the risk factors for complications are really related to age, less than a couple of years, and interventional procedures. If you look at the larger series the use of contrast and types of contrast do not really fall out in terms of major issues for risk factors.

There are, however, well-known and well described risk factors associated with contrast that is currently used. Transient renal failure occurs, is dose dependent, and there are allergic reactions that I think have been discussed. That being said, we are becoming more and more specific with the use of some of these additional imaging

modalities in terms of our judicious use of contrast in the cath lab, and these complications or side effects are being reduced.

[Slide]

What adjunct imaging modalities are currently used and associated with interventional treatment? The one that is most common at our institution would be MRI or magnetic resonance angiography, particularly as it pertains to arch abnormalities, coarctation, pre and post anatomy evaluation, as well as flow determination and patients who have right ventricular dysfunction, pulmonary insufficiency, particularly tetralogy or flow patients. I should add that at other institutions CT might, in fact, be the imaging modality of choice in this setting but in our institution it tends to be MRI.

[Slide]

You have seen some beautiful examples of that so I won't belabor this. This is an example of an MRI image of coarctation. The way we use that in interventional is we obviously can get very detailed anatomic definition of how big the vessel is, how long the stenosis is, and what tools we are going to need during the procedure to then address

that.

[Slide]

This is just an angiogram of a coarctation that we would then bring to the cath lab, evaluate prior with angiography with a nonionic contrast and then repair with a stent implantation--I apologize, I gave you two pre's and one post. It looked great, trust me!

[Laughter]

[Slide]

There are limitations currently with the use of some of these additional modalities and the tools we currently have in intervention. This is an example of an MRI after we implanted a stent. Right now, currently available stents are all stainless steel based.

[Slide]

This is the image artifact you get on implantation of a stainless steel image in an MRI. So, we have this beautiful arch. This is where the stent is and we see nothing in and around the area because of artifact. So, there still is a disconnect. All our tools are really based in fluoroscopy angiography at this point wo we do need some work in that area certainly.

[Slide]

Nuclear medicine perfusion scan, particularly as it relates to lung perfusion, is an adjunct modality we use quite a bit with respect to interventional treatment, particularly as it evaluates branch pulmonary artery stenosis in a large number of patients who have had surgical repair.

[Slide]

This is just an example. This is an infant with a complex congenital heart lesion called pulmonary atresia, VSD, and these patients are born with no central or true pulmonary arteries. Their arteries come off abnormal blood vessels arising from the aorta, which you can see here. The surgeon can do a remarkable job of recreating lung arteries by sewing them together and bringing them back together but, in fact, these children are left, as I think Tal Geva mentioned in his presentation, with significant abnormalities to their blood vessels afterwards. They do quite well and yet have very abnormal blood vessels. So, we need some method of assessing how abnormal those different areas of the lung are and nuclear medicine is quite effectiveness at looking at those

areas where there is too much flow and areas where there is too little flow so when we take that patient to the cath lab we can address our attention to those vessels that most need it.

[Slide]

This is just an example of a patient who has had this type of repair. You can see in this right lower pulmonary artery that there is quite a bit of narrowing, as well as the right middle pulmonary artery. That patient had limited flow to those areas. So, we can bring them to the cath lab and can use balloons to work on those arteries and afterwards assess with angiography to show that we have had quite an effect on those areas. Then we follow-up with additional pulmonary flow scans, nuclear medicine scans, to look at the effect and to follow those patients long-term.

[Slide]

As I have hinted at, there are significant limitations to angiography and radiography, the most significant of which is anatomic soft tissue detail. In addition, as has been mentioned for CT, there is radiation exposure which is quite dramatic in these patients. Then, this is a very expensive technique and non-portable so that makes quite a

bit of limitations, particularly with application worldwide in small centers.

[Slide]

To just give you a glimpse of what the future of interventional may hold, it is going to be directly related to what you are talking about today and that is the use of additional imaging modalities and the development of better imaging drugs. Certainly, MRI/MRA is the area that has the most activity and interest in terms of use for interventional cath. CT is a definite possibility. Not much work has been done yet. Then, 3D echo, if that modality continues to develop, may have some application.

[Slide]

Let me just talk for a minute about what has been done in the MRI area. That is the one that I am the most familiar with and which has had the most activity. Obviously, MRI is an excellent diagnostic and imaging tool and over the last number of years the magnets have gotten small enough that we can now get to the patients when the patients are in the magnets. In addition, the speed at which the images can be obtained has improved enough so that we can actually get

real-time imaging of the heart as it beats. So, that has opened the door for us to now consider using the cath imaging modality as a direction for interventional techniques.

[Slide]

In fact, there are a number of combined MRI fluoroscopy interventional labs that have been put in place, a few in the United States and a number around the world, that really consist of an angiography suite and an MRI suite that are connected by an interconnecting table that can slide a patient from one to the other, with a set of doors that slide in between that allow isolation of the magnet from all the metal in the fluoroscopy area.

[Slide]

This is just a picture of the suite we have at UCSF. This is a 1.5 tesla short-bore magnet and a Phillips C-arm rotating angiography suite. It is separated by these isolating doors. This table slides between the two so you can work in one room or the other and move the patient back and forth.

[Slide]

This is just an example of moving the

patient from the MR scanner back across to the angiography suite.

[Slide]

This is just showing that with these short-bore magnets you can actually get to the patient, either their head for neck vessel access or to the other side to their groin for leg access so that we can do some of these interventional procedures right in the scanner. In fact, you have an image monitor there that you can look at in live image and that can be swung all around the room in front of the operator so they can watch what they are doing while they are moving.

[Slide]

This is just an example of a catheterization in the MRI scanner. This is something that we have been working on. This is a prototype catheter that allows you to detect the tip of the catheter very obviously. You can see the soft tissue images nicely as the catheter moves up and around the aortic arch towards the left ventricle. So, this is opening up the potential for use of this modality for catheterization and, in fact, last year there was nice work done by a group in Germany, developing a device specific for

the atrial septum that can be used in the MRI scanner.

[Slide]

We have done some work at our institution that shows that even with currently approved devices they can be used. This is an animal model closing an ASD, which is seen right here. This is an Amplatzer device being deployed, the left atrial side of it being deployed in the left atrium. This is live MR fluoro. Here is the right atrial side of the device being deployed and then the device being released. Obviously, the potential advantage here is that instead of just seeing the intravascular space we can see soft tissue around as well and help guide our interventions.

[Slide]

This is just showing what you can do in terms of a soft tissue look at a variety of different types of stents that are currently available. This is some work we did in the pulmonary arteries. You can see that the image quality can, in fact, get quite good if you can match some of the tools with the imaging modality. You can see the chain-link fence of the stent sitting in the right ventricular outflow track

pulmonary artery in this model.

[Slide]

This is just an example of a stent being deployed in the right ventricular outflow track in an animal model that really shows us that we can use these images to guide some of these techniques.

[Slide]

Just to sort of summarize for you, I would say that the current radiography or angiography techniques that we use and the agents that we use really are quite safe and useful for pediatric interventional catheterization, and it is not clear to me that there needs to be a whole lot of study in that area.

But advances in interventional cardiology are really going to come from advances in 3D imaging in these other modalities, MRI, CT or 3-dimensional echo. In fact, safe and effective contrast agents will be key to allowing these interventional advances because our image quality will need to increase substantially.

[Slide]

The challenges for this include faster acquisition time, which we are getting towards and which no doubt will come in the next few years.

But the other issue is image resolution. We really need to be able to define images down to 1-2 mm in size for pediatric work in some of these procedures. Right now, that is going to depend primarily on improved contrast agents.

[Slide]

I would just say my view of the future is the combination of real-time 3D imaging with some improved contrast agents for the use of interventional cath to really bring interventional repair to a new level, both improved accuracy but, more importantly, the ability to repair complex congenital heart disease in the cath lab. Thank you very much.

DR. CHESNEY: Thank you very much. It has been suggested by our colleagues at the FDA that maybe we need to take a break at this point. I don't know who has shown that they are not totally alert but somebody picked up on it.

[Laughter]

So, maybe we could take a ten-minute break now and come back at 2:55 for our next speaker. Thank you.

[Brief recess]

DR. CHESNEY: Thank you, all. Just a

business issue, we, as in the proverbial "we," have made a decision not to try to finish tonight. I think for many of us for whom this information is very new, very interesting but, as a result of all the time and work that has gone into preparing for this meeting, I think that we probably will need time to do a little more thinking and absorbing all the material that you all have given us. I understand that all of our consultants are going to be back here in the morning so we will try to finish on time tonight and reassemble in the morning. That means that we need to have transportation back to the hotel. So, I wonder if everybody who would like a ride in a van from here to the hotel at the end of this session would please raise their hands. Dr. Santana is going to stay here for the night!

Thank you for bearing with us. Our next speaker is Dr. Craig Sable who is going to speak to us on contrast enhanced cardiac ultrasound.

Contrast Enhanced Cardiac Ultrasound

DR. SABLE: Thank you. I would like to thank the FDA for inviting me to speak. I am the Director of Echocardiography at Children's National Medical Center.

[Slide]

The topic I have, contrast use in echocardiography, is a little bit of a dichotomy in that by far and away of all the imaging modalities we are discussing today echocardiography is the most common. About 18 million per year are performed in the United States. With that number ever increasing, especially as the machines become more and more portable, probably a conservative estimate, although there are no data, is that about one million of these are performed in children.

It is done in real time. It is low cost. it is portable. It is very widely available. There is almost no discomfort. There is no radiation. It is primarily used for cardiac structure and cardiac function, both systolic and diastolic. It gives us considerable information about hemodynamics. It helps us with regional wall motion, both at rest and during exercise where the imaging is more difficult.

The dichotomy is that even though echo is the most widely used, if you look at the data that Dr. Geva presented earlier, probably ten-fold more than all the other modalities combined but there is the least amount of information on contrast in

echo, especially in children.

[Slide]

There are some limitations to echocardiography that contrast has the potential to overcome. Many patients have poor acoustic windows which may make it difficult to look at structure, the endocardial border, regional wall motion and Doppler signals. Patients at particular risk for this include those with pulmonary disease, obesity, chest wall deformity, postoperative patients and after exercise. The consequences of these suboptimal images include misdiagnosis, low diagnostic confidence, need for additional tests and higher inter-observer variability.

Finally, echo without contrast does not help us very much with coronary perfusion. Probably a conservative estimate is that up to 5 percent of all the pediatric patients, probably tens of thousands per year, could benefit from contrast echo.

[Slide]

Well, what can contrast echo do for us? Why use it? These agents are intravenously injected and may enhance the echogenicity of blood. The goal would be to delineate the echocardiogram

by opacifying the cavity, enhancing Doppler signals and allowing us to image perfusion of the myocardium. This would increase the sensitivity of the test, heighten the diagnostic confidence, improve the accuracy and reproducibility and enhance clinical utility.

[Slide]

This is not an uncommon example of an older patient, trying to see the endocardial border. This is after contrast echo and the endocardial border can be shown right here. It is much better seen with contrast echo. I will show you some more examples as we go through.

[Slide]

The desired contrast agent properties are that they are non-toxic. They can be intravenously injectable either as a bolus or continuous infusion. They are stable both during passage through the heart and the lungs. They remain in the blood pool or have a well specified tissue distribution. The duration of the effect will be comparable to the study itself, and they will be very small size.

[Slide]

To give you some historical perspective,

the original contrast agent was agitated saline. Agitated means that we literally put it in a syringe and we shake it up, mix it up with a little bit of air. It is very helpful to identify shunts, particularly atrial septal defect shunts. But the limitations are the bubbles are too big so if you inject it in the right side of the heart and it goes through the lungs you won't see it very well on the left side of the heart, and the bubbles dissolve very quickly.

You can inject directly into the heart with agitated saline or into the coronary arteries but, again, that definitely has some limitations. The size itself can cause complications and it is invasive and impractical.

[Slide]

There have been newer generations of contrast agents that have come out in recent years that have tried to overcome some of these problems with agitated saline. Albunex was the first agent that came out. It is highly echogenic on the left side; It is only 2-4 micrometers, which is about a third of the size of the red blood cell, but it is only effective for about 2 minutes.

So, second generation agents use gas

instead of air, and the two that are most commonly used and are FDA approved are Optison and Definity. These either have perfluoropropane or carbon or other gases. These act for a longer time. There are even third generation agents with newer gases and different shells that have even more exciting properties that I will touch on as we go through.

[Slide]

Air is highly soluble but it has low persistence and stability and diffuses rapidly versus some of the gases that are in the agents like Definity and Optison that have higher molecular weight, low solubility and are very persistent and stable.

[Slide]

This is just a cartoon on the left of Levovist, showing the contrast agent as it kind of adheres to the blood cells, and then an electron micrograph reproduction of Optison in the blood stream next to the red blood cells.

[Slide]

This is a list from the article that I put in your handout from 2000. There are newer lists but this is just an example. This is in the latest statement by the American Society of Echo on

contrast echocardiography listing some of the agents out there.

