(Recess.)

DR. RAMSEY: We're going to go ahead and begin with our afternoon presentation. So if everyone would please come in and take a seat, we're turning the podium over now to Dr. Udo, who will tell us about nitrogen-13 clinical pharmacology, pharmacology, and toxicology.

Thank you, Dr. Udo.

DR. UDO: Thank you. Good afternoon, ladies and gentlemen. I am David Udo, a reviewer with the Office of Clinical Pharmacology and Biopharmaceutics of CDER.

The information I'm going to present today is from reviews of literature articles on pharmacology, toxicology, and clinical pharmacology of N-13 ammonia. The pharmacology/toxicology review was done by my colleague, Dr. Adebayo Laniyonu. The clinical pharmacology review was done by me.

These reviews were focused on the use of N-13 ammonia for measurement of myocardial blood flow by the PET technique in patients with known or suspected coronary artery disease.

In this presentation, we will cover the following aspects of N-13 ammonia: The concept of blood flow measurement, pharmacokinetics, and metabolism. An attempt will be made to relate pharmacokinetics or metabolism to safety. And then in the end a summary will

be provided.

Following intravenous administration of N-13 ammonia, the blood takes it to the coronary vasculature. And for our purpose, I'm going to say that we're going to find in the myocardium N-13 ammonia in the blood flowing in the coronary capillaries from where it entered the extravascular compartment of the myocardium and, finally, into the intracellular compartment where, in a reaction mediated by glutamine syntheses, it is transformed into glutamine and trapped therein. That is, inside the cell.

And so we can see that we have three distinct compartments in the myocardium where you can find N-13 ammonia for kinetic purposes. This can be presented schematically, as shown. K1 and K2 are intercompartmental real constants for the blood in the capillary and the extravascular space of the myocardium. K3 represents the rate of metabolic conversion of N-13 ammonia to N-13 glutamine.

Our focus is K1. K1 is a composite rest constant which represents blood flow and the single pass extraction of ammonia from the capillary into the extravascular space. Since the extraction is very close to 1, then K1, which is a product of E and F, already defined, approximates F, and therefore provides an estimate of measurement of blood flow.

Now how do we obtain the value of K? K is obtained by solving the three-compartmental equation which described the time course of N-13 ammonia in the myocardial tissue. And we have said K1 is the blood flow. So, by obtaining data and putting in the appropriate concentrations, K1 can be determined which approximates blood flow.

Now, let us examine the pharmacokinetics aspects of N-13 ammonia. In the literature, articles revealed that doses that were administered were mostly in the range of 10 to 20 millicuries. This was associated with a mass dose of 0.05 to 0.1 micromole of N-13 ammonia, which translates to 0.80 to 1.60 micrograms.

The physical half-life of N-13 ammonia is approximately ten minutes. It's half-life in the blood, as determined by accurately taken blood samples, is approximately three minutes. It's half-life for myocardium and the brain, as determined from imaging data, are no more than two minutes and three seconds, respectively.

Now how is N-13 ammonia handled in the body so as to show it its way out? That brings us to the subject of metabolism. N-13 ammonia is metabolized to N-13 urea, which is its major metabolite. Other metabolites of this imaging agent include neutral amino acids, and traces of acidic amino acids, mainly glutamate and aspartate.

Now, could anything that relates to pharmacokinetics effect the safety of this imaging agent? And so we get back into examining what really is the amount of ammonia that is already in the body produced by various metabolic processes. The normal range of ammonia in humans is 12 to 55 micrograms per deciliter, which translates to 720 to 3300 micrograms in a 70 kilogram man. And so, if you throw in this 0.80 to 1.60 into that amount, it appears to me that it is like throwing a teaspoon full of salt into an ocean; it will not change the salinity. So I think that this amount would not cause any significant increase in the amount of ammonia in the body and, subsequently, would not effect a net drug imbalance of the body.

In reference to metabolism and safety, we find that urea is readily eliminated in urine. And the small amount that is generated from the small dose of N-13 ammonia then would not be a real problem, in my opinion. Amino acids are normal components of body tissues. So based on this, it is reasonable to expect that the metabolic products of N-13 ammonia would not significantly affect the safety of this imaging agent.

And so the next thing I had to look at was radiation absorbed doses to various organs of the body. I had to go to the information that is published by the ICRP and then generate a dosimetry table in the units we usually

use in regulatory arena; that is, rem per millicurie. And so this would do is that the clinician can use the dosimetry table as a calibration curve to determine the radioactivity dose that would cause acceptable radiation exposure in different tissues. This is only a small part of the table. The whole table is in the review that has been put in the files of the FDA.

And to summarize, we can say that due to the high extraction of ammonia from coronary capillaries into the myocardial extravascular space, the value of K1 obtained via the three-compartmental equation that describes this time course in the myocardium can yield a reasonable estimate of myocardial blood flow. As we see, ammonia is effectively eliminated from the body.

I've already talked about the dosimetry thing, that it would be a calibration curve which allows the physician to determine a dose that is appropriate for a given population. And finally, we can say that the pharmacology, toxicology, and pharmacokinetics of N-13 ammonia do support its use for myocardial indications. Thank you.

DR. RAMSEY: Thank you very much.

I think we will hold questions until after the second presentation, and the second presentation is entitled "Safety and Effectiveness in Oncology," by Dr.

Florence Houn.

DR. HOUN: Good afternoon again. I'm going to be talking about N-13 ammonia in use of PET for myocardial perfusion. My teammates include Sonia Castillo, who helped with the review. She's a Ph.D. from the University of Washington in Seattle, and a postdoctorate from the Harvard School of Public Health, and she's been with the FDA for three and a half years. Also, Ms. Kaye Cho was the project manager. David Hussong was our microbiologist. Ravi Kasliwal was the chemist. Dr. Laniyonu was the pharm/tox reviewer. Dr. Udo did the biopharm.

My preliminary conclusions are a finding of effectiveness to assess myocardial perfusion in the evaluation of coronary artery disease in patients with known or suspected coronary artery disease through stress and rest testing. In the literature, single doses of up to 25 millicuries were studied, usually administered as two IV doses, during rest and then at stress, up to 20 millicuries each.

I'm going to kind of run through these slides because I've talked about them before in terms of the general structure of the talk. You've heard about our guidances and how we've been using them. I'm going to discuss the intended use of N-13 ammonia, the external standards of truth for the studies, our search methodology,

selection criteria, review of findings, and conclusions.

I'm not going to talk very much on this. Again, the guidance for clinical effectiveness was discussed, when studies in the literature could be used to support indications.

The draft medical imaging guidance also provided some structure for me in terms of looking at what should be included in studies in terms of adequate and well-controlled design.

In terms of its intended use, a cursory review of the N-13 ammonia literature found a couple of different uses for this drug, including identification of malignancy, perfusion of various organs, and the assessment of myocardial perfusion. The bulk of the literature focused on myocardial perfusion, and that's what I focused on in terms of trying to find effectiveness.

The advantages for this agent in terms of evaluating myocardial perfusion include that it's minimally invasive, there are kinetic models available to allow for quantification, there is the ability to correct for photon attenuation because of body habitus. Also, it provides a functional or physiologic claim in terms of looking at perfusion, and ammonia tissue concentration almost linearly relates to the flow over zero to 300 CC's per minute per 100 grams of tissue. It's highly extractable, as Dr. Udo

was talking about, from the circulation into myocardial cells, where it's rapidly metabolized.

In terms of an external standard of truth for myocardial perfusion, many studies were done comparing to coronary angiography. Angiography is typically viewed as a gold standard for anatomy, for coronary artery disease, and at times for blood flow. We know it's good in terms of identifying anatomy. It presents two-dimensional information, but there are problems with coronary angiography in that the endpoint in terms of percent stenosis on an angiogram doesn't take into account many factors, such as the geometric complexity of the actual atherosclerotic vessel.

There are variations in terms of the extent of the length of the stenoses, diffuse disease. There's collateralization, viscosity. Angles of various takeoffs of vessels affect flow rate, hypertension with or without hypertrophy, and even heart rate.

So in trying to address what can be used as a standard to look at myocardial perfusion, one solution that authors had looked at was the use of quantitative angiography through validated software programs to try to eliminate observer bias and allow calculation of coronary perfusion as a function of flow. In some of the papers I'm going to talk about, the use of stenosis flow reserve is

presented, and that's defined as the flow at maximum vasodilation versus at rest.

The search criteria you've heard earlier: the same time period, from 1990 to 1998; online databases that were in English and that dealt with human clinical trials information. We got a lot of assistance from ICP in finding articles as well. In all, 76 articles were generated from the above search criteria.

In terms of selection criteria, we looked at N-13 ammonia PET studies that compared to an appropriate clinical standard of truth. Some of this would be in terms of anatomy relating it to angiography. In terms of a functional standard for microperfusion, we looked at various other comparators, such as wall motion through echo or through ventriculography, exercise testing. A variety of other standards were used in terms of trying to assess microperfusion.

We also looked at articles that had a relevant clinical study question and were not experimental in design. A well-described clinical population was included, and there were some types of procedures to reduce bias, such as masking, randomization. In all, the selection criteria generated 14 articles. Two of them I'm going to discuss at greater length. These were the larger studies. One is a feasibility study that led into the larger

published studies, which I'll talk more about.

I'm also going to be going through some of the other controlled published studies. These had various study hypotheses. Some of them had retrospectively selected patients. Others used normal volunteers and assumed that they would have angiographically-defined negative disease, although these normal volunteers did not undergo angiography. These were smaller studies. There were nine other published studies that had a wide variety of hypotheses but still supported the idea of using N-13 ammonia to define coronary perfusion.

Also in my review I included myocardial blood flow quantification algorithm papers, much as what was summarized by Dr. Udo earlier.

The two studies I'll focus in on are Gould, published in 1986, which is a feasibility study, and Demer, published in 1989 as the follow-up larger study to the Gould study.

Other controlled studies are listed here: Schelbert, Di Carli, Gerwitz, and other supportive studies are listed in alphabetical order. You see them here and on the next slide.

The quantification algorithms are listed here, three studies that I really will not be talking about, but they're included in the review for completeness.

In terms of the first study we'll spend some time on, Gould in 1986 published this from the University of Texas Medical Center. It was a feasibility study for diagnosing coronary artery disease with rubidium and ammonia N-13 using rest and stress testing with IV dipyridamole and hand-gripping. Now, 23 of the 50 subjects received ammonia in this study, and these people were presenting for work-up of chest pain. They were being evaluated status post-MI. Some of them were pre- and post-angioplasty patients. Some of them were pre- and post-plasmapheresis for cholesterol control patients. So a variety of types of patients were in the study.

It was a prospective study, and it compared angiography results to PET results. The image protocol involved masking. PET images were re-read three times using three presentations. There was gray-scale presentation, a tri-color presentation, and an isocount color format which ended up to be what the investigators felt most correlated between PET and angio results. The isocount color format had defects defined by the color format and the continuum of changing count densities being reflected in hue gradations in each of five primary colors corresponding to steps of about 3 percent maximal counts at rest and stress images.

The dosage of N-13. People got between 10 to

20 millicuries two times, at rest and at stress, of either N-13 ammonia or rubidium. It depended on what was available from the generator. X-rays were digitized and allowed for the measurement of stenosis dimensions and allowed for calculation of coronary flow reserve. That was scored between zero to 5, zero being no flow and 5 being normal. They defined having a significant coronary flow reserve problem as less than 3.0 on the angiography, and this was defined prospectively. There were 22 patients that met this definition of having significant coronary artery disease. There were 9 patients without coronary artery disease defined as greater than or equal to a score of 4, and there were 13 patients with mild disease, between 3 and 4.

The paper stated in a caption that the percent isocount reduction on PET was proportional to the percent decrease of coronary flow reserve. So I'm making the assumption that this is the equation in terms of relating coronary flow reserve and PET scores.

The sensitivity of this study showed 21 out of 22 patients who were identified as having significant CFR picked up by PET, and a specificity of 9 out of 9 who were disease-free were picked up as PET-negative. The qualitative comparison of N-13 ammonia and rubidium-82 was just stated in the study to be comparable. There was no

separate stratified data on how each of these agents performed.

The Demer study also came out of the same university as a follow-up to the Gould study. The specific objective was to look at accuracy of N-13 ammonia in evaluating coronary artery disease using rest and stress testing compared to coronary angiography. The sample size included 111 patients who received ammonia. The remaining patients received rubidium. There was a total of 193 patients, of which 174 were analyzed. Nineteen patients were excluded from the analysis, and the reason stated was the infarct-related stenoses they had had undergone acute revascularization, and they were excluded because residual stenosis severity would not be comparable to perfusion defect on PET.

The inclusion criteria were all patients who were undergoing catheterization, and this included the population suspected of having the disease, and including some that were disease-free. There were 143 men, 50 women. They included people undergoing work-up for chest pain, abnormal stress test results, thrombolytic therapy. They were being evaluated for renal transplant. There was also a cholesterol lowering program involving coronary angiography and PET testing, and these patients were also enrolled.

The design of the study was comparing stenosis flow reserve, which resulted from digitized angiograms that allowed calculation of SFR, and they defined SFR as the intersection of flow at maximum coronary vasodilatation relative to rest flow. They compared this score to PET defect scores.

The endpoints were continuous scales. SFR was measured from zero to 5, and I have here 5 being normal, but it's actually greater than or equal to 4 being normal, less than 3 being significant coronary artery disease. The PET defect scores were also zero to 5, but going in the reverse direction, 5 being severe perfusion defect, zero being normal, 1 being possible, 2 being probable, 3 being mild, and 4 being moderate. So significant coronary artery disease was defined as a PET score of greater than 2 and an SFR of less than 3.

The image protocol involved masked readers. They were independent in reading. Each image was re-read twice. The rest and stress images were read side-by-side using the isocount format. Scores for PET were averaged. This study talked about tracking inter-observer variation. Dispute resolution was described for eight cases. These cases were re-read, and either there was an agreement in two cases or they averaged the scores in six cases.