[Slide]

Just to kind of summarize, Albunex is FDA approved but not very commonly used. Optison and Definity--I believe there is one agent out there that is also approved that isn't used very frequently but Optison and Definity are the two FDA approved contrast agents that are most commonly used. Then, Levovist and Echovist are approved in Europe. There are several other contrast agents that are likely to be approved in the near future.

[Slide]

For us to understand how contrast agents are useful in ultrasound we need to know a little bit about how the ultrasound and contrast interact because that will become very important in understanding how these agents are used and how the machine is used with the agents. The bubbles themselves, in addition to reflecting the ultrasound, are actually resonating with the frequency of the ultrasound beam.

Just to review, with ultrasound we are sending ultrasound waves at a frequency much higher than human sound, anywhere from 1-7 MHz, even up to

12 MHz. The ultrasound bubbles actually resonate at the same frequency as the ultrasound beam. The key, as someone mentioned earlier, that we need to have our echo machines do is differentiate the echo from the contrast from the ordinary tissue.

[Slide]

But it is not quite that simple, and to understand this a little bit further there is the principle called the mechanical index, which is essentially a measure of the energy at which we expose the tissue and ultrasound bubbles when we are doing an echo and it is displayed on the ultrasound machine. All the ranges I am going to display are proven to be very safe. At less than 0.1 mechanical index the bubbles oscillate, just as I told you. At higher power they actually oscillate at several different frequencies, and higher still they actually break.

[Slide]

This is just a cartoon kind of showing that at low power they resonate in a linear pattern. At higher power they resonate in a harmonic manner, which I will talk about in a second. This is the way that most echo machines function. Then at a higher power still the bubbles

will disrupt, which is very important for perfusion imaging.

[Slide]

Just to briefly review the principle of harmonic imaging, normally bubbles resonate at the frequency of ultrasound but at higher MI bubbles will have multiple different frequencies, the loudest being twice the normal frequency, or the second harmonic. The resolution of ultrasound is higher at higher frequencies. So, the fact that these bubbles can resonate at twice the normal frequency means we can significantly improve the resolution and that is a huge advantage of contrast echo.

However, there is a caveat. Tissue also has second harmonic imaging and the good news is that, just in a happenstance way, contrast echo allows us to have this new way to image tissue with much better image quality. The bad news is that turning on the second harmonics of the echo machine doesn't necessarily completely distinguish the tissue from the ultrasound bubbles. But just keep in mind that for purposes of this talk we are generally using second harmonic imaging to image contrast.

[Slide]

This just shows the first harmonic and second harmonic peak.

[Slide]

This is just an example. The time at which you can image is much greater using second harmonic imaging. This is an image without anything. This is harmonic imaging without contrast, and the best image of all is harmonic imaging with contrast.

[Slide]

There are even some more higher grade technologies that I won't get into in detail, but they allow the bubbles to actually break and help us with perfusion. So, harmonic imaging is best for tissue opacification and breaking the bubbles is best for looking at perfusion.

[Slide]

With left ventricular opacification, as I said before, it helps with poor windows; left ventricular systolic function; stroke volume calculations; space occupying masses such as clots and tumors; and regional wall motion both at rest and stress, both with exercise and drugs.

[Slide]

This is just an example of a four-chamber and two-chamber view with and without enhancement. With using contrast agents, a multi-center study, published in The American Journal of Cardiology, showed that 91 percent of patients got adequate enhancement using contrast.

[Slide]

This is just another example of an unenhanced image, and then with Definity the endocardial border is much better defined. You can see a little bit of hypertrophy here. If this were a clot or something like that, again, that would be much better defined with contrast.

[Slide]

Another study done in AJC using Definity looking at patients that had terrible images or non-diagnostic exams, the percent of patients with diagnostic exams was increased from zero percent to 70 percent with Definity.

[Slide]

This is opacification, looking at different segments during a stress echo where it is very critical to evaluate wall motion. This is without contrast and this is with contrast. Again, the segmental wall is much better seen in four

views with contrast than without. Both at rest and exercise contrast echo improves regional wall motion detection and left ventricular opacification.

[Slide]

It can also help looking at Doppler signals. We use Doppler signals for a wide variety of things in echo. One of the things we use it for is pulmonary vein Doppler to help with diastolic function. This is just an example of a pre- and post-injection of Levovist with contrast echo. Again, the signals are much more clear with the contrast.

[Slide]

Perfusion, as we have alluded to with MRI and other modalities, is really what we are moving towards in the field of imaging. We look for structure. We look for function. But if we could really get a handle on coronary perfusion the field would be moved tremendously forward. What we want to try to do is identify ischemic tissue and viable pericardium and find areas that are at risk. So, we want to try to get ways to image the microvasculature in a non-invasive way.

[Slide]

This is just an example of a normal perfusion scan. We are actually breaking the bubbles. This is just the myocardium here using power imaging. This dark area here is an area of apical infarction. This is a similar patient with apical infarction both on contrast echo and on SPECT nuclear scan, and SPECT scans are still the gold standard but there are several adult studies comparing perfusion using contrast echo versus SPECT with very good results.

[Slide]

This is an image using pulse inversion. First you will see the endocardial border light up and then after a little bit of time you can actually see the myocardium light up, very similar to one of the images that was shown in the MRI talk looking at the perfusion of the myocardium itself--incredible potential.

[Slide]

There are additional applications. One that we are using in adults is treatment of hypertrophic cardiomyopathy by injecting alcohol direct into the coronary artery of the hypertrophic myocardium. When you are doing that procedure, you definitely want to make sure that you are injecting

in the right part of the heart and contrast echo is used to identify that.

The really exciting thing is that these contrast bubbles--and, hopefully in the next five to ten years we will be back here talking about them for that particular use--can be the magic bullet for treating things like clots, injecting genes in certain parts of the heart or other parts of the body, doing some interventional things like opening up ASDs or dilating valves and even treating cancer. As the field of pediatric cardiology has moved from diagnostic caths to interventional caths with less diagnostic caths and more diagnostic echo, hopefully, in the future we are actually going to move towards therapeutic echo, and using some of these contrast agents of the future could definitely get us there.

[Slide]

This is just an example of using contrast to identify the area of a ventricular septum that has hypertrophied and injecting ethanol to ablate that area and treat hypertrophic cardiomyopathy.

[Slide]

Well, we are really here to talk about safety. Hopefully, I have given you an idea of

what contrast echo can do in adults. The safety has been established and there are two ways to think of contrast. It is a drug and, as a drug, it has been very well established, using very stringent criteria, that there are very minimal side effects. I will show you a few examples. There is only one study in pediatrics.

But then there is the ultrasound-contrast interaction where there are some biological effects of the sound waves and the bubbles working together. In terms of a drug, there have been very few side effects.

[Slide]

There is only one study I could find that had any substantial amount of side effects. This had Optison being used at 100 times the current recommended dose and only 70 percent of patients had side effects, only one of whom needed to be treated. Those included headache, nausea, vomiting, flushing and dizziness. Again, this is at 100 times the dose. There were no side effects in an interoperative study when it was given in 57 patients.

[Slide]

In terms of the ultrasound-contrast

interaction, at exposure levels well above clinical use and clinical power of ultrasound, there could be bioeffects in the tissue itself. You could actually heat up the blood to the point where there could be potential problems, but using ultrasound levels identical to normal exams that is unlikely to happen and has been shown in repeated animal studies to have no bioeffects even though ultrasound is disrupting the bubbles and this could theoretically lead to cavitation at very high temperatures. But it is something that has not been shown to happen in animals, but as we go forward it may be the basis for some studies.

[Slide]

As I said, there is no evidence of bioeffects at conventional imaging with normal hematocrits, a mechanical index at 1.9 which is higher than we ever use, and agent concentration less than 0.2 percent which, again, is much higher than we ever use. At very high concentrations, high ultrasound energy and very low hematocrits there have been reports in animal models of hemolysis, platelet lysis and pulmonary hemorrhage.

[Slide]

There are alternatives to contrast echo,

including transesophageal echo, MRI, nuclear studies and angiography, but contrast echo has the advantage that it is not invasive; it can be widely available; and it can be done at the bedside.

[Slide]

So, based on all of this data, the American Society of Echo recommended in their 2000 statement that physician and sonographer competence is critical, but any echo, either standard or stress, that has suboptimal views, meaning that you can't see 2/6 apical segments, and/or there is inadequate Doppler, contrast echo could be considered to be indicated. However, your lab has to have the ability to have the highest quality standard equipment before you move to contrast echo for left ventricular opacification. For myocardial perfusion it is still considered investigational.

[Slide]

To summarize the adult data before I get into the pediatric data, in the past we have used it to identify intracardiac structures and shunts. Presently, we can do intracoronary myocardial contrast. We can enhance endocardial borders and do Doppler. In the near future--myocardial perfusion, stress perfusion and viability, and in

the far future drug gene delivery and clot lysis.

[Slide]

Pediatrics is a little bit different. We look at structure more than function. We have less experience with wall motion assessment. We do have better windows because the heart is closer to the chest, and we have higher frequency transducers. There aren't very many large multi-center trials, and we do use drugs in an off-label manner quite a bit.

[Slide]

But there are many potential uses for contrast. We use it for shunts. We have about three-quarter of a million adults with congenital heart disease in this country. That number is going way up. Many of them have complex disease, or are in the postop setting or have single ventricles. There is a large number of pediatric patients with coronary disease, maybe not typical atherosclerosis but we have a huge population of children and adults with Kawasaki disease. We have a large transplant population. And, some of the diseases, such as transposition of the great arteries, are at risk for coronary artery disease. And, there is a growing field of stress echo in

kids.

Some limitations--putting an IV in a little baby is kind of a big deal but in an older child it really isn't. There is very little data and it is a little harder for us to get the volume needed to have competence. Coronary artery disease is somewhat uncommon and in many of our patients image quality is satisfactory so getting an appropriate volume to have competence is somewhat of a limitation. And, contrast agents are relatively expensive.

[Slide]

There is one study in pediatrics. When I first thought about this talk I thought I would just show you this study and let you all think about it. But, clearly, this is an issue because we have a long way to go. Dr. Kimball, in Cincinnati, published this study in 2003 looking at patients referred for stress echo, Kawasaki disease, transplant postoperative patients and atypical chest pain.

[Slide]

Here is the stress echo protocol using dobutamine or bicycle. They used 0.1 mL to 0.2 mL kind of empirically for the contrast protocol of

Optison, using 25 mg as a cutoff. The adult dose is 0.5 mL.

[Slide]

They followed by a saline flush and monitored saturation heart rate and blood pressure for 45 minutes after the injection. They got standard parasternal and apical views using harmonic imaging with a mechanical index of 0.4.

[Slide]

They tried to look at 16 myocardial segments. Six are seen in two views. There was a total of 22 segments that were graded on a scale from 0-3 by one blinded pediatric cardiologist, both with and without contrast.

[Slide]

They looked at 22 children over a 14-month period. Their diagnoses are shown here, 19 were dobutamine studies and 3 were exercise. The smallest patient was 8 months old.

[Slide]

They had no hemodynamic changes or complaints. Image quality was improved in 21/22 studies, especially in the apical segments. When talking to Dr. Kimball recently, he said that they have since done about 20 more patients, again, with

zero side effects reported.

[Slide]

In summary, contrast echo has been proved to be safe in adult patients. It has been endorsed by the American Society of Echo for left ventricular opacification studies at rest and exercise. There are important additional uses for contrast that are likely to be developed and approved in the near future, including myocardial perfusion and tissue specific delivery.

[Slide]

In pediatrics we are a little bit behind the adults, but echo is the most commonly used diagnostic modality in children with cardiovascular disease and there are important potential uses for contrast echo, as I said earlier, probably tens of thousands of patients per year. Based on Dr. Kimball's study we can begin to conclude, from his study at least, that contrast echo can safely be performed in children and it improves the quality of stress echo. But there are obviously limited data. We are only looking at 22 patients published evaluating the use of contrast echo in children.

[Slide]

My recommendations would be that we need,

as a pediatric cardiology community with the support of the FDA, to develop dosing for pediatrics, assess safety and establish specific indications. Hopefully, we can get together with the American Society of Echocardiography and develop specific guidelines that will serve as a resource for additional pediatric cardiologists to use contrast echo.

Finally, I would like to acknowledge Dr. Weissman, Dr. Rychik, Dr. Kimball and the American Society of Echo for contributing to some of the content of this talk. Thank you.

DR. CHESNEY: Thank you very much. Our last speaker for the afternoon session is Dr. Dilsizian who is going to speak to us on radiopharmaceuticals in nuclear cardiac imaging.

Radiopharmaceuticals in Nuclear Cardiac Imaging

DR. DILSIZIAN: Thank you very much. I appreciate the invitation to be part of this panel. My background is that I am an adult cardiologist who is also double-boarded in nuclear medicine. I have spent the last 13 years at the NIH doing work in hypertrophic cardiomyopathy involving also the pediatric population. Currently, I am the Director of the Cardiovascular Nuclear Medicine at the

University of Maryland. I have been there now for a couple of years.

[Slide]

We have heard about a lot of technologies and if I were sitting in the audience I would say it seems like everybody is showing function, perfusion and all this nice stuff and you say why would I even want to use nuclear? Just the name itself is scary and why would we even bother with this?

So, what I would like to do is I would like to say to my colleagues that as far as anatomy is concerned, echo, CT, MRI--it is great. Any time you think about nuclear you have to think about the physiology and metabolism. Okay? So for anatomy, nuclear has no business. Whenever we think about the physiology or metabolism we should be thinking about nuclear medicine.

Why? It is because unlike some of the flow tracers that they have mentioned so far, the beauty of nuclear cardiology--which, although the field was back in the 1940s the real perfusion imaging began in mid-1970s--because of the fact that it has been used for the last three decades in the adult population to detect coronary artery

disease, it has passed the test of time and we respect that field.

Now, there is something about perfusion imaging in nuclear that has to be important and unique. What is it about it? It is because when we inject a tracer like thallium-201, technetium, maybe tetrofosmin, rubidium-82 with PET and N-13 ammonia with PET we are not only looking at flow, we are looking at retention of that radiotracer in the cell. It is a very, very unique characteristic of nuclear medicine. The isotope that you inject and that is attached to a radio ligand is being actually intercepted and retained in the cell. No other technology can do that. With tetrofosmin they will enter the mitochondria and, therefore, they tell you about the intactness of the mitochondria where ATP is formed and no other technology can do that.

SPECT imaging stands for single photon emission computer tomography, while PET is positron emission tomography. The only difference between these two terms is the P and the SP, which means that what differentiates these two technologies is the radiotracer. Radiotracers used with PET are positron emission radiotracers. The tracers used

with SPECT are single photon emission radiotracers. I don't want to get into that detail. All that you need to know is why do we need to move into the PET technology which has also been around for a couple of decades. It is because as we move from thallium-201 to technetium perfusion to PET what we are trying to do is we are trying to get the same biological/physiological behavior, yet reduce radiation exposure.

So, this is a very important concept. Thallium-201 is an elegant biological tracer, a potassium analog injected as a salt. What is the problem? Physical properties, low energy, high physical half-time of 72 hours, long physical half-time. Therefore, we are limited by the dosimetry, 5 mCi is all we can get. That limits our quality of images and diagnostic capabilities, especially in large patients. It may not apply to kids but in kids we are not talking about large size, we are talking about the long physical half-life and, therefore, we want to limit the body distribution, limit exposure to the kids.

Moving to technetium-labeled perfusion tracers, its physical properties are 6-hour half-life, 140 K energy. Again, why do I need to

know that? It is because the energy is much more appropriate for the current gamma cameras that are available. Tomorrow, if we change the sodium iodide crystal we may choose another radiolabel but the ligand remains the same. So, short half-life and, therefore, we can give 25-30 mCi. Suddenly, we have been able to get similar information, if you will, but getting a higher count and that allows us to not only get myocardial perfusion but also function with the same setting--very important concept. Where does PET come in? Well, let's push the envelope further. Now we are going to use radiotracers that, because of the energy characteristics, you are going to have much better, higher count rates. In addition to that, you can have attenuation correction. It may not be important for kids again. But more importantly, what is important is that rubidium-82 has a very short half-life, 32 seconds. Ammonia N-13, ten-minute half-lie. So, now we are talking about not only physical properties that are shorter and shorter but biological properties. Rubidium goes in and goes out 32 seconds later. Therefore, the radiation exposure to the kids will be limited and now we can concentrate on the physiology. That is

what is exciting about nuclear medicine.

In the era of genomics and proteomics you understand that we are really in the field that is becoming the molecular imagers. So, now let me go into clinical applications based on this background.

[Slide]

The main applications will be congenital heart disease, diagnosing coronary circulation anomalies. We have heard all of that and I don't want to show you any images; Kawasaki disease, hypertrophic cardiomyopathy or monitoring chemotherapy which can be done with echocardiography or MRI, but in some patients you actually want to know reproducibility with very accurate numbers.

[Slide]

I want to pick specifically hypertrophic cardiomyopathy. That hasn't been discussed much and I want to tell you why. One is because I have done a lot of research on this but the other thing is that it exemplifies where perfusion imaging with nuclear has an advantage over other technologies.

We have learned in the last several years that with hypertrophic cardiomyopathy, which is

really thickening of the heart and it can be asymmetric septal hypertrophy or concentric hypertrophy, there are some genetic diverse features. When I was in medical school I was taught that the prevalence of hypertrophic cardiomyopathy in the general population was 3 percent. That was my education and that is based on what? That wasn't based on genetic studies. Those were just learned recently. That was based on echocardiographic or abnormal EKG findings. The prevalence, therefore, actually may be higher. And, I am going to show you that now that we are getting into genetic identification we can identify that there is a higher prevalence perhaps in the general population than 3 percent.

What is important here in kids is that sudden death, unfortunately, occurs commonly in young patients. What do I mean by that? If you diagnose hypertrophic cardiomyopathy in a child between ages 1 and 14, 50 percent of those kids after diagnosis will die in 9 years. That is scary. Okay? Therefore, everything that I am going to say now about radiation exposure you have to put in perspective of what we are talking about and what we are identifying because I think at the

end of this we have to say what is the added potential fatal cancer in these kids versus their survival. Again, this is one subset of patients that exemplifies how we have to think about nuclear imaging.

[Slide]

I mentioned to you that there was recently an elegant publication in The New England Journal that told you the prevalence of where some of the genetic abnormalities can be in patient populations. Now you can screen them, especially if there are increased sudden deaths in those patients.

This is one pathologic slide from a young patient who died suddenly with cardiac arrest. This is the septum and you can see all of this red stuff is scarring. You see these small vessels here. They are thickened. This is a young patient that has an unusual interstitial structure and coronary arteries that causes these kids to die. You have heard about these athletes playing basketball and dying suddenly. This is the same patient population.

How do I identify these? In the traditional way we say, well, you know, I will do

CT angiography. Guess what, the coronaries are normal. So, CT angiography is not going to give you the information. Now, what is it that I am going to do? What I would like to do is identify ischemia. Right? Ischemia is a supply-demand mismatch. Even though the vessels may be normal, the demand component may be abnormal because it is a thickened heart.

Now, one of the strengths of nuclear medicine is that we are going to put patients on the treadmill. All of the other fun stuff we have heard is pharmacologic stress. It is not what patients actually do. We are looking if someone is running on the basketball court--running--is he going to have arrhythmias, is he going to die? That is what I want to know and, therefore, I am going to reproduce that on the treadmill and inject a nice radiotracer which will tell me if that patient is ischemic or not.

[Slide]

We did this study at the NIH and here is a very nice example. This is a young kid, 8 years old. Obviously, the dark area would be lack of blood flow. This patient has no coronary disease. We are talking about ischemia based on a

supply-demand mismatch that is completely reversible. So you say, well, why is this important? Why do I need to know that? Is there any relationship between ischemia and sudden cardiac death?

[Slide]

Again, what I want to show you is that even though that is done with thallium, you can get the same information with Sestamibi or tetrofosmin. Again, it is flow tracers. If the body distribution is such that the kids are getting less radiation exposure, obviously you will be moving in this direction and perhaps PET in some direction. I just want you to have that in mind, that we are not just stuck in the 1970s. We could actually be in the 21st century as the technology moves with the radiotracers as long as we are getting the signal that we need for a patient.

[Slide]

Again, this is patient before and after treatment with verapamil. You can see that the extent of ischemia is actually better, just medical therapy. Therefore, now I can follow the patient and say that by treatment with a beta-blocker and verapamil am I really impacting ischemia and am I

going to impact sudden cardiac death?

[Slide]

Again some pathological--these are thickened arterial walls.

[Slide]

This is the data that I want to share with you which I published in 1993. So, 23 patients presenting to NIH--these are kids. They presented either with symptoms of cardiac arrest or syncope and they obviously survived a syncope episode, or had a very strong family history of cardiac arrest. So, now these patients were being evaluated with EP studies looking at arrhythmogenicity and you can see that by doing EP studies, inducible VT was only 27 percent of these cardiac arrest or syncope kids, and none in those who had family history of cardiac disease.

On the other hand, the thallium SPECT study showed all of these guys who had syncope or cardiac arrest actually had ischemia, and 3/8 with the family history also had ischemia. Now you would say, well, how do I know this is not--you know, is it too sensitive; it may not be specific? On the other hand, you are seeing more kids than you would. They didn't have any symptoms; they

didn't arrest. And, the follow-up is very interesting. All of these kids obviously had AICD placed and were treated with verapamil and beta blockers. You treat them medically and you also have a backup. You know, these are kids. They may not take their medication. Four out of the 15 patients with cardiac arrest had further episodes on anti-ischemic therapy. Three of the 4 events were temporally related to discontinuation of the medication. The kids didn't take it.

How do we know the patient was going to have an arrest? AICD fired which could capture it. You know these three patients here, this is one-year follow-up. One of the kids was playing basketball and had sudden cardiac arrest. So, not only were we right, we actually predicted it.

[Slide]

So, I want us to think about radiotracers and what decision we are going to make regarding research or clinical indication vis-a-vis risk/benefit of radiation. Coming to the bread and butter of our meeting here, how do I look at radiotracers and how do I decide? How do I translate an adult dose to a pediatric dose?

What did we do? What we did was simple.

In the 1980s we just dosed the thallium based on the kid's weight. That is all we did. So, that is one way to do it. The other way is to do it on body surface area. Right?

Well, one interesting approach would be why don't we just look at the relative dose based on radiation exposure? That is, can we take a millicurie administered to a child and decide that dose based on the same absorbed radiation of 1 mCi administered in adults, that is, the radiation exposure translated into millicuries rather than some body weight or body surface area?

[Slide]

Let me emphasize two points. One is what I would like to do is whatever patient population I am studying. As you know, no kid is going to undergo nuclear study unless there is a real diagnostic dilemma or question. Right? So, the last thing I want to do is inject the radiotracer in a kid and get non-diagnostic, poor quality images because I didn't give enough dose. So, I have wasted a dose. I don't have any information or, worse yet, I don't have the right information because the images were of poor quality. Okay? That is critical.

The next question is everything is risk/benefit, not just imaging. Forget about nuclear, everything we talked about, everything is risk/benefit ratio. That is part of medical decision-making. So, hopefully, today and tomorrow we are going to have to decide what is it that we are talking about. I mean, obviously we should not be studying kids unless they are going to be benefiting from that technology. Therefore, we have to put into perspective how much risk are we willing to take based on that technique versus the benefit.

[Slide]

What is different about radiopharmaceuticals versus X-rays or CT? The difference is that when you inject a radiopharmaceutical it is not a total body exposure; it is a non-homogeneous exposure because these are targeted agents. Hopefully, we are targeting the liver; we are targeting the heart. That is the goal. If we just went equally everywhere, then we would not be doing the right thing. So, we are creating radiotracers to target specific organs to do the right thing. If that is what we are doing, therefore, you understand that

it is not one number. It is an uneven distribution and each tracer has its own distribution.

[Slide]

How do we go about deciding what is exposure? A couple of ways have been done. As you know, one is to look at the total-body or whole-body dose. That is the total energy deposited in the body divided by the mass of the body. This approach assumes a uniform whole-body exposure to radiation. We just discussed that that is not the case in nuclear medicine.

What is the other approach? Well, the other approach is a very clever approach I think which is the effective dose or the effective dose equivalent. That is, you say, you know, here are multiple organs, the top nine or ten most commonly involved in the radiotracer you are using and you use weighting factors and summing the individual contributions of the single dose organ to come up with a number. When you inject thallium or rubidium or tetrofosmin or FDG, this is the body exposure and these are the weighying factors. What are weighting factors?

The tissue weighting factors we are going to use for different organs--very nice in that each

of these account for fatal cancers or risk of disease above the normal incidence per unit of ionizing radiation for each organ system. Okay? In essence, we are taking each organ system and we are saying what is the potential risk and weighing each and coming up with a number. I think it seems to be the most logical thing to do, at least at the present time.

[Slide]

Now you take that and you sum it up for patients and it is going to give you some tabulation. These are the weighting factors or the risk that I just mentioned for each of these organ systems. The remaining organs you can estimate to be about 0.5.

[Slide]

Let's take a patient example. I just picked an adult, 10 mCi FDG which is a fluorodeoxyglucose. It is a PET agent that is commonly used. Now you use the weighted factors and the 10 mCi dose. This is the body distribution and you come up with an effective dose for the total body, which is unity. Right? If you add up all these weighted, it should be 1 and it is 0.68. Now you take that number and you say if 0.68 is my

effective dose I need to know what is the incidence of fatal cancer per rem for that age group. We have different age groups and we have the risks for each age group.

[Slide]

These are the nominal probability coefficients for stochastic effects. This is detriment times 10 -4 per rem in ICLP. Just quickly, I think it is an important thing to look at. Here are the children. Fatal cancer is 8 times 10 -4 per rem; non-fatal cancer, 1.6; severe hereditary effects, 1.6; the total is 11.2.

Adults, you can see fatal cancer is 4; total, 5.6. Geriatric--I didn't think over 50 is geriatric but I am approaching geriatric age, I am afraid--total cancer is 1 and fatal cancer is much lower even compared to the rest of the population.