The dose and administration section of the

study was supplied, and the results were presented as a Spearman correlation coefficient of 0.77 per patient, scores with the most severe PET score and SFR score. What that meant was for each patient, regardless of the location of the vessel that was being considered, the most severe score for PET and for SFR was correlated. So these may not be of the same regions in the testing modalities.

Also, per-vessel analysis done by 243 stenosis defect pairs was correlated, to have a Spearman correlation coefficient of 0.63. In terms of rubidium and ammonia use, the study stated the following concerning the two agents: "Images obtained with rubidium-82 and N-13 ammonia tracers were qualitatively similar." There was no breakdown in data of how rubidium performed relative to ammonia, but there was some information in terms of the total enrolled patients of 193. There were two false-positives, of which one was from rubidium, one was from ammonia, and there were seven false-negatives, of which two were from rubidium and five were from ammonia.

This 193 and the two false-positives and seven false-negatives was not the actual data set they analyzed, which, if you recall, was 174, because they excluded 19. So in trying to use the data that was presented, I know Dr. Links was hoping FDA would move away from sensitivity and specificity. Nevertheless, we moved towards it in this

study, to trying to use Figure 3 in the study, which I'll show you in the next slide, which is a graphical representation that does permit some estimates of N-13 ammonia PET sensitivity and specificity using the data of the plot versus mean stenosis flow reserve score versus subjective PET defect severity score.

So if you go to the next slide, I think it's kind of hard to see but it is included in your review. The upper representation is the per-vessel analysis. If you total the N's here, it deals with 243 vessels. I'm going to first talk about the lower representation, which is the per-patient analysis, which, if you totaled all the N's here, comes to 174 patients.

I'm going to orient you. This is the PET score severity, zero to 5, zero being no disease or PET-negative, and a score of 2 or more being significant artery disease as defined by PET. So a PET-positive score is 2 to 5. So all these people here are PET-positive. These are the numbers of the people and their average scores. These are the error bars associated. There are 106 patients here in the study that were defined as PET-positive. Over on the right-hand side, these are the PET-negative people. There are 68 patients here defined as PET-negative.

Now, if you go on this axis, stenosis flow reserve score, it's the reverse, where zero is severe

disease and 5 is considered non-disease. Here a score of 3 or less is considered significant disease based on the angiography results. So this box of people are considered disease-positive based on this gold standard of angiography stenosis flow reserve, and the people below a score of 3 on SFR are considered normal.

So what we have here is the making of a 2x2 table, except that there are some overlaps. The number here is 4, and there is some overlap in that probably two out of four of these patients are false-negatives, meaning that the PET score is less than 2 but their stenosis flow reserve score is greater than 3. We also have patients here who are false-positive, where their PET score is greater than 2, meaning they're PET-positive, but their angiography results are less than 3, meaning that they're not diseased according to angiography.

So what you have is the makings of the 2x2 table, and if we advance one slide we have the totals based upon that graphical representation. We have one degree of freedom, in that if I fill in one box, everything else must add up. So if I fill in one box, I'm obligated to come out with the totals on the end. What I've done is I've estimated that error bar that was a false-negative, two out of four, putting the 2 here as a false-negative score, meaning that the PET score was less than 2 but the stenosis

flow reserve was less than 3, signifying disease.

Based on that 2x2 table, we get a sensitivity of 98 percent and a specificity of 85 percent. This is the per-patient analysis.

Now, if we go back to the graphical representation, I've done the same thing also for this per-vessel analysis, using this corner as the PET-positive/disease-positive cell for my 2x2 table. This would be my PET-negative/angiography-negative cell in my 2x2 table, and the offsetting two boxes would be my discordant cells, meaning PET-positive/angiography-negative, and here would be PET-negative/angiography-positive.

Using an estimate of the error bar here, saying that that's about two out of the five total patients, if you go forward two slides, I've put in two here, and again with one degree of freedom, all the other cells fill in, and I can estimate a sensitivity of 99 percent and a specificity of 74 percent. So if you advance one more slide, these are the numbers that we got with the confidence intervals figured in. For patients, 98 percent sensitivity with a 95 percent confidence interval between 92 to 99.7, a specificity of 85 percent with a confidence interval between 75 to 92 percent.

The strengths of the Demer study were that the

inclusion criteria were rather broad and allowed for diseased patients and non-diseased patients to be entered in. The images were read by two readers independently. They were masked to the angiography results. Inter-observer differences in PET readings were tracked and analyzed. There was graphical data with enough detail to look at the sensitivity and specificity. Dispute resolution was defined. There was detailed information on readers' performance, on the reader variability, and there was a relatively large number of patients.

In terms of weaknesses, we do not actually have a stratified study of rubidium versus ammonia results. We have some indication from the false-negative and false-positive of the total 193 patients what false-positives and false-negatives did occur. We know that in terms of sex and age distribution, age was not presented. There were certainly more men, 143 compared to 50 women. Nineteen patients were excluded from the analysis, so this was not an intent-to-treat analysis.

In terms of other controlled studies, these were more variable in their hypotheses. Their patient populations were selected retrospectively at times. There were small numbers in sample size. Normal volunteers were selected to represent coronary artery disease-free patients in some of the studies. Schelbert in 1982 from the

University of California-L.A. published a study to try to correlate angiography and N-13 ammonia PET results. It was a very small study of 32 patients who had coronary artery disease on angiography, and there were 13 normal volunteers who underwent PET imaging, rest and stress testing, but who didn't undergo angiography, and they were assumed to be normal in terms of disease-free for angiography.

Eleven patients with coronary artery disease did also have stress thallium testing as a small sub-study. There were two readers reading through consensus. They were masked to the findings of the angiography. The agreement of these readers were tracked. We have dosage and administration, as well as acquisition information from the study.

The results show a sensitivity, based on a percent stenosis of 50 percent or more, of 97 percent, 31 out of 32 patients, and a specificity of 13 out of 13 patients.

The major weakness in this study was that it was a retrospectively selected study population, and it really didn't test how the diagnostic test is going to be used in a clinical population. The same size was very limited, but nevertheless it was a study that could be viewed as providing information on proof of concept.

Di Carli in 1994 from the University of

California at L.A. School of Medicine published an article on the relationship of collateral flow, wall motion, and viability as defined by metabolism of F-18 FDG. The sample size was 42 consecutive patients, with a total of 78 vessels, with coronary artery disease defined by angiography with LV dysfunction. This was a comparative study of PET viability patterns and the severity of perfusion defects between three groups of angiographic collateral flow grades.

The findings were that there seemed to be separate information provided by angiography from PET and that they were contributing different types of information about flow. Fifty-eight percent of patients that had collaterals on angiography had decreased N-13 flow, and 50 percent with no angiographic collaterals had N-13 flow. This study was included in the review as providing information on this aspect of microperfusion that is above and beyond what angiography can provide, because angiography will not be imaging vessels less than 100 meters in diameter.

The next study was in 1994 by Gerwitz from the MGH in Boston, and it was to try to determine a minimum level of myocardial perfusion, and this I think was referred to earlier in discussions about is there a flow rate beyond which viable myocardium cannot be sustained.