So, what is the point here? For children, you can see that the risk is two to three times greater than for adults--cancer or total. Okay? For individuals over 50 years of age the risk is one-fifth or one-tenth. So, you know, when we are making decisions about radioisotopes you can say, well, based on these we should, again, optimize the dose and for this patient population, the so-called

geriatrics, who cares? Because we are really not having much effect here.

[Slide]

Here is the calculation. We take that 10 mCi FDG for adult patients and we come up with a number of 0.68 effective dose. We multiply that by the fatal cancer rate, which is 4 times 10 -4 and we come up with the probability. The probability is what? It is 0.27 percent. As was brought up before, we know that the natural incidence for fatal cancer is 25 percent over someone's lifetime. Right? So, now we say what is the added incremental fatal risk of doing this procedure with FDG? You say, well, it is 0.3.

Now, in kids I am going to make it very simple. It is double. Right? It is 0.06. So, all we are saying is that this is going to be 25.0-something, 24.06, 24.09 but that is the risk for that procedure. Now we have to make a decision, is this worth the procedure versus the benefit? That is really what we are discussing here.

[Slide]

So, NIH--and I am proud to have been there and I consider the Radiation Safety Committee a

pretty bright group of individuals--have recently changed their requirements for research. Perhaps we should take guidance from this. As you know, previous guidelines said organ dose--organ, not total-body effective dose--should be 3 rem quarterly or per injection or 5 rem annually. That is what we have been doing all this time. They have decided that, you know what, that is too conservative and, therefore, for research subjects at the NIH the total effective dose now is 5 rem and that is a significant drop. The guidelines, again, for pediatrics were to do one-tenth of the dose. Now they are saying one-tenth of the dose of the total effective which is much, much better.

So, just food for thought, I mean, we don't have to reinvent the wheel. We can always kind of look at how NIH came to this conclusion. Perhaps we can take it from there and move forward. Thank you very much.

DR. CHESNEY: Thank you. If you ever wondered what your classmates in medical school who majored in physics as undergraduates did when they got out of medical school, I think we now know!

[Laughter]

It is pretty overwhelming to some of the

rest of us! I wanted first of all to say that the handout you received during this talk, reducing radiation risk from computer tomograph for pediatric and small adult patients, came from Dr. Andrew Kang who is with the Center for Devices and Radiological Health. Questions for the speakers? Dr. Fink?

Q&A for the Speakers

DR. FINK: Just to try and put things in perspective, I read a long time ago that air flight at 35,000 ft gave you an exposure of about 0.01 rem per hour. Is that still an accurate figure for air flight?

DR. DILSIZIAN: I am not exactly sure about the number but it is equivalent to about a chest X-ray or so, yes, just going, say, from Boston to California.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I guess I would suggest we reserve radiation risk as its own particular discussion. The question I would like to ask is throughout the presentations at times I didn't get a very clear sense about where in the development of some of these agents you would need to use children, as opposed to where you would be able to

get the answers from using adults. For example, if the question is the accuracy of imaging at 1-2 mm--likely adult vessels that are 1-2 mm or in the breakdown, for example, of a chelation compound what is different about the milieu of the pediatric patients' blood stream as opposed to adult blood stream and clearance. I mean, what is it that we need to use children for, not in terms of what we can use it for diagnostically because, obviously, that is very impressive, but what do we need to use them for in terms of development of new products as far as testing to get them to a point where they can be used safely and effectively?

I didn't hear that specific question come out. Because in research the principle is you use the adult first if you don't need to use the child to get the information. Once you have it, then you can use it clinically. So, I am just curious both in terms of imaging capabilities but also metabolism and excretion for compounds such as the chelated gadolinium compounds. What do you really need to use kids for, for research?

DR. CHESNEY: Dr. Geva?

DR. GEVA: I am not sure about the radiopharmaceuticals but as far as, certainly, MRI

and echocardiography and perhaps CT, as well as in the catheterization laboratory, I would say that as a rule extrapolation of data from adults to pediatrics is fraught with potential danger.

Just to give you an example, if you are looking at gadolinium dosage and use of contrast agents in MRI, there are considerations that come into play that the adult imaging folks do not have to contend with, such as small body size, signal to noise ratio, fast heart rates and things of that nature that all impact on what we do and the kind of data that we get and the type of contrast agents that we have to use.

DR. SABLE: I think I can just add from the echo perspective. I do agree that the indications are clearly a different issue. I think there is some needed information for safety, not because the adult data isn't very clear but because some of the data needs to be obtained to make kind of a segue into the pediatric community. I think not having any pediatric studies definitely hurts the perception that these drugs can be used at all in pediatrics.

I think the main role I would think of in studies for contrast echo would be to establish

minimal dosing guidelines that may be efficacious. One study just randomly picked a dose between 20-40 percent the adult dose but it would be very important to establish specific dosing that would be acceptable. I think that is probably the main role that I see.

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: Yes, I think that with trying to extrapolate adult data down to kids, I have to agree with Tal that it is fraught with danger in terms of being able to know exactly what you are dealing with, especially with the small size. When you inject, for example, gadolinium in a baby it reaches the heart in, like, 2, 3, 4 seconds, whereas in an adolescent or an adult it make take 10, 15 seconds before it gets there. There are all these differences in kids versus adults and, as you alluded to, metabolism. I think in kids we really have to get a handle that we potentially don't have if we try to extrapolate it from adults. So, I would strongly recommend that children be studied.

DR. CHESNEY: Dr. Fost?

DR. FOST: It is on a different subject. Are we still on this one? I wanted to change the subject. So.

DR. CHESNEY: Dr. Moore?

DR. MOORE: I would just take a little different approach I guess, and that would be that obviously there are limited resources and that we do get an awful lot of information from the adult studies that is applicable. But the specific areas that probably vary quite dramatically, as I think both the previous speakers hinted at, are the smaller children and infants. In particular, I think that extrapolation is a bit much. So, if one had to focus one's resources in the pediatric population for these agents, I would say that the dramatic differences are down in the younger age groups because of the difference in metabolism, the faster heart rates in particular, and the smaller body and image size that you need to detail that makes dramatic differences.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: Just as a clarifying question so I understand, a lot of the need out here is in terms of the ability to capture effective images and to accomplish what you, indeed, want to get but does that also translate into what I would consider sort of basic metabolism issues? Do they break down the gadolinium? Do they chelate and do they

disassociate any differently? If you know the GFR of a neonate, do you really need to know what your clearance of the drug is, etc.? That is very different from imaging modalities related to heart rate and, you know, when do you start turning on the scanner, etc. I just want to get clear about where the differences are. Is it in the imaging areas or is it in the actual basic metabolism and dosing?

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: Well, I don't think we know that. I mean, I don't think we have the data in terms of metabolism and safety in kids to be able to extrapolate that from adults. We have seen a number of presentations today already that showed that the cancer risk and other things are dependent on the age at which you are actually doing the study. I mean, we don't know. If we are injecting gadolinium in kids how do we know that when they are age 40 that those people who had that long-term effect many, many years ago are all of a sudden going to start turning up with cancer of some organ system? The fact that we don't know this, and that we don't know what the long-term effects are, and we don't have as much of a handle on the metabolism

and how the body handles gadolinium or other contrast agents make it important that we, one, start doing the testing now; two, we start making a log of the people we are testing; and, three, hopefully in the future we will be able to get follow-up studies 10, 15, 20 years down the road to be able to say, yes, we did this kid a service or maybe we did the kid a disservice by doing it. I don't know.

DR. CHESNEY: Let's see, Dr. Sable, Dr. Moore, Dr. Geva and Dr. Siegel.

DR. SABLE: I think it is tempting to start to separate out the device from the agent but, especially with ultrasound, you really can't because the agent reacts to the ultrasound and in children, especially small infants, the transmission is closer to the chest and you are using different frequency transducers so it is almost impossible to separate out the device because the device determines the actual properties of the agents and they could be different with different types of devices and different heart rates. So, it is all kind of intertwined together.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: With ionated or contrast

agents there is a lot of experience out there so, to address your first question, is there a need for doing this in children per se, if we look at the reactions to contrast agents for CT, the reaction types are different. In adults they are more severe type of reactions; in children they are usually milder or intermediate. That is important if you are going to talk to a parent and say we are giving a contrast agent but in children we will expect this, and you can tell them that the reactions will be minimal rather than that there is a great risk that you are going to have some type of severe reaction. So, I think based on that, there is a need to look at children.

As far as your second one goes on metabolism, I believe even with the contrast agents for CT we are still not sure at this point why it happens. We think there are obviously two types of reactions, either direct drug toxicity or something due to their idiosyncratic reaction. I am not sure we will ever be able to work that out but I think it is important to know what the risk is in children per se and, based on that previous evidence, it does differ.

DR. CHESNEY: Dr. Moore?

DR. MOORE: I would just make the argument that I think there are precedents set in other pharmacotherapeutic areas where the metabolism and response in small children is different, and I would be quite concerned, particularly with some of the new MRI agents and the blood pool agents that are going to spend a lot of time in the circulation and are cleared by a variety of mechanisms including hepatic mechanisms, that their response may be different to the younger age group, and those probably should be looked at a priori as opposed to after the fact.

DR. CHESNEY: Thank you. Dr. Geva?

DR. GEVA: I would just make a distinction between the metabolism and the behavior of gadolinium agents. There is actually a fair body of knowledge, including pediatrics and including infants. That literature goes back to the late '80s and early '90s. But what is unique and hasn't been discussed in great detail is the clinical indications. If there is any discussion about labeling for use of these contrast agents for specific diagnostic indications, then there are gaps in knowledge. Otherwise, gadolinium is being used or has been used on a large scale for many

years for known cardiac indications and information can be used from that experience.

DR. CHESNEY: Dr. Fost, Dr. Gorman and then Dr. D'Agostino.

DR. FOST: This is directed to anybody in the room, the experts, the FDA or anyone else who can answer. How close are we to nanotechnology becoming part of this whole question--devices, coding of devices, drug delivery devices? My understanding is that the EPA for example is still stuck in thinking of a chemical as a chemical. It is benzine and we have rules about that, and the notion that it might be in a much smaller particle size and different format has not yet penetrated. The developmental effects of these devices or particles might be, obviously, much more worrisome for children than for elderly adults. What does anybody know about that? Is anybody yet manufacturing things? Is it in the pipeline? Is it a year away or ten years away? And, how will we react to that? That skips the question of whether you would want different studies. I think you would have to have very different studies for developmental studies for children than adults in the early phases of that. Does anybody know

anything about that?

DR. CHESNEY: Nanotechnology for our experts? Dr. Fogel?

DR. FOGEL: I have read a little bit about it in terms of reviews and my understanding, both from a medical standpoint as well as an electronic/technology standpoint, is that that is like 10, 15 years down the road at a minimum, although they are making large advances every single day and I will probably have to eat my words in 5 years. But I think at least the estimates from the people who are really into it are that it is at least 10, 15 years down the road before we see anything.

DR. CHESNEY: Any other consultant want to speak to that issue? Dr. Gorman?

DR. LOEWKE: Dr. Chesney, I am sorry, I wanted to follow up on the last topic. Before we get too far away from it I just wanted to ask a question. Most of the comments about extrapolation appear to be from a safety standpoint and I was wondering how you feel about efficacy from the adult population and extrapolating that to the pediatric population.

DR. GEVA: I think there is an easy

answer. I think it is a big no-no. I think you simply cannot do that. It is just a different animal.

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: Yes, I mean I think we are, one, dealing with different disease processes; two, we are dealing, as we all mentioned before, with kids who are very small, with very tiny blood vessels and that can make a real big difference, and I don't think you can extrapolate one from the other.

DR. CHESNEY: Dr. Sable and Dr. Siegel.

DR. SABLE: I would agree with those comments. There may be some diseases that have a few exceptions--adolescents with heart transplants versus adults. But I think the vast majority of the diseases we do see in pediatric cardiology are different though there are some that have enough of an overlap that would be a starting point to use adult studies.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: I am going to agree with the rest of the panel. Children are different. Their heart rates are faster. They are not going to cooperate. They can't hold their breath,

particularly if we are talking under five or six. They have less fat. So, you can't really extrapolate the efficacy from the adult studies. I think when you get to the adolescent population you probably can but in the younger population it is going to be very difficult.

DR. CHESNEY: On the same issue? Dr. Danford?

DR. DANFORD: We are going to be asked to discuss what specific kinds of heart lesions might be special categories that warrant special investigation. I am going to throw that out for the panel of experts but I am going to ask you about a specific one, and that is shunt lesions and do you find that you need to dose your contrast material differently for any of these modalities in the setting of a shunt where your contrast might go places that you don't necessarily want it right away?

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: Well, for CT the dosing will not change with the lesion. We have a set technique and that is what we use. What might change is the timing of the study, whether I do it during an earlier arterial phase or perhaps later

in a venous phase, or trying to do just one phase if it is possible. But we use a very standard dose.

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: When we inject gadolinium what we do is we actually watch the gadolinium flow through the body before we put our foot on the pedal, if you will, to start the imaging for freeze frame or, if it is time resolved gadolinium we always have basically our imaging so we can tell where the opacification is going to happen and then start the imaging. So, in terms of not seeing things when we want to because of the shunt itself, we can time exactly when we start the imaging to see when we want to actually grab that freeze frame to do it.