This looked at 26 patients with chronic MI referred for thallium and PET testing. It compared wall motion in the PET FDG study with N-13 ammonia perfusion.

The results of this study showed that perfusion correlates with wall motion and that in patients with chronic myocardial infarction, myocardial viability is unlikely when a basal regional myocardial blood flow was less than 0.25 ML's per minute per gram. Again, this information, although the study was small, provided proof of concept of how to use N-13 ammonia as opposed to anatomical definition that's traditionally looked at from angiography.

Other studies that were reviewed -- and I don't intend to really go into detail because these also were wide-ranging in their hypotheses. Some of them were uncontrolled. Some of them had very small sample size. In some of them, experimental intervention was the goal of the study, and PET testing and angiography results were part of looking at how well intervention worked for the patients. Most of these studies were retrospective in nature.

The results of these studies talked about either how angiography correlates with PET or, in severely diseased patients, how PET detects microperfusion when angiography is negative.

Beanlands in 1995 from the University of

Michigan Medical Center studied myocardial blood flow reserve and angiography and did a correlation in terms of lumen diameter and flow rates. There was detailed patient information in this study.

I know I'm going to slaughter many people's names here. Dr. Czernin in 1995 from the University of California School of Medicine studied myocardial perfusion's response to conditioning, exercise conditioning. There were 13 volunteers, of which four had coronary artery disease, and there were eight non-randomized, non-concurrent controls that were normal volunteers. This study showed an improved flow in cardiac endpoints with conditioning. What this study allowed us to do was to look at the pressure heart rate product and exercise as a reflection of flow and microperfusion as a functional comparison.

Di Carli in 1994 from the University of California Los Angeles School of Medicine used PET and angiography to try to predict survival. Ninety-three consecutive patients with severe left ventricular dysfunction were studied, but this was not a randomized assignment in terms of 50 getting medical treatment, 43 getting revascularization. Rather, treatment was based on the referring physician who was aware of the PET results. Management decisions in terms of how the referring

physicians used PET to change patient management was not tracked, but the results in terms of survival were tracked.

The next study by Gould in 1994 from the University of Texas Medical School was of 15 patients with greater than 50 percent stenosis to try to assess perfusion after a cholesterol reduction program, and they were randomized to three 90-day programs to decrease cholesterol. It was a treatment-control sequential trial, and PET was correlated with better cholesterol results, better exercise capacity.

Gould in 1995 published in JAMA his randomized clinical trial of 20 patients who received active risk modification for coronary artery disease, along with 15 patients who received usual care. Quantification of PET and angiography results were done initially, and then after five years, and there was a correlation of PET results in terms of size and severity of defect and angiography results in terms of percent stenoses, absolute lumen area, and SFR.

Haas in 1997 from the University of Munich, Germany, published a study to assess PET's correlation with outcomes of CABG decisions. This again was a retrospective study. It was non-randomized in terms of treatment. There were 76 patients, of which 35 were selected to undergo a CABG based on angiography, and 34 of 41 underwent CABG

based on angiography and PET results. This study also tracked survival.

Laubenbacher in 1993 from the University of Michigan published a study involving 29 patients with coronary artery disease on angiography and 23 controls to evaluate automated analysis of 3-D myocardial blood flow algorithms. ROC curves were generated from this study. Agreement of software and observers' interpretation also resulted.

Sambucetti in 1995 from Pisa, Italy, studied myocardial perfusion in collaterals. There were 19 patients with coronary artery disease, 13 normal patients. PET results were compared to angiography at rest and stress, and the results of this study again supported that angiography and PET provide different information when it comes to collaterals, that collateral-dependent myocardium maintains a residual blood flow reserve at stress not appreciated by angiography at rest.

Soufer in 1995 from the West Haven VA Medical Center studied reverse redistribution in thallium studies. A new or increased defect was defined as reverse redistribution after thallium stress testing. Basically, the study results of the 32 patients with coronary artery disease and reverse redistribution contributed information on PET wall motion and microperfusion correlations. There

were 50 segments with reverse redistribution. Thirty-six of the 50 -- that's 72 percent -- were PET-positive for a perfusion mismatch, and after a mean follow-up of 14 months, 50 percent with cardiac events had reverse redistribution and PET viability -- that's 5 out of 10 -- compared to 9 percent, 2 out of 22, who didn't have a cardiac event.

We've talked about the weaknesses of the literature. In the ammonia data set, the studies were certainly a lot smaller than the ones that were reviewed for FDG oncology, and also in terms of consistency, there was much more variability than for FDG in myocardial hibernation that Victor reviewed. The data set was much smaller, and the hypotheses were much more variable in terms of supporting myocardial perfusion.

Nevertheless, some of the data did suggest support for the intended use to assess myocardial perfusion. These findings were consistent with the perfusion indication not only from an anatomical point of view but also from a microperfusion point of view for functionality. The studies were done in diverse populations. We were able to calculate sensitivity and specificity based on the larger Demer study, and we did have information not only on blood flow as defined by anatomical blood flow but also functional blood flow in

terms of microperfusion.

The safety information has been discussed by Dr. Udo. A small amount of ammonia is introduced to the body, with known metabolism and excretion, a very short half-life. Dosimetry information was given to you earlier.

So in my preliminary conclusions, I would invite the advisory committee to help us in terms of discussion of effectiveness to assess myocardial perfusion in the evaluation of coronary artery disease for patients with known or suspected CAD. Again, this is not a screening test. This is done specifically in a diagnostic population, people with symptoms or people with known CAD.

Thank you very much.

DR. RAMSEY: Thank you, Dr. Houn.

I think we'll go on to the next presentation, and this is Dr. Jamshid Maddahi from the University of California in Los Angeles. This is part of the open public hearing portion of the program.

By the way, we will not take up tomorrow's program today. That will be presented tomorrow. Thinking ahead while we set up, we probably will not take all day, probably just the morning. We should be done by noon. I imagine so, but obviously you can never predict. But that would be what we're looking at, without holding me to that, please.

But nonetheless, Dr. Maddahi. Thank you.

DR. MADDAHI: Thank you very much for the opportunity to be here. I thought that I would show some case examples of how this test is used at our clinical PET center at UCLA and how we make patient management decisions based on this. Also, I thought that, as Dr. Ed Coleman drew cases from last Wednesday, I'll draw cases from several years ago because I wanted to show you how these tests actually help the prognosis of patients as well, in addition to diagnosis.

The first case that we'll be looking at -- could we please have the slides on? This first case is a 58-year-old physician, a radiologist actually, who was admitted with severe resting anginal pain, and myocardial infarction was ruled out in the hospital. On the resting electrocardiogram, there was some T-wave inversions in ADL. In order to find out whether this pain is cardiac, the patient had an exercise test, did very well, went for 10 minutes with a good heart rate response, good blood pressure response, no chest pain, but there was some questionable ST segment depression on the treadmill test.

Because of the fact that the patient did have a recent onset of angina and had some questionable ECG changes, then the decision was that we needed some more information, at least non-invasively, as to whether this

patient has coronary artery disease.

I'm going to show you in two different formats the slices. These are all the slices that we get, and I'll reorient them in the short axis. The red is the myocardium that is perfused from apex to the base of the heart in the resting condition and stress condition, and vertical long axis the same way, and axial cut. In order to appreciate what the abnormalities are, these are the selected cuts in the vertical long axis at the time of stress and rest, short axis stress and rest, and axial stress and rest. That shows normal myocardial perfusion in this patient, absence of stress-induced ischemia.

Based on the data that you already heard from Dr. Houn that the specificity and sensitivity of the test is quite good based on several published literature, although they used different criteria, here you obviously cannot, based on a negative study, you cannot ever on a non-invasive test draw the presence of coronary disease with 100 percent, but the sensitivity of the test is in the 95 percent range, and the specificity is in the same ball park. Therefore, we were quite confident that the likelihood of coronary artery disease in this patient is quite low.

Treating this patient was not very easy. For those of you who have had physician patients, you'll

appreciate my comments. So the patient insisted on having an angiogram also, as a gold standard, just to see what's going on. And sure enough, my arms were twisted to refer him for coronary angiography, which actually turned out to be completely normal, to confirm that the results were okay.

This patient actually has done quite well. This study was done in 1992, I believe, and he's done quite well for these past seven years and has not had any problems.

We'll go to the next patient.

I'd like to point out before we go to the next patient that we do actually do quantitation with a polar map approach. This is the flattened-out myocardium. If you imagine the myocardium being like a semi-open umbrella, a cone-shaped structure, we're opening it up, looking at the entire myocardium, with the apex at the center, and then the atrium ventricular group in the periphery, and the different colors indicate different degrees of uptake of ammonia in this case, which is entirely normal, except for the apex, which has a normal pattern of apical thinning that we see in patients.

The next patient is a younger gentleman. He is about 48 years old. He also presented to the emergency room, also with a similar kind of scenario, with several

hours of chest pain, and the myocardial infarction was ruled out, and a subsequent rest and stress PET study was done. Here I'm showing it to you in black and white. This is the way we analyze these images. They're either in the gray-scale color or in color scale. Here you can see again that there's a normal perfusion throughout the myocardium, and everything was normal at rest and during pharmacologic stress.

Here is the representation of the color slices of the same patient, showing normal myocardial perfusion, and the polar map display quantitation shows again some apical thinning and normal perfusion in the myocardium.

This patient agreed that he's not going to have an angiogram. He took the suggestion that this is a low likelihood of having coronary disease. Even more importantly, this is a low likelihood of having coronary events in the future. This patient has been now for five years after the study and he has not really had any coronary events or any problems. He is one of 173 patients that we have followed for a period of about two and a half to seven years now, with negative studies, and we were curious to know what the prognostic indication or the prognostic significance of a negative study is in these patients, and we found in the 173 patients that there was no mortality in these patients. The event rates were quite

low, about a quarter percent per year, which is a 0.28 percent per year event rate in patients with a negative test.

Now, we know from nuclear cardiology, from thallium testing, and from the sestamibi testing literature also, that the event rate in patients having an entirely normal study is quite low, is in the less than 1 percent range. This, in fact, appears to be slightly better, meaning that it is more predictive of lack of events in these patients.

The way we would use this information, obviously, is that we could, based on the strong negative predictive value of the test, which is over 99 percent -- when we're talking about a quarter percent event rate per year, we're talking about a negative predictive value that exceeds 99, is 99.7 percent negative predictive value. This becomes a very, very powerful test in patient management. I think we have avoided coronary angiography in many patients who have had negative studies, even though they have presented with symptoms that were suspected of having coronary artery disease, and they have had good prognosis.

Here is an example of another individual who has had some pain, and his physician, with repeated treadmill testing over a period of time, he has only seen a

very slight and insignificant ST segment depression on the treadmill, and he wasn't convinced that this patient's chest pains are cardiac and has been assuring him that his pains are not cardiac, until he insisted that he needs another step beyond treadmill testing to find out what's going on with him.

Here you're looking at the stress perfusion with pharmacologic stress and the resting ammonia distribution. The resting study is normal, as you can see, a complete doughnut-shaped pattern in the short axis and the horseshoe pattern in the vertical long axis and axial planes, but there is a significant reduction of perfusion in the lateral wall that extends to the inferior wall. It involves approximately 30 percent of the myocardium. This was interpreted as indicating the presence of a very severe proximal disease in this patient. The patient subsequently went to coronary angiography and was found to have 95 percent proximal stenosis, which then subsequently underwent angioplasty, and that resulted in the resolution of this patient's chest pain.

Now, whether we need to do a prospective study of whether these defects, if they are left alone, would cause more events, I think this goes back to another issue that was brought up earlier today, that although ideally we want to have prospective randomized studies to evaluate the

effectiveness of various prognostic indicators, I believe that we have learned enough in the field of PET, and perhaps even with some other agents, that it becomes increasingly difficult and perhaps unethical to conduct prospective studies and randomize these type of patients. If I was a patient who had such a defect, I would not want to be randomized to no treatment in order to provide data to support that this kind of an abnormality is associated with higher incidence of death or myocardial infarction.

So I'd like the group to keep in mind that we have a dilemma as researchers, that we cannot actually conduct in certain areas randomized studies anymore because of the fact that the knowledge is out there and it has become unethical to conduct these types of studies.

Here the polar map display also shows very nicely that a big chunk of the myocardium, one-third of the myocardium is severely hyperperfused during stress, while the resting perfusion is normal, indicating that this patient has not suffered prior infarction, but these are all areas that become hyperperfused during stress, indicating coronary disease.

I'd like to move on to another challenging case. This was a patient who presented after acute myocardial infarction. The first three cases that I discussed with you were cases who were suspected of having

coronary disease but they did not have known coronary artery disease. But the role of the myocardial perfusion imaging with PET and ammonia goes beyond this group of patients and extends into patients with known coronary artery disease.

This is an example of a patient with a prior known anterior myocardial infarction, and he was complaining of chest pain about two weeks after an acute myocardial infarction. He was a patient who presented with his MI with sudden death. So he was resuscitated at that time. He is now complaining two weeks after resuscitation and after acute myocardial infarction with chest pain. The question was whether something should be done about this patient.

The patient went to coronary angiography first, and what was seen was a single 80 percent lesion in the left anterior descending coronary artery. This is when I think most cardiologists, especially the catheterizing cardiologists -- I may say these things because I'm a cardiologist myself, so I'm sure they will not be taken wrong by anybody -- they may go by this reflex that we call the occluding dilating reflex, that they see stenosis and they want to dilate the stenosis. They think that this will cure the problem.

Now, in this case they asked my opinion of what

should be done, and as a consultant I decided that we need some functional information in this patient to know whether that 80 percent stenosis is supplying viable tissue, that by opening that stenosis up, we're going to help this patient. There's 80 percent stenosis. Is this supplying dead tissue or viable tissue?