I have to say that in all the gadolinium studies that we have done, even those with shunt lesions, we have never really had a problem in terms of opacification. Now, if we had studies that were done that would decrease the dose and keep ratcheting down the dose to its minimum effective dose to decrease whatever safety issues there might be, then, yes, I think that we might have to take into account shunt lesions versus

non-shunt lesions. But at the doses that we are giving, at least with MRI gadolinium, we don't really see any difference in terms of opacification.

DR. CHESNEY: Dr. Sable?

DR. SABLE: With echo contrast there is absolutely no data. Theoretically, if you are trying to light up the left ventricle, if you had a right to left shunt, you may actually have to use less but it obviously depends on where the shunt is and the size of the shunt. It would be an interesting thing to study but since all the studies are done on opacification of patients without shunts there really is no precedent for even trying to answer the question accurately.

DR. CHESNEY: Same subject or a different one?

DR. NELSON: The same one.

DR. CHESNEY: Go ahead, Dr. Nelson.

DR. NELSON: I am trying to figure out why I am confused, and it may be because I am a simple critical care medicine doctor.

[Laughter]

I mean, if a company hands me a catheter I decide if I am going to be able to stick it in a

vessel or not as long as they tell me the catheter is safe. And, I am trying to figure out what is it that we are going to ask--since ultimately I am assuming that this kind of conversation would find its way into written requests, etc.--what is it that we are going to ask the sponsor to do versus what it is we are going to then do with whatever tool they give us.

So, it is unclear to me if what we would want them to have to do in order to fulfill the requirement of the written request is to demonstrate that it is better to image this lesion doing it this way versus that way, using all the different modalities, and the like, that have been beautifully demonstrated. It is clear that you can't be a cardiologist unless you have very good computer skills in imaging, and the like. So, it is unclear to me that you would expect them to do that as opposed to give you tools that are safe, that have been demonstrated that you can put into someone at a certain dose. Then, from there, it is up to the field to then do those kinds of studies.

So, that is where I am getting a little bit confused about a discussion of safety versus efficacy. It is not that it doesn't have to be

done but in my mind it is a question of who does what. What do you expect to be done in the development of the product before the trials are done to show whether it is better to do it by contrast echo versus MRI or combination modalities, etc.? It is not clear to me that that would be part of the actual agent development program.

DR. CHESNEY: Dr. Hudak?

DR. HUDAK: I am glad you said that because I am just a simple neonatologist and I am having the same confusion. I mean, you are the experts. You have brought all these techniques forward. You showed marvelous pictures. You have shown us lots of different ways that these methods sort of amplify the diagnostic abilities and amplify your physiological understanding of different situations. So, in terms of efficacy I have the same confusion. I mean, you are the experts; you know if this works or not; you know if you are seeing what you want to see; and you are the ones really to tell us. I don't know that there is a role for requesting studies that demonstrate efficacy.

With respect to the echo, I have one particular question and that is what sort of a time

window do you have after giving the injection to be able to conduct your study?

DR. SABLE: I will answer your second specific question and then comment on your first comment. There have been several adult studies looking at this. If you do a bolus injection you probably have 5-7 minutes. So, if you are doing a stress study you would probably give 2 boluses. I didn't show this in my slides but I have several slides on this topic. If you do a continuous infusion with a very low dose you can probably do it for 20 or 30 minutes. A typical echo without exercise, just looking at functional wall motion, probably can be done in 10 minutes. So, a single bolus--the goal of it is to last the length of the study.

In terms of your first question and comment, I think echo is much more immature in terms of how contrast echo has been used in children than the other modalities here. So, from my own field I would make a plea that we definitely do need help in trying to get some pediatric studies off the ground looking at efficacy.

DR. HUDAK: I guess with regard to that I am not sure what the role of the FDA or this

committee is with respect to that issue. I mean, I think that the way these technologies have progressed--I mean, they are out of the box and going forward before agencies like this even get a chance to get a handle on what is going on.

With regard to the other issue, the safety issue, I couldn't agree more with the safety concerns. I think, again, the critical issue, as Dr. Fost suggested, are the things that we are not going to necessarily know for years to half a lifetime. I think that certainly with any of these new agents or new technologies or sonicating funny bubbles in the blood and in the organs, one needs to carefully consider what registries or long-term follow-up one needs to establish on these patients to have some sort of mechanism to see exactly what happens to these patients. It is certainly not going to be a randomized, controlled study but I think that, you know, 20 years from now we certainly want to know if there are any major complications from some of these techniques.

DR. CHESNEY: Can I just ask--and I don't know how good an analogy this is but we have been using antibiotics for years and not knowing dosing; not knowing really precise efficacy. We knew they

worked in adults. We extrapolated to children. We didn't know about the metabolism. And, I think that is what I am hearing from our colleagues here, which is that maybe they would get better pictures if they had a different concentration of the drug or understood its metabolism better. Dr. Fogel?

DR. FOGEL: I am just a simple cardiologist; let me say that.

[Laughter]

For me, I think that when one looks at a drug one not only has to consider--I keep getting the sense that a lot of people are trying to separate the efficacy and the safety. We have always been taught, you know, that it is a risk/benefit. For example, we may be using 0.1 mM/kg in kids and seeing that things are fine but how do I know that with 0.5 mM/kg I couldn't see something just as fine. You know, in general, although it is not a general rule, one thinks that the lower the dose you give the better the safety profile of the drug would be, and that is not necessarily the case in every single drug but in a substantial portion of the drugs that are out there you would think that common sense would tell you that that would be better.

So, for me, I would want to see, one, clinical trials, controlled clinical trials not open-label Phase IV reporting, rigorous controlled clinical trials looking at various doses and dose response, and then safety and then having a log of patients who are getting it and, hopefully they would consent to it to be able to follow them up in 10 years.

DR. CHESNEY: Dr. Loewke?

DR. LOEWKE: I agree. We definitely look at things from a risk/benefit perspective and we look at the safety of the product and the efficacy of the product in the patient population. Much of what we are talking about here, and the drugs that are being used, and for the purposes for which they are being used are not approved in kids. So, we don't have knowledge that these products, when used in kids, would give us the right information to go forward with. We don't have that information and that is why we are also talking about efficacy here.

If you talk about extrapolation and extrapolating efficacy data from adults to kids, we stated that then you could use the adult data as your basis for efficacy to support efficacy in kids

and then you would do additional studies, pharmacokinetic studies and safety studies in pediatrics. But here I am hearing, if I am correct, that you feel we need to pursue efficacy as well as safety in the pediatric population.

DR. CHESNEY: Can I just make a comment? Is it safe to say that efficacy in your world is a better image? Is that a fair statement or not? What is efficacy as you see it? Dr. Siegel?

DR. SIEGEL: Well, I don't think efficacy is a better image. We would love to have that. But is it an image that provides useful clinical information? Does it get it right? Is it accurate? Can you make a diagnosis with it? That is efficacy. I mean, is it an accurate imaging test, whatever we use it for--for diagnosis or improving patient management? We like pretty pictures. Of course, we would like them to look better but when we are talking about efficacy I think that is it. Safety is obviously its own issue.

I am not sure where dose is falling into, if it is safety or if it is for efficacy to get prettier pictures. But I think we all work under the assumption that less is better. If we can give

less contrast, that would be better for the patient, although we don't know that and we really don't know what dose works out there and what the risk factors are. When we report the adverse reactions we never say really what the dose was that was given. We presume it was just a standard dose. So, dosing would be important, if we could have a study that would say at different doses we get different outcomes or reactions--safety; and also different diagnostic quality.

DR. CHESNEY: Thank you. I think that is similar for almost every drug we use, the lower the dose, the better. In my world of antibiotics if you give less, wouldn't that be better in the long run? Dr. D'Agostino and then Dr. Sable.

DR. D'AGOSTINO: It would help me greatly, and I also am simple-minded--it would help me greatly if I could have some discussion from the experts on what is, in fact, the indication. We have been told by the FDA there are four indications that they are interested in--structure delineation, disease detection, functional/physiological assessment and diagnostic. Like, in the MRI it seemed like you could do everything. In the CT it seemed like it was only

diagnostic. It would help me very much when we come to these questions if I sort of knew what these were aiming at, and what is it that this population should look like, what the sample should look like. Is that reasonable to ask of the speakers, if they could just sort of rattle off what they think their modalities are aiming at?

DR. CHESNEY: Dr. Loewke?

DR. LOEWKE: I think that is one of the major questions to the panel for the discussion that we have planned.

DR. D'AGOSTINO: Well, the speakers didn't necessarily present their material in that way. If we could start having the speakers tell us what they think is going on, then I think we could agree or disagree with them. I mean, they use quite different vocabulary.

DR. CHESNEY: Did you want to propose a vocabulary that we should ask them to use?

DR. D'AGOSTINO: Well, we have been given the vocabulary by the FDA and the speakers didn't necessarily use that vocabulary. So, if you could just rattle off, each of the speakers saying is it a diagnostic tool that they have; is it a structural delineation tool that they have?

DR. LOEWKE: It may vary depending on the population you are studying, what your endpoints would be and what type of indication a manufacturer would seek. So, I think if we have our discussion about what populations you feel need additional study for the drug classes some of that is going to come out as we go through the questions tomorrow.

DR. D'AGOSTINO: Why do you not want to have the speakers tell us what they think--is there any reason?

DR. LOEWKE: Time-wise--

DR. D'AGOSTINO: I am talking about something that would take two minutes at most on the part of the speakers. I mean, the one for CT said it is for diagnostics. Does that exclude others? It would help us I think in terms of answering the questions.

DR. CHESNEY: As long as it only takes two minutes for each speaker and each speaker understands what you are asking for because I am not quite sure I do. But if you all are clear, then let's go ahead.

DR. D'AGOSTINO: The FDA said there are four indications. I am not asking something profound. The FDA said there are four indications,

structural delineation, disease assessment, functional assessment, diagnostic. When Dr. Fogel made his presentation he chose to use the words--let me see if I can fish it out--anatomy, blood flow, tissue characteristics. Are they all structural? Are they different? I mean, it is a different vocabulary.

DR. CHESNEY: Dr. Geva, Tom has singled you out.

DR. GEVA: I think it is actually quite complicated and perhaps one can differentiate between an outcome variable for a trial as opposed to what is clinical reality. In clinical reality I think that in most cases what we are being asked to do is to evaluate a set of clinical questions and it depends on the imaging modality that you are using, but it is rare to really draw these concrete boundaries between structure, anatomy--this is somewhat artificial.

DR. D'AGOSTINO: But we are asked to design or help them design clinical trials so you are going to have to do that.

DR. GEVA: Exactly, I agree. As I said, it is useful perhaps to distinguish between defining endpoints for clinical trials and to try

and formulate the indications for the use of specific contrast agents sort of in an all-inclusive fashion. I do think that we need to make that effort and one of my hopes for all of these discussions is to be able to come to a conclusion about indications for use of, let's say, contrast agents in pediatric cardiac imaging.

DR. CHESNEY: I think maybe Dr. Loewke was referring to this, that maybe this is something we should address in the morning with respect to specific endpoints, specific studies, specific conditions and so on, whereas now I think we are more asking questions of the presentations that were given, although Dr. D'Agostino's is a broader question. Dr. Loewke, did you want to comment? I have a whole list of questions still here that people are asking.

DR. LOEWKE: I agree. I think, as we talk more about the populations that need additional study and what endpoints you would recommend, we will be able to figure out from that what types of indications could be sought based on the population studies and the clinical value of the information you are going to obtain.

DR. D'AGOSTINO: Why wouldn't you ask the

question the other way around? If you want structural delineation, then what type of population and what type of study would you run, as opposed to a diffuse question--well, here is a population, what kind of indication do I want? Why aren't you addressing it the other way around?

DR. LOEWKE: We are trying to assess how these products are being used out there, and that is the information--

DR. D'AGOSTINO: That is what I am asking, how are they being used, and then that will tell us how to, hopefully, put studies together.

DR. CHESNEY: Can we tackle this long list here? I have Sable, Ebert, Fogel, Nelson, Fink, Moore. So, Dr. Sable, you are first on the list.

DR. SABLE: In terms to referring to his comment or just previous questions?

[Laughter]

DR. CHESNEY: Whatever!

DR. SABLE: I just wanted to add one thing to the efficacy/safety issue. In many cases we move from one modality to the other as we get better at them. If echo is the least invasive and safest thing to do, if we find new reasons to do echo it may lead to safer management of our

patients overall. So, I think, again, it is almost impossible to separate safety and efficacy because we are really trying to do both with everything we do. If I come up with new ways of keeping kids out of the cath lab, if Dr. Moore comes up with ways for keeping patients out of the operating room, then we have achieved both and I don't see any way to separate them.

DR. CHESNEY: Thank you. Dr. Ebert?

DR. EBERT: I don't want to belabor the point on dosing but I would like perhaps some of the experts to address the issue of dose ranging and how well that has really been established in adults. We are talking about dose ranging of these agents in pediatrics but my impression from some of the presentations is that we may not even have the dose ranging established for these agents in the adult population. There was some mention of different infusion rates for example, but there may be some benefits of trying to do this in adults so it is not an extrapolation per se but if we can show that this is a relatively flat dose-response relationship or a steeper curve, does that give us some information in the pediatric population?

DR. CHESNEY: Dr. Dilsizian?

DR. DILSIZIAN: I can answer that from the nuclear perspective. For example, if you take a traditional thallium stress study and go back to the literature, the usual dose of injection is 2 mCi for adults, but the range is up to 5 mCi. With time it has gone up to 3 mCi, 3.5 mCi. Now we double the dose and the reason for that is, obviously, the quality of the images or maybe the obesity population. Maybe the weight change also dictates the dose. But we have a range and the range is pretty large. Also, even with technetium perfusion tracers, although the package insert will say 8 mCi at rest and 22 mCi with stress, if the patient is large we can give up to 30, 35, 40 mCi. So, we do have a range.

How do we decide that? Well, it has been more anecdotal. It hasn't been a series of patients, for example, with 20, to 30, to 40 to say, you know, well, if you are above 100 kg, which is what I do in my lab now--I say above 100 kg I want to do two large dose technetium studies because in my experience that is what is shown. But no one has shown that 100 kg is the cutting edge. Maybe you would like to have that type of study, maybe some dose escalation with some

methodology to say, well, what is the optimum dose and what is the range.

DR. CHESNEY: Dr. Fogel, Dr. Nelson, Dr. Fink and Dr. Moore.

DR. FOGEL: At least with the gadolinium--and I have to say I am not as familiar with the adult dose ranging trials and I don't even know if there were any--I know in children, for example, when not as much gadolinium got in as was intended we have had less opacification and less diagnostic imaging than we would like. I would personally like to know what the minimum dosage would be in the various age ranges that I could use to get a diagnostic study but I have to say, from an anecdotal standpoint, there must be some dose response and it is probably steep in the small dose ranges and that is where I want to be.

DR. CHESNEY: I think this is fascinating. I am glad you brought this to us because I think most of us just assumed that this had all been worked out; you know exactly what you are giving and why; and when we send a patient down for an X-ray it is guarantied safe and effective, and now we are discovering that it has never been done. This is very interesting--at least in children.

Dr. Nelson?

DR. NELSON: I would like to change the topic to one that I notice isn't on our questions for tomorrow but it might become a part of the discussion of CT scans and the nuclear area, and that is the radiation risk that was mentioned by a couple of speakers.

I guess my question is to what extent, other than the one study that was quoted which I have not looked at, to what extent are a lot of the figures about radiation risk extrapolated based on a linear theory of risk? I will say that at least in my institution we have deviated from that and have, in one case, approved up to 2 rem on a SPECT scan for a non-therapeutic, non-direct benefit procedure on the argument that there is, in fact, no documented risk of any radiation and that most of this is all just linear extrapolation. Except for that one study, which I would have to look at and see where that would fit in with all the data, some of the other studies that have looked at epidemiololy have shown no evidence of radiation risk at low levels. So, we concluded in looking at it that one couldn't say there was any risk below 5 rem and then felt that under those circumstances it

might be appropriate to go forward.

So, I just put that on the table because 5 rem strikes me as an exceedingly low number if, in fact, you are going to be doing studies that are outside of the potential for benefit. Now, if you are doing studies under that rubric you are not as limited to the risk, thinking of the IRB categories, but I just wanted to get that on the table to have some conversation about that, whether that will be a backdrop for discussions of those two development plans tomorrow or not.

DR. DILSIZIAN: I am glad you brought this up. Obviously, that was my conclusion in that that is very low. If you look at even PET radiotracers with short half-lives, if you look at the body distribution even in research in kids to make some new diagnostic metabolic finding in cardiomyopathy, we are not allowed to if we follow the 0.5 rem rule. So, we need to, in essence, come up with a better endpoint. I agree.

DR. CHESNEY: Dr. Fink, Dr. Moore and Dr. Siegel.

DR. FINK: Yes, as the discussion progresses I guess one of the questions that occurs to me is have we done our homework? We don't have

a lot of background data and if we are going to study these agents in kids, don't we really need some of the background data? Particularly in the imaging field it would seem that this is an arena that is particularly well suited to going back to animal models; that animal models could answer many of the technical questions in terms of dye dosage. You have a range of different sizes you can look at; different heart rates. You can even answer some of the questions of pulmonary capillary toxicity to particulates. You can put in catheters. You can measure minimal changes in oxygenation. And, should we be discussing human studies and using children as guinea pigs when we have guinea pigs?

DR. CHESNEY: I am going to think that was rhetorical.

[Laughter]

Point well taken. Drs. Moore, Siegel and Gorman.

DR. MOORE: Just a follow-up to the radiation comment, that is the one thing I think you do have to keep in perspective with these patients is that these procedures are repetitive diagnostic follow-up procedures on these patients.

So, the exposures you are talking about acutely certainly are relevant but many of these patients start in infancy and continue throughout their life and throughout their adult life to go ahead and accumulate these radiation exposures. So, I think that just needs to be considered in that particular issue with this patient category. It is very different than some other areas.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: To respond to a few of the points, first of all, dose. The dose that I stated was 2 mL/kg. We use that; we know that it is safe. I mean, the contrast agents are sort of maturing and I think it is an issue of the safety there; we have been there. But when it comes to dose, that is an area that can be investigated. CT has much better resolution. That is why we like it. We get thinner sections; we are able to see more anatomy. We should be able to do less in the way of dose and volume. I do but I am one person and it works if I get down to 1 mL/kg. I know it does. I can't necessarily get in the full volume but I can't prove that to anybody unless we do the research with that.

Let me just get to the animal models and I

will go back to radiation. We are using animal models actually. We are doing research now on animal models that are closer to adults I think, looking at the amount of contrast we need to get a diagnostic examination--the amount of the concentration that I talked about, all the parameters. I have looked at the issue of doing this also on animals that would be similar to infants. It is difficult. Of course, doing animal research is even becoming more difficult than doing human research so nothing sounds that easy in this world. But I think if we can get the support out there, that is what we need to be able to do, to get back to the basics and show it there.

Radiation dose--most of the radiation dose that we are talking about with CT, this being, you know, a new use for CT now, a lot of it is going back to the atomic bomb and, you know, doing this extrapolation. We have no data on CT and we are talking about different types of, you know radiation and different exposure times and different intensities in any one moment in time. So, there is a lot of work to be done out there to look at this dose factor, this radiation dose factor and then the diagnostic or efficacy ability.

DR. CHESNEY: Dr. Fogel and then Dr. Gorman.

DR. FOGEL: In terms of the radiopharmaceuticals and the radiation exposure, I guess I am not 100 percent clear that I am totally sanguine with the notion of the effective dose and tissue weighting factor. I guess if you read the definition correctly it takes into account fatal cancers and the risk of hereditary disease. So, that means that non-fatal cancers, ones that we have 90 percent cure rates for, are not taken into account when we look at the total effective dose. So, I guess I am wondering doesn't that minimize what the risk is? What if it induces cancers that have a 90 percent cure rate and that doesn't count in the total effective dose? What if the radiation induces cardiomyopathy in children? That doesn't get factored into this total effective dose. So, I guess I am not 100 percent happy with using total effective dose as a number by which one can then hang their hat on, saying this is a safe dose or this is not a safe dose. I am wondering if there is any comment.

DR. CHESNEY: Not this late in the day--hold back until tomorrow morning! Dr. Gorman,

and we do have two speakers for our open public hearing today--three? I am sorry.

DR. GORMAN: One of the issues that is becoming increasingly clear to me as I have listened to you talk is that we have at least three different technologies and at least three different maturities of the contrast agents we are talking about. I think when we talk about ionizing radiation, whether the cath lab or CT, we have a lot of information. When we go to the MRI we have less and when we go to echocardiography we have even less. I would like our experts to postulate, looking into the future, is there going to be enhancement of the technology of the device or enhancement of the contrast agents that are going to lead to increasing diagnostic ability of your technology?

DR. CHESNEY: Dr. Sable?

DR. SABLE: I think with regard to ultrasound it is probably going to be both but probably more with the agents themselves as we begin to think about therapeutic ultrasound. As I said in my talk, I think the biggest gap is between volume and use of contrast. Pretty much every catheterization uses contrast and most MRIs and all

CTs usw contrast, and echo. We are using it in zero percent of our studies; we probably should be using it in some number far greater than that. But, clearly, the agents have to get a little bit better. The machines are pretty much there for us to use it in their current state but the potential to go much further is certainly there.

DR. CHESNEY: Dr. Fogel?

DR. FOGEL: I think with gadolinium agents, just like echo, it is probably both, again, more weighted towards the agent itself. I am thinking more along the lines of the blood pool agents and molecular imaging. I would also have to say that with 3 tesla machines coming on line and with the software always becoming better and faster scans we will be able to do more and more with the agents we already have and, hopefully, more and more with the agents that are coming.

DR. GORMAN: When you talk about increasing the magnetic strength of the coil, what does that do for you? Does that give you increased resolution or increased speed or both?

DR. FOGEL: Both.

DR. CHESNEY: Dr. Siegel?

DR. SIEGEL: As you stated, the CT is more

mature so I think the advances we will see there will be more in the device, basically how fast we can give it and the time to start scan. The only thing in the contrast agents, as I mentioned, might be the concentration. It is already out there, the 400 mg of iodine. The question is can we change the viscosity. Most of the advancements at this point will be in the new technology that is coming out in the device.

DR. CHESNEY: Yes?

DR. LOEWKE: Dr. Chesney, can I ask a question? As you mentioned, many of these modalities can be used without the contrast agent. As Dr. Siegel pointed out, she is not doing cardiac CT unless she is using a contrast agent. I would like to know, in your routine clinical practices for the patients you see, do you do non-contrast images? They are not effective and then you move on to contrast? Do you automatically start with contrast enhanced images? Then, and I don't know if you can do this, what is the first-line diagnostic? Is it ultrasound and if ultrasound doesn't give you the answer do you go to MR? Is there a hierarchy or a path you follow? And, are there certain patient populations where, if this is

non-diagnostic, you move to this test, if that is not diagnostic--if you could give some input.

DR. CHESNEY: Dr. Sable?

DR. SABLE: In our practice and I think most pediatric cardiology practices ultrasound is definitely the first-line of imaging modalities. Then you kind of take your pick as to what comes next.

DR. LOEWKE: That is non-contrast?

DR. SABLE: In our practice we don't use contrast yet. As I said, there is one group out there--a few places are using it a little bit but there is only one group that has done enough to publish. So, unlike all my other colleagues, we would almost never--we are thinking about starting a contrast program but we haven't done so yet. There is a small percentage of our patients that we think clearly would benefit from contrast echo. Those patients are now getting sent to MRI, CT or angiography. So.

DR. CHESNEY: Dr. Siegel and Dr. Fogel.

DR. SIEGEL: As far as non-contrast goes, we don't use it. If you are doing cardiac it really is contrast. There will be an occasional exception. If you are looking for calcification

you might do it but the contrast resolution is so poor that all you are doing is wasting radiation. In that instance we will go for the contrast enhanced because of that issue.

As far as first-line of imaging, I totally agree that if it is cardiac or intracardiac related we will be using echo. But our approach if it is extracardiac where we are wondering about mediastinal great vessels is, if there is a vascular ring or abnormal arch, then we are going to CT. So, we sort of will do stratification based on the lesion that we are interested in.

DR. CHESNEY: Dr. Fogel and then Dr. Geva.

DR. FOGEL: In terms of MRI and contrast versus non-contrast, we actually view contrast as an adjunct to the non-contrast images. We will always get the non-contrast images first unless we are doing viability and perfusion, in which case we do contrast very early on in the study. For the most part we will do the non-contrast ones first. That is because if you do the contrast ones first you can't get good dark blood images if that is what you are trying to do. Plus, we feel that in terms of it being an imaging modality, in and of itself it is more of an adjunct with some rare

exceptions, like viability and perfusion. It adds to the diagnostic information but we always get the non-contrast ones as well.

In terms of the order in which one gets imaging studies or the protocol by which one gets imaging with relation to a specific disease or specific clinical syndrome, I think we do echo before we do something like MRI or cath. I have to say that there is some good justification for it. There are times when that is done because the people who are managing the patient's course aren't necessarily educated enough in terms of all the diagnostic imaging modalities to tell which one is the optimal one to do first, and because echo, as Tal said, is being used almost like a stethoscope it almost comes like a knee-jerk reaction, "let's get an echo first and then whatever we can't do we will get by another non-invasive imaging modality." But there are certain things that have been shown to be nearly gold standards like vascular ring anatomy by MRI, ventricular function parameters by MRI that are clearly better than echo but, yet, we will generally see an echo always being performed first. I think that is because of the education of our colleagues rather than the fact that it is a

better imaging modality for those specific types of disease entities.

DR. CHESNEY: Dr. Geva?

DR. GEVA: I agree with what Mark has just said. Just to add, I think that what you are hearing here is a little bit a reflection of variations in access to technology and expertise around the country in various centers. That all comes after the echocardiogram. As far as use of contrast agents in pediatric ultrasound, I agree with Craig, at this point in time it is esoteric; it is rare. It is being used in very, very small numbers.