Here, looking at the resting, first we looked at the viability pattern with FDG and ammonia. The resting ammonia shows a big hole in the distribution of the left anterior descending coronary artery. We no longer see the doughnut-shaped pattern, and the apex and the anterior wall is missing, and you can see a match to defect. That was the pattern that was discussed earlier today with FDG. There's a match to defect in exactly the same area, with almost absence of perfusion and absence of FDG uptake.

This indicated to me that there's really no viable tissue within this area that would benefit from opening up that artery.

Another question that may come up in this situation is that these are all resting images. Do we know whether we're going to make other portions of the left anterior descending coronary artery ischemic during stress? So we proceeded to do also the protocol of stress/rest study. The resting study is the same one that you saw before, and then we did pharmacologic stress, and we see

absolutely no change in the pattern of perfusion. These were quantified, and the size of the perfusion abnormality was identical to the resting size of the perfusion defect.

The conclusion here was that not only is there no viable tissue within the infarct zone, but there's no stress-induced ischemia in this patient, so the patient really would not benefit from angioplasty, and I resisted that. Now it is about four years after this test and the patient is doing quite well. There is no problem with that stenosis.

Now, where did the chest pain come from? It turns out that after a while we did some x-rays of the chest, and we found out that during the initial resuscitation, the patient had a fractured part of the junction, and it was the reason for the patient's chest pain, not myocardial ischemia.

I'm going to show you two more cases. The two more cases are again patients with known coronary artery disease, and the orientation, now that you are quite familiar with what these look like, I'm going to show you a whole row of data. Here the resting study is on the top and the stress study is on the bottom. We're looking at a patient here -- perhaps this is the clearest view, the vertical long axis, that shows an area of severe decrease of activity in the anterior wall and apex, which is normal

at rest. Here you can see the same thing, that the apex that is missing during stress is normal at rest.

This is a patient who has had angioplasty of the left anterior descending coronary artery, and because it was a high-risk angioplasty, meaning that the lesion was quite complex and statistically there was a high chance of recurrence, the physician who did the angioplasty was quite concerned that this patient would have a high likelihood of re-stenosis. But the patient was asymptomatic, so the dilemma was whether there's anything we can do to evaluate this patient non-invasively rather than doing another angiogram, and we proceeded to do a PET study.

As you can see clearly, there is evidence of significant stress-induced ischemia in the left anterior descending coronary artery territory. Here are the polar maps at rest, resting perfusion, and stress perfusion, which is significantly worse than the resting perfusion in the left anterior descending coronary territory.

We also see that even resting perfusion is not entirely normal, indicating that perhaps during the first angioplasty the patient had suffered a non-transmural myocardial infarction, perhaps as a result of dislodgement of the placque distally. There is a small apical myocardial infarction in this patient as well.

This led to a repeat angiogram in this patient

that confirmed that there has been significant re-stenosis in this patient.

Another case is a patient who has had bypass surgery already and comes about four years after bypass surgery with a chest pain episode that again statistically puts the patient in the category that, knowing from the literature that vein grafts may close, about 50 percent chance of closure about five years out after bypass surgery. This patient is in an intermediate likelihood of having one of the vein grafts having a problem and is presenting with chest pain.

Doing a nuclear evaluation with PET ammonia, resting images are shown on the top, and stress images are shown on the bottom. At first glance things look to be okay, except for a very, very small area here in the posterior lateral wall that is a non-reversible defect. I'll show it on the polar maps. There's a very, very small area of lack of perfusion at rest that remains unchanged during stress.

This patient had a known occlusion or infarction in the distribution of a branch of the circumflex coronary artery, which is the second obtuse marginal branch, and that correlates perfectly well with that old known small myocardial infarction that did not even show on the resting electrocardiogram. But it was

known that the patient had a second marginal branch occlusion. But beyond that, we don't see any evidence of stress-induced ischemia in this patient, and this was a reassurance that this patient was in a low-risk category for development of events.

There is, again, nuclear data, not necessarily with ammonia, but rest and stress perfusion has been excessively used in the single photon arena. I've shown this concept that the negative test after revascularization is indicative of good prognosis in these people, and currently data with PET is accumulating in order to establish the prognostic significance of these findings, similar to what we know from the single photon data in the PET data in patients following acute myocardial infarction or in patients who have had bypass surgery.

Thank you very much for your attention.

DR. RAMSEY: Thank you very much.

I want to thank all the presenters this afternoon.

Now we are in open discussion and the question and answer period. Specifically, I'd like to ask if the FDA individuals have any specific questions or any specific things you want addressed.

DR. HOUN: I'd like to hear the committee's comments on their evaluation of effectiveness. I mean, I

think the studies that I've presented are certainly smaller in sample size, very diverse in their hypotheses, but as a whole I'm just interested in hearing the positives and negatives about the group of studies reviewed and how people are feeling in terms of effectiveness for perfusion with N-13 ammonia based on the data.

DR. CHOYKE: Can I just begin with a technical question, because I'm perplexed by it. Perhaps you can address it.

You have an agent with a 10-minute half-life, and I'm trying to figure out how you can do rest and stress and do all these things while the decay is happening. How technically demanding is this study, and is it really reserved for a sophisticated center, or could an average center do it?

DR. RAMSEY: I have a corollary to that, too. That is, I also don't do cardiac imaging, so coming from lack of knowledge here, how often is it done? Who does it? Where is it done? How many cases per year or per week or whatever?

DR. MADDAHI: I think these are all very important questions. It is a technically demanding type of study. It requires certain things. One is that the cyclotron that produces ammonia has to be on site. Unlike FDG, that has a future and is currently being used as

having regional cyclotrons that can ship FDG to remote sites within a two-hour distance from the sites, with N-13 ammonia, we cannot do it that way. The cyclotron has to be on site. Because of that, it creates a technical difficulty there.

The second thing is that timing is very important. We have pneumatic tubes that connect the cyclotron directly to where the patients are being imaged. We're in contact with them to know when the ammonia is introduced, and then we will just have the patient ready to inject. So it is technically demanding as well.

At the present time, there are not many studies being done because of these technical difficulties. But whether there will be more of them done in the future, I would guess that the use of -- this is not going to be the type of procedure that would be done 5 or 10 a day or anything like that. I think that this is going to be perhaps much more limited than that, and the reason is not that the disease is not common. We all know that coronary artery disease is very common, and centers that do non-invasive evaluation of coronary disease with other techniques such as single photon imaging, they often do 10 patients a day, 15 patients a day.

But here I think that we're not going to be getting to that. I think that for centers that have access

to both ammonia and to other agents, the first choice would remain those that are more practical, and then ammonia would be perhaps reserved for a very specific type of patient population, perhaps those where attenuation correction is very important. We know that one of the sources of artifact with imaging is breast attenuation in women and diaphragmatic attenuation in both women and men.

Attenuation means that the activity that is coming from the heart going through the tissue would register on the camera as being an area that has decreased activity, and the more tissue it goes through, the less activity would show. So it becomes confusing at times to interpret. So I think that perhaps is one of the fortes of this technique. But I think that the use of it is not going to be very widespread because of these technical limitations.

DR. CONTI: Can I interject?