DR. CHESNEY: Dr. Sable?

DR. SABLE: The other thing I think to keep in mind when you listen to us speak, we are somewhat of a biased group when you have MRI and CT and cath experts from around the country. If you go out into the community in small pediatric cardiology practices I think it is even more weighted toward echo because of the availability and the portability, not that it is a better technique. It is just so easily obtainable.

Open Public Hearing

DR. CHESNEY: I think maybe we should move

on to the open public hearing. We do have something that I have to read but my understanding is that Dr. Gelfand and Dr. Duffy, on Dr. Gardiner's behalf, will be making presentations, and the other two speakers are just going to provide us with handouts. Am I correct about that?

MR. PEREZ: No, there is one additional handout and two statements. The handout is in your packets.

DR. CHESNEY: So, we have three altogether, people who are going to speak--four people who are going to speak.

This has to be read before the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. 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. For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

Our first open public hearing speaker is Dr. Michael Gelfand.

DR. GELFAND: I am Dr. Michael Gelfand.

[Slide]

I am the immediate past president of the Society of Nuclear Medicine. My trip was funded by the Society of Nuclear Medicine, which is the large professional organization in nuclear medicine, a scientific organization. I have no current relationships with any of the manufacturers in the drug field. I have never been a consultant for any of them, nor have I ever received any honoraria from them. I am Professor of Radiology and Pediatrics at the University of Cincinnati and the head of Nuclear Medicine at Children's Hospital.

[Slide]

I basically want to point out the context of pediatric nuclear medicine with some reference to cardiac imaging. There is going to be some deviation from that but, basically, the pediatric nuclear medicine is alive and well and growing.

[Slide]

The number of nuclear medicine procedures done in children's hospitals--I was able to get the figures from Boston and Philadelphia. This is the annual volume in 2003. These are hospitals that do about 150,000 total imaging procedures per year in each case. So, it runs to 3, 4, 5 percent of the total imaging.

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The distribution of studies is quite different from adult nuclear medicine and varies a lot from hospital to hospital. What studies are being performed?

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It turns out that the largest percentage of what we do is GU studies. We do tumor imaging, GI imaging, bone imaging which is a fair component of it, and others.

[Slide]

To break that down further, GU cases include cystography in our institution. Just to give you an idea of the radiopharmaceuticals that we are using, some of these are heritage radiopharmaceuticals that go back many, many years; some of them are more recent.

[Slide]

We do tumor imaging. I might point out that half of our tumor volume is with agents that are either in a gray area or are fully approved by the FDA. This is an IND agent. FDG-PET is sort of in a gray area. There is a special NDA type of situation for FDG right now which will change according to congressional mandate at some point. Actually, a lot of cardiac imaging is lung imaging, as was pointed out at the University of California at San Francisco, probably two-thirds of this, and this is done with technetium-MAA.

I might point out here is an example where safety is not in the package insert. If my technologist were to mix 1 mCi of technetium or 5 mCi with the kit and make it up and then I was to give this dose in an appropriate amount to an infant, we would have a problem. We would have a clinical adverse effect because, in fact, this

infant may be getting 30, 50 times as many particles as an adult would get, perhaps even more. This kind of information is often not in package inserts.

We do brain perfusion, endocrine and mostly thyroid, and we do heart imaging at our hospital but in our particular case we do not do as much as, say, Boston or Philadelphia where they do substantial amounts.

[Slide]

At Cincinnati Children's Hospital we have experienced continued growth in nuclear medicine volumes, but at a somewhat slower rate than the total number of imaging exams.

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We have been growing at 4.8 percent per year in nuclear medicine. I might point out that this is the year that I was president of the Society of Nuclear Medicine and half of this year, and when I came back and paid attention to what I did for a living we had the best half year we have ever had. We have been having a 7.5 percent increase a year in the radiology department.

[Slide]

Boston and Philadelphia, according to the

information I was given by the department chiefs in those areas, are also reporting increasing volumes from year to year. Pediatric nuclear medicine case volumes are dependent on having an imaging physician who is interested in pediatric nuclear medicine. If the staff imaging physicians in a hospital are disinterested or believe that nuclear medicine is likely to disappear or pediatric nuclear medicine is likely to disappear, this becomes a self-fulfilling prophesy.

[Slide]

The numbers of myocardial perfusion imaging studies, according to manufacturers' data, were about 4,000 per year in the U.S. in 2002. It may actually be slightly more if you brought in another brand. Boston does about 100 per year or over 1 percent of their nuclear medicine volume. Philadelphia did 224 last year, which is about 3 percent of their nuclear medicine volume, and this number is not that far below the number of MR contrast administrations for cardiac imaging according to the information we were given earlier.

[Slide]

What can you do myocardial perfusion imaging for? In children one is Kawasaki's

disease, as was alluded to. In a study published in The Journal of the American College of Cardiology, in 46 patients myocardial perfusion defects were present by mibi; in 37 percent of 27 patients who had normal coronary arteries by angiography; in 63 percent of 11 who had resolved aneurysms; and in all the patients who still had aneurysms. So, that is one indication that is solid.

Another, we are getting information about hypertrophic cardiomyopathy. Another possible indication is after the arterial switch operation where there are fixed perfusion defects in a considerable number of children. In this one study almost all the children had fixed perfusion defects by mibi imaging after the switch operation a number of years later.

[Slide]

Myocardial perfusion imaging in pediatrics with technetium-labeled radiopharmaceuticals--one of the technetium agents has a shorter half-time and a considerably lower radiation dose; thallium-201, better image quality, flexible timing of image acquisition and you can do a gated wall motion study as well as get information about wall

motion, which may give you some feeling as to what is working and what is not working.

[Slide]

Radiation exposure from diagnostic pediatric nuclear medicine procedures is acceptable. Comparisons between different radiographic procedures, and between radiographic procedures and nuclear medicine procedures is accomplished by use of effective dose calculations. This is really the industry standard. It has taken over from whole-body dose. It has taken over from exposed dose from individual organ doses because of the weighting. Of course, any weighting scheme is going to be somewhat imperfect but that is the best we have and it is the industry standard.

[Slide]

Effective dose has a weighting factor for each tissue and a calculated dose for each tissue. If you sum it up across a number of tissues, 10, 12, 15 tissues, you have an estimate of the risk to the patient. Implicit in that radiation dose it should have a lot to do with what the patient would get if they just got a whole-body exposure, you know, standing 5 miles from the Hiroshima bomb for example.

[Slide]

To give you an idea of how some of these things fit in, in tumor imaging, CT of the chest, abdomen and pelvis, and this is using the low dose Tc, as was alluded to by Dr. Siegel. This is probably a third or fourth of what people used to get in a lot of places--very comparable to what we do with tumor imaging in PET, and less than gallium which is a long half-life radiopharmaceutical, 2.7 days. It turns out that our neuroblastoma imaging with I-123-MIBG is about half of either of either of those two.

One of the interesting things too is when I was preparing the article with Mike Staven on pediatric dosimetry, we talked about weight basis. It turns out that smaller children, if you accept the Hiroshima Nagasaki data that are presumably more at risk, actually get lower effective doses as they decrease in age for a given radiopharmaceutical that is given on a weight basis. So, generally the infants are getting about half the effective dose of what teenagers and adults are getting when it is given on a weight basis.

[Slide]

CT of the chest, abdomen and pelvis imaging for infection, white cells--very similar dose of gallium because of the longer half-life. One of the things again here is you have a target organ. Spleen gets radiation doses for white cells but when you factor in the exposure in the effective dose calculation it is not a huge risk. You get to renal infection only and it turns out that nuclear medicine studies are considerably lower than CT.

[Slide]

Heart and lung, MAA studies for lung perfusion are low. Technetium agents are considerably lower than thallium. We can give extremely low dose when we start doing things like cystograms. You know, we are talking about flying from here to St. Louis, or something.

[Slide]

Bone and brain, again low doses. Renal agents, very low doses. Sometimes we are a little higher than the equivalent X-ray procedure; often we are lower; often we are in the same range.

[Slide]

Why we need implementation of the Best Pharmaceuticals for Children Act, we basically have

been doing this whole thing off-label for children under 18 years, for 30 years within nuclear medicine off-label. There is a mandate in the Best Pharmaceuticals for Children Act to look at pediatric data to work with drug manufacturers. To do so, you know, there is some point to this. You get safety data our of it. You may get effectiveness data out of it as well.

[Slide]

As I pointed out, you can have problems if you don't use radiopharmaceuticals intelligently in very small children because there may be a non-radioactive component that will cause you a problem when you give 50 times as much on a per kilo basis to the patient. So, there are reasons to do this.

[Slide]

Another thing that Dr. Dilsizian alluded to was the whole concept of what happens when you try to do research, and the mechanism in a lot of the basic research in radiopharmaceuticals is the Radioactive Drug Research Committee and it basically states what he went over, that the radiation dose for an adult subject for a single study conducted with one year--and they have limits

here--and they say that basically from a single dose the whole body, the blood and the lens of the eye shouldn't get more than 3 rem and other organs shouldn't get more than 5 rem.

[Slide]

Then, they say under 18 years of age you have to cut that to 10 percent. First of all, we are talking about whole-body dose which is an obsolete concept and, secondly, it doesn't address the whole problem that there isn't a radiopharmaceutical around that has a target organ that has only 60 percent more than the whole-body dose. They are all 5, 10 times higher. But when you factor back in the effective dose this is not a significant factor.

[Slide]

For example, fluorodeoxyglucose for myocardial viability and for tumor imaging, for standard adult dose you are looking at an effective dose that is above that 0.3 limit. You are talking about a bladder dose that is way above that. As you go down, as effective doses drop a bit as the patients get smaller, if you give it on the same weight basis you still have bladder wall doses and effective doses that are way above those limits.

[Slide]

For a whole series of radiopharmaceuticals that are particularly of interest in tumor imaging at the moment, again everything is higher. Effective doses are higher. Here you could probably sneak in with carbon-11 methionine but the bladder doses are higher and it is either the kidney or the bladder that is the target organ in each case. But these doses are factored into the effective dose and they stand out here but it doesn't mean that there is a huge amount of risk associated with them. What this means is that the whole area of molecular imaging becomes an area that you can't approach in pediatrics.

[Slide]

Well, could you use a faster camera? Well, there are some faster cameras but if you drop the dose 50 percent you are still not there. Can you reduce the administered activity another 50 percent and double the imaging time? You are still not there for most of these agents.

[Slide]

Basically, effective dose takes into account all these risks. We have regulations for experimental use of radiopharmaceuticals that have

an arbitrary standard that no target dose should exceed the whole-body dose by more than 67 percent. We don't use whole-body absorbed radiation dose anymore and target organ dose for most radiopharmaceuticals is way above that 67 percent.

[Slide]

With the current RDRC regulations, molecular imaging technology will not be readily available for the study of pediatric life-threatening diseases, including cancer, but also heart disease. With the current RDRC regulations you can't evaluate new molecular imaging techniques and we should develop an up to date standard based on effective dose that permits the study of children with life-threatening diseases including cancer and heart disease.

[Slide]

Finally, I would just like to point out what others have said, that children and adults may differ in the pharmacokinetics of drugs. Pediatric disease processes are very different from adult disease processes, and I think you have been getting that kind of information all through this. Finally, pediatric data from adequate and well-controlled clinical trials are better than

extrapolated adult data. Thank you.

DR. CHESNEY: Dr. Cerqueira is our next speaker.

DR. CERQUEIRA: Thank you very much. It is a pleasure to be here. My name is Manuel Cerqueira. I am a cardiologist at Georgetown Hospital here, in D.C., and I am representing the American Society of Nuclear Cardiology. I drove myself here so they are not paying my expenses in any way. I am a former president of the American Society of Nuclear Cardiology.

The American Society of Nuclear Cardiology is pleased to comment on pediatric cardiology and the use of imaging agents. ASNC is a professional medical society of more than 4,500 members which provides a variety of continuing medical education programs related to nuclear cardiology. We develop standards and guidelines for training and practice within nuclear cardiology and we promote laboratory accreditation and physician certification in this sub-specialty to guarantee overall quality.

We are principally an advocate for the use of nuclear cardiology in both adult and pediatric populations. The Society believes that the medical necessity for the use of cardiac radionuclide

imaging in children can really be included in four different areas. There is a handout which is available at the back of the room.

These areas include congenital heart disease, including anomalies of the coronary circulation and the presence of cardiac shunts. Anatomic methods of imaging, which have been described by some of the other presenters, do not always identify the physiological consequences of abnormal communications between the various chambers of the heart. The radionuclide techniques, however, are able to adequately describe the passage of the radionuclide throughout the heart and allow detection of these physiological changes that are present.

Another area in which we believe there is value for nuclear cardiology in the pediatric population is Kawasaki's disease, which is a systemic vasculitis syndrome occurring in early childhood which affects the coronary arteries and may cause aneurysms as well as thrombotic occlusions both at the time of the acute disease, as well as later on in life. Long-term, it may affect coronary artery blood flow and the degree of perfusion to the myocardium. Initial obstructive

lesions may be difficult to evaluate and long-term there may be formation of aneurysms, and optimal management of these patients should include assessment of cardiac function as well as blood flow at a minimum of one-year intervals. This was published in the guidelines that were put out by the American College of Cardiology and the American heart Association for the use of cardiac radionuclide imaging.