DR. RAMSEY: Yes, please.

DR. CONTI: This is Peter Conti from USC. I'd also like to just mention that, of course, we do rubidium in the field, which has a shorter half-life, and also is technically challenging. So this is not necessarily something that's novel to the PET community. I would also add that the technologies that we currently use for stress/rest are not necessarily that technologically

undemanding either. It requires a fair number of visits to the scanning suite, the studies are more protracted, and when the systems are down, they can actually be quite simple with 13 ammonia, as long as there's a reliable delivery system in-house.

DR. RAMSEY: Any other questions or comments? Jonathan?

DR. LINKS: Just one point of clarification. When you do a stress and a rest, it's two administrations. So you're not trying to fit two different imaging protocols into a 10-minute half-life.

DR. CHOYKE: Could we maybe change the subject a little bit back to your question? I'll pose it back to you a little bit, because I was confused about what is the ideal gold standard in these tests. I mean, you've reviewed all the literature, and I was confused. I mean, if you had to design the ideal study, what would it be, and how far away are we from those ideals?

DR. HOUN: I think that for N-13 ammonia, it's been studied in the literature according to a variety of standards because the indications that these investigators were studying were of a wide variety. Some of these investigators were focused in on correlating N-13's use in terms of revealing anatomic information. In that case, coronary angiography was used. In other cases,

investigators were trying to look at N-13's ability to detect microperfusion where people would be angiographically negative, and they compared microperfusion as detected by N-13 ammonia to other kinds of functional standards, such as exercise endurance. They looked at wall motion by echo or ventriculography.

So I guess there are a variety of standards used because the hypotheses about what this agent is trying to indicate, what it's trying to be used for are varied.

In my review, I wanted to try to encompass both types of indications, an anatomical indication, which is certainly supported by the Demer paper, as well as a functional indication that's supported by the various studies that used wall motion, exercise endurance, and those other kinds of standards.

Now, perhaps I'm stretching too much. If people are more comfortable with an anatomical description, I'd like to hear that. If people feel that the stretch is okay, I'd like to hear that too. But that is the struggle, you're right. I do think this agent is able to do more than just anatomical information, and I'm just wondering whether the studies support the microperfusion and functional indications.

DR. KONSTAM: Maybe I can comment. First of all, I think that this, with the caveats that we discussed

this morning about not having an NDA before us, I think that this application is extremely strong. I actually favor the wording that you've used very much.

I think that in terms of an ultimate gold standard of what you would want, I guess what we're seeking is something resembling clinically relevant abnormalities of myocardial perfusion. I guess that's sort of what we're trying to capture. There is no gold standard of that, as far as I know. Actually, I think if you look through the literature, there are many places where the combination of N-13 ammonia and FDG has been used as the gold standard for that. So what gold standard do we have outside of that? I think we don't really have one. So what do we know?

I mean, we know that this agent follows myocardial perfusion based on other markers of myocardial perfusion in experimental models and in patients. So I don't think that there would wind up being any doubt about that. The next thing you get to, and that's really the analysis that you focused on in your review, is how does it relate to abnormalities in the epicardial coronary circulation, and the answer is pretty well. So even if you sort of set that up as what you're after to identify anatomic large-vessel coronary artery disease, I think it does pretty well at that, and that's useful because there's a lot we know about the clinical importance of epicardial

coronary disease.

So if that was all it did, I think that would be okay, and I think getting beyond that, again in the absence of any external gold standard for clinically relevant myocardial perfusion abnormalities, which is not provided by the coronary angiogram really, I think the next thing you get into is outcome studies. For whatever reason, there has not been -- and Dr. Maddahi touched on this -- there has not been randomized data to really look at outcome information in the best possible way, but there's been a wealth of cohort analyses looking at clinical outcomes of patients who have undergone revascularization versus those who have not, and looking at it in cohort analysis, this agent, often together with FDG, tends to mark those patients who are better served by bypass surgery than not, within the caveats of the cohort analyses.

So, I don't know. I think without a sponsor doing a large amount of other work in this area, I think it's a pretty strong indication.

DR. RAMSEY: Dr. Herscovitch?

DR. HERSCOVITCH: I would agree, and although I don't vote, I'm not voting, I would not vote yes on this application with this wording. I understand your reservations about the literature review and the fact that

perhaps some of these papers weren't as extensive in terms of the patient population as the earlier ones, but I still think there's a tremendous amount of supporting data that you presented.

But there's another whole body of data that I might suggest be considered in this type of application, and that is the use of animal data or clinical research studies to show that in this case, it's an effective agent for myocardial perfusion, and this speaks to the more general issue of how the FDA in the future will study radiopharmaceuticals, not just PET radiopharmaceuticals, in which the indication has at least a partial functional basis, and that is for virtually all PET radiopharmaceuticals, there usually is a rather large and often very well done literature with basic studies in which the measurement being made has been validated against another gold standard, and also various physiologic manipulations have been made to show that whatever it is you're measuring with the agent varies appropriately.

I would suggest, or urge almost, the FDA to include in their evidence for proposals such as this not only the clinical studies but also the basic physiology studies. In this case, there is a large literature going back 15 or 20 years on the suitability and the limitations of N-13 ammonia as a myocardial perfusion agent.

There is perhaps another caveat. If you had trouble selecting appropriate papers to include in your review as a surrogate for NDA-type protocols, selecting appropriate research papers might be even more difficult but not at all insurmountable. So again, I would just urge you to look at animal studies which have been done with most PET agents to validate the physiological function of these tracers. In fact, on page 13 of the guidance -- it says "Draft," so I don't know if I'm allowed to quote from it, but really there's a very nice paragraph, the second paragraph, which shows how animal data might and even should be used in applications such as these.

DR. HOUN: The animal data and preclinical data reviews are included in the pharm/tox and biopharm reviews. So that has been considered.

In terms of putting them as part of the clinical effectiveness review, usually the human studies are looked at at that point. But certainly the animal data is considered in terms of the overall package for the drug.

DR. HERSCOVITCH: Peter Herscovitch again. I might add, though, that there is considerably more data supporting the use of ammonia as a myocardial perfusion agent than was addressed in this package, and I guess we'll discuss this tomorrow, but the O-15 water package had really minimal, if any, animal data supporting the use of

O-15 water as a cerebral perfusion agent. Again, if part of the indication is based on the function of the radiopharmaceutical, I would suggest that those data be included, not to the exclusion, of course, of the clinical data, but to buttress or lend further support to the clinical evidence.

DR. KONSTAM: I don't know if I take a little bit of issue with what you're saying. I mean, I think that, to me, a clinical application has to be supported by the clinical data, period, except that I think that the mechanism by which an agent works or a drug works can be very important in going beyond the clinical data and saying, well, where else might it work, are there concerns we might have about what's the population? I think it's very helpful. But, to me, I think that a clinical application really stands on the clinical data.

I mean, I agree with everything you say, but it doesn't surprise me that we wouldn't spend a lot of time on it.