Risks associated with Kawasaki's disease include subsequent stenosis and thrombosis leading to myocardial infarction as well as sudden death. The incidence of Kawasaki's disease in the year 2000 requiring hospitalization was 4,248 patients. The median age of these patients at the time of admission was 2 years old. Again, many of these children will benefit from subsequent long-term following with radionuclide methods.

Another area in which radionuclide techniques can be useful in children is the identification of myocardial ischemia in patients with hypertrophic cardiomyopathy.

The fourth area is radionuclide ventriculography or MUGAs, as they are commonly called, to monitor children receiving Adriamycin as

part of therapy for various tumors. Echocardiography and some other techniques can be used but the reproducibility of measurements has not been as well established and standardized as we have for the use of radionuclide techniques. For that reason, this will provide a very valuable method.

Physicians make medical decisions daily in the diagnosis and treatment of children. Within the practice of medicine, medical judgment has supported use of available radiopharmaceuticals in the treatment of children. The advantages of using myocardial perfusion imaging in children include, one, reducing a potential long period of sedation which may be required in some children; two, reduction of overall radiation exposure associated with conventional angiography; and, three, providing a more accurate diagnosis in many cases.

Having affirmed a role for cardiac radionuclide imaging in the pediatric population, the Society wishes to point out that there is a paucity of clinical studies in this area. Clinical guidelines relative to pediatric populations are estimates based on the best available information. General agreement has been achieved to use as low a

dose of radiation as possible and to carry out the procedures as quickly as possible. However, we do not have criteria for identifying appropriate pediatric referrals, nor do criteria exist to determine optimal protocol or technical settings for the imaging studies.

In approaching the pediatric population we know that children are more sensitive to radiation than adults; the number of radionuclide-enhanced phases must be minimized; and automated dose reduction technology exists; and inappropriate referrals can and should be eliminated in many cases.

Several questions remain however. How little radiation is needed to ensure accurate results? How are dosages for various ages determined or differentiated? How can the medical profession develop criteria for appropriate pediatric referrals?

The American Society of Nuclear Cardiology looks forward to working with the FDA and with other interested parties and stakeholders to resolve these questions. Thank you for the opportunity to comment on this important matter.

DR. CHESNEY: Thank you very much. Our

next speaker is Dr. Peter Gardiner from Bristol-Myers Squibb.

DR. GARDINER: Dr. Chesney, thank you. I will actually be very brief and, in the interests of disclosure, not only did the company pay for my travel but they pay my salary as well.

[Slide]

We consider ourselves worldwide leaders in cardiovascular imaging research. Our current product line includes Cardiolite, which is a technetium-labeled radiopharmaceutical, as well as Definity, the ultrasound contrast agent. You have heard quite a lot already today about both of these agents in their respective technologies and, in the interest of time, I will really just skip to my summary slide in that basically the points that I would have made have been covered already.

[Slide]

I would just like to point out that nuclear imaging is the only modality approved by FDA for the assessment of both myocardial perfusion and function in adults. There is clearly extensive experience, and you have heard much of that today, in the adult population. Again, as you have heard, there is limited and variable experience in the

pediatric population. There are certainly some challenges in terms of how to conduct clinical research in that population and that is certainly something that we look to continue to work with the agency and others, whether it is looking for creative ways to actually gather the information that has been discussed today.

Perhaps to Dr. Maldonado's point, certainly as a company we very much support the FDA's initiatives to evaluate nuclear cardiac imaging and, in fact, other cardiac imaging modalities in the pediatric population. So, thank you.

DR. CHESNEY: Although we deeply appreciate your brevity, I wonder if you would want to comment just a little bit more about how you would support pediatric studies or support the issue today, and in what ways or where do you see the most important need?

DR. GARDINER: I think it is really in many of the topics that have been discussed in terms of defining the appropriate dosing, the appropriate efficacy and the safety of these agents; the challenges, the size of the population and the variety of the pediatric population, and

clearly some modalities are more appropriate than others. But I think the areas that have been touched on are certainly ones that we would see as being important in terms of the questions to address, the questions that are going to be the subject of discussion tomorrow.

DR. CHESNEY: Dr. Maldonado and then Dr. Gorman.

DR. MALDONADO: Actually, I wasn't even aware of the CFR regulation that Dr. Gelfand presented. I see these CFR regulations that he said are obsolete and probably might be an impediment for studies, and I can see your lawyers stopping you from doing the studies although they may be very good. But if there is another law in the Code of Federal Regulations with limits, it may be problematic. I don't know if there is a solution to this because that can be also an impediment. As obsolete as it is, it may be an impediment and I think that Dr. Nelson may have the answer.

DR. GARDINER: It may be the difference between investigational clinical research and clinical practice that may have some bearing on that question.

DR. CHESNEY: Dr. Nelson, do you want to address this issue?

DR. NELSON: Yes, it might depend on your RDRC but often if it is an intervention that is designed for the possibility of benefit they won't apply those restrictions to it. If it is an intervention that is of no benefit but for research purposes only, they would apply those restrictions. So, it depends then on how you construct the trial and how it is designed. It sets up a whole other set of issues you need to address but it is possible to go above that exposure if it offers the possibility of diagnostic benefit. Then, how much evidence do you need to establish that would then be the question.

DR. GARDINER: Dr. Gelfand I believe would like to make a comment, if he is allowed to.

DR. GELFAND: I don't believe that the RDRC limitations apply to an IND by an investigator, and an investigator by a company. So, that would not be a problem in that situation. The second aspect is I have generally found that many, many RDRCs are terrified of going over those limits, regardless of what has just been said about possible benefit to the patient.

DR. CHESNEY: Dr. Loewke, would you like to comment on this issue?

DR. LOEWKE: Basically I wanted to say that 361.1 is non-IND research. For these products, if they are administered following the regulation, the research can be conducted and they do not have to submit an IND.

DR. CHESNEY: Dr. Gorman, you had a question?

DR. GORMAN: If you are willing to share this information, was Bristol-Myers Squibb responsible for the two PPSRs to this division? And, if so, what are you intending to study?

DR. GARDINER: That is not something I am prepared to discuss at this point.

[Laughter]

DR. CHESNEY: Thank you very much. Our last speaker in the open public hearing is Dr. Jack Rychik from the American Society of Echocardiography.

DR. RYCHIK: Thank you. I will just read a brief statement. Good afternoon. My name is Jack Rychik. I am a pediatric cardiologist with a specialty interest in pediatric echocardiography. First of all, I would like to congratulate my

friends and colleagues here in the field of pediatric cardiology who I think have done a superb job today in really framing this question very well, and I truly enjoyed your presentations today so thank you.

I am a staff member at the Children's Hospital of Philadelphia. I have served as director of echocardiography at that institution from 1996 to 2003. Currently, I am the director of the fetal heart program at Children's Hospital of Philadelphia. I come before this committee as a representative of the American Society of Echocardiography and as chair of the Pediatric Council of the American Society of Echocardiography, and they have paid for my Amtrak to get down here from Philadelphia.

The American Society of Echocardiography is an organization of nearly 9,000 professionals committed to excellence in cardiovascular ultrasound and its application to patient care through education, advocacy, research, innovation and service to our members and the public at large. As a member of this organization and a physician with a strong interest in the clinical application of non-invasive imaging modalities in children, I

am here to advocate for the promotion of the safe and effective use of ultrasonic contrast agents for cardiovascular imaging in children.

Ultrasound imaging of the cardiovascular system, or echocardiography, is, as we have heard, the most commonly used modality for imaging of the cardiovascular system in infants and children. The application of echocardiography in children has over a 30-year track record of safety; is an imaging modality which is highly reproducible with excellent temporal and spatial resolution; provides for real-time data on both cardiac structure and function; and is a mobile technology which means it can be performed repeatedly and serially at the patient beside. As such, echocardiography has become the first-line modality for imaging in children with cardiovascular disease and has grown tremendously in its use, again as we have heard today.

Despite its first-line use, however, there are still some limitation, primarily related to difficulties in ability to acquire a complete and satisfactory image in every patient in every specific subtype of lesion. Ultrasound is dissipated within tissue as it travels through long

distances and is impaired by bony structures and air. These issues become of primary importance in older or larger patients, however oftentimes acoustic windows, even in small children, can be poor which can lead to poor image resolution. The usual sharp distinction between the borders of blood and tissue can be blurred, thereby making it difficult to reliably measure cavity volumes and wall thicknesses, and consequentially impairing our ability to measure ventricular ejection and wall motion abnormalities.

Hence, for our adult cardiology colleagues, the advent of echo contrast agents has been extremely helpful. Intravenous injection of ultrasound contrast agents has been documented to improve endocardial border delineation. Contrast enhancement of the blood-tissue boundary has improved assessment of ventricular wall motion, wall thickness, ejection fraction and delineation of structural abnormalities.

Recent experimental results indicate that echo contrast has the potential to provide qualitative and quantitative assessment of myocardial perfusion and coronary blood flow. This would add tremendously to the diagnostic

capabilities of echocardiography. As we have heard, the safety profile of the echo contrast agents in adults has been well defined and there are currently several third generation products approved for us, but its utility and its safety in children has not been defined.

We believe that the time has come for children to reap the potential benefits of this form or cardiovascular imaging. There are some great potentials for its use and let me give you some examples:

One can utilize echo contrast for endocardial border, volume and ejection fraction as we have talked about. It can be used for evaluation of intracardiac shunts and in particular, for example, in cases of patent foramen ovale in patients who have had stroke.

It can be used for visualization of complex baffles and channels. This is specific for congenital heart disease in cases of Mustard or Senning operation for transposition of the great arteries or in the Fontan operation for single ventricle.

Contrast agents could potentially be used to improve visualization of thrombus in venous

pathways of patients after Fontan operation for single ventricle. Visualization of thrombus by conventional surface echocardiography is oftentimes a difficult task due to the scatter created by the synthetic patch material that is used. Contrast agents may be extremely helpful in reliably identifying thrombus and avoiding the need for further testing, such as transesophageal echocardiography or more invasive modalities such as angiography.

As well, as we have heard, it can be useful in the assessment of coronary artery flow and myocardial perfusion. Although coronary atherosclerotic disease in infants and children is rare, there is still a great need to reliably assess coronary blood flow in conditions such as congenital coronary anomalies before and after surgery; Kawasaki disease; after arterial switch operation for transposition; after Ross operation in which coronary re-implantation is performed; for aortic valve disease and after palliation for hypoplastic left heart syndrome in which aortic reconstruction is undertaken and coronary flow potentially impaired.

From personal experience, I can tell you

that I would conservatively estimate that approximately 5-10 percent of our patients coming to our echo labs at Children's Hospital of Philadelphia could potentially be candidates who could benefit an in incremental manner from the addition of a contrast evaluation. At our single center, where close to 15,000 echocardiograms are performed each year, this means that approximately 1,000 patients per year could potentially benefit from this additional modality.

The American Society of Echocardiography has in the past taken the lead in providing a synthesis of available evidence justifying the adoption of relevant new technologies in the field of echocardiography. In addition, the ASE has played a key role in establishing guidelines for training and experience in these various modalities and uses of echocardiography. An example is one that Dr. Sable mentioned early, the position paper that was published in 2000 on the use of contrast echocardiography in adults. I can tell you that an update is currently being planned for utility, again, in adults. The ASE, therefore, plans to take an active role in the process of promoting the safe use of contrast echo in children.

With growing interest in the subject, we have formed an ad hoc committee of the Pediatric Council of the American Society of Echo to look specifically at this issue of safety and utility of contrast echo in children. This committee is comprised of experts in pediatric echocardiography as well as adult echocardiography, professionals who can share their knowledge and experience in the use of contrast agents. It is the desire of this ad hoc committee, the Pediatric Council of the ASE and the ASE as a whole to promote and advocate the expansion of the safe and effective use of contrast echocardiography in children and to develop guidelines for use and training.

We look forward to working with the FDA and acting as a professional resource to them as they move forward in these endeavors. Thank you all very much.

DR. CHESNEY: Thank you.

DR. LOEWKE: Dr. Chesney, may I just make one clarification, back again to the CFR 361.1 just so people fully understand that that applies to basic research. It is not IND drug development clinical trials where you are actually looking to develop and ultimately manufacture a new drug.

DR. CHESNEY: I think that brings our afternoon session to a close. On behalf of the committee and the FDA, I want to thank our speakers enormously for the incredible expertise you brought, and we look forward to working with you tomorrow to answer the more specific questions.

With respect to administrative issues, the van will leave the hotel tomorrow morning at 7:15 to bring us here. I understand there is a van to take us back to the hotel now, those of us who are not going to the Ritz Carlton--

[Laughter]

Did the FDA want to make any other closing comments today? I guess not. Thank you all very much.

[Whereupon, at 5:20 p.m. the proceedings were recessed, to resume at 8:00 a.m., Wednesday, February 4, 2004.]

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