DR. HERSCOVITCH: Just two things. First of all, I'll quote Lou Sokoloff, who is the developer of the deoxyglucose method, which went on to FDG. Taking a purely clinical approach -- and I hope nobody will be offended by this word, but it wasn't my invention -- one could, in fact, using radioactive shoe polish, and showing it has a

certain sensitivity and specificity, but without a firmly based understanding of how the tracer behaves, you're only doing a correlational work and specificity and sensitivity. Understanding how the tracer behaves not only supports an indication which says here, "Imaging of myocardial perfusion," but it also helps you understand those conditions or diseases where the tracer may or may not be valuable.

For example, with FDG, it's been shown not to be particularly valuable looking at brain metabolism in ischemia, for a lot of theoretical reasons which have been experimentally justified. So knowing how the tracer behaves I think will not only buttress the clinical indications but also help support certain caveats as to how the tracer may or may not be used in certain diseases or when you have physiological or pathological variance, such as diabetes. The whole concept of why one should even look at diabetes and blood sugar came from an understanding of how deoxyglucose and fluorodeoxyglucose behaves, issues which one wouldn't be concerned about if one were only looking at radioactive shoe polish.

DR. LINKS: To follow up on this a little bit, I think we have to be careful about the phrase "clinical indication," because basically what we have here is a set of four categories of clinical indications, and assessment

of myocardial perfusion falls under one of those categories as intrinsically, now, a "clinical indication." It seems to me that if that's going to be the case, then the challenge is to expand our thinking on what it means to validate it. For me, if I want to know if this agent measures perfusion, I'll do microspheres. I'm going to have a hard time doing that study in humans, but that to me would be an obvious study to do. Of course, it's been done, and it does track with microspheres.

So I think if we're going to expand what we mean by a clinical indication, we have to correspondingly expand our willingness to accept all sorts of very different types of data than we have in the past when clinical indication was more narrowly defined.

DR. KONSTAM: I guess I'd respond to that by saying -- and I sympathize, and I agree with almost everything you said. So I sympathize with the concept. But I guess I'd respond to what you said by saying that if I did a microsphere study in rats with the agent and found that it was a good marker of myocardial perfusion, that would not be sufficient for me to support a clinical indication. When I say clinical indication, I'm talking about an indication in patients. That's what I mean.

Now, I understand the nuance of saying that an indication can be, in the case of tracers, let's say,

physiologically based, if we can identify something that would fit into that category. But nevertheless, I'd like to at least know that in patients.

DR. RAMSEY: I'd just like to ask for clarification since I think we're getting to where we have to vote on Question 3. Dr. Herscovitch, you said you would vote against it. I think I heard you say why, but could you say why you would vote against it again?

DR. HERSCOVITCH: Perhaps I was being too smart by half. I was saying that I'm not allowed to vote, but my non-vote would be yes, and I strongly support this application as it is worded.

DR. RAMSEY: I totally misunderstood you. Boy, am I glad I asked that question.

DR. HERSCOVITCH: I apologize.

DR. RAMSEY: Any others? Mr. Hammes.

MR. HAMMES: If you were to draw up a lecture and describe the ideal human radiopharmaceutical to do perfusion imaging, you would probably describe ammonia. You have an endogenous substance, you have a very favorable energy in the particle, you have a high specific activity, and you have a short half-life so you can do repeat studies. The only limitation is that you need the cyclotron there.

I mean, we are looking at what we will consider

the gold standard in the future, I think. The only real limitations are with the instrumentation and what you can image. So in terms of the drug, I think this is the biggest no-brainer in terms of approval you're ever going to run into. What its use will be I think is going to be determined by the requirement that you have the cyclotron right there. But I think we're looking at the gold standard.

DR. HERSCOVITCH: I just have a question of clarification. The first presenter gave a table of dosimetry which also included pediatric patients, and that just led me to think will there be any guidance or discussion of the use of this agent or the other agents in the pediatric population.

DR. HOUN: None of the studies reviewed had pediatric population in them. So the indication would be supported by the literature for adults. I guess in terms of the pediatric section of the label, we would indicate that no information is available from the literature review that we did.

DR. RAMSEY: Dr. Conti?

DR. CONTI: Let me just address this issue of dose. This actually is available, this material, in N-13, FDG, and water. So I think we can get that for the label.

DR. RAMSEY: I'm not sure I heard the answer

there. It's available for adults or children?

DR. CONTI: For children.

DR. RAMSEY: Or both?

DR. CONTI: For children and adults. There's a scale, basically, that's available for reducing the injected dose based on radioactive exposures for children for all those isotopes.

DR. RAMSEY: But that's extrapolated data, or it's been done in children?

DR. CONTI: We do it every day in the clinic. I mean, it's done. It's based on doses, radioactive doses. So this material is available.

DR. RAMSEY: Thank you.

DR. MALCOLM: But I think the question is, I think the review had no children in the studies. That's what we're asking. There are no children.

DR. CONTI: That actually doesn't matter. It's the radioactive material that's given and how much exposure the child gets versus the size of the child. It's not a dose of ammonia per se. It's a dose of the radioactive material.

DR. MALCOLM: I understand extrapolation. I don't have a problem with that. But what I'm saying is, I think what the FDA is saying is that the studies that they reviewed and what we're approving, from the information, is

in adult patients. It's not in children. So I think the question is, are we going to use this material in children? I think that's the question.

DR. HOUN: I think the question for approval does not include children, and certainly if there is more information, it can be submitted as a supplement to get pediatric labeling. But at this point in time, the literature doesn't comment on its effectiveness in children.

DR. CONTI: Well, let me be the child's advocate in this case. There's no reason for it not to be applicable in a child with ischemic heart disease. What is the difference between a child with ischemic heart disease, Kawasaki's disease, which we study all the time, with conventional nuclear isotopes, which give a higher radiation dose, and with N-13 ammonia?

DR. RAMSEY: I'll jump in here on that. As a neuroradiologist, the myelographic concentrations were utilized for a long time and approved only for adults. We used it in children all the time, but it was not approved. I think that's the same thing we're looking at here.

Correct me if I'm wrong from the FDA side.

DR. HOUN: There's a labeled indication, and how physicians want to use the drug in their practice is up to them.

DR. CONTI: This would apply, then, to all the radiotracers we're discussing today as well. But I will tell you again that radiation information is available.

DR. RAMSEY: Thank you.

Yes?

DR. MADDAHI: I just want to make sure that I haven't misled the committee here about the complexity that I spoke about. I think the issue of complexity that I referred to was the issue of the need for an on-site cyclotron. But I just want to tell you that in our experience of thousands of these perfusion studies that we have done of rest and stress, even in the pediatric population, I don't recall any study that we couldn't read because it was technically unreadable or it was not good quality. These are excellent images, excellent studies, although it requires, obviously, technical ability of the people who work with this technique, like anything else.

The complexity I was talking about is the instrumentation complexity, not the agent itself, and not the quality of the images that we get.

DR. RAMSEY: Thank you.

Any other questions or comments?

(No response.)

DR. RAMSEY: Okay. I think we'll move to the question, then. This is Question 3.

"Based upon the presented literature reviewed, do you think ammonia N-13 injection is safe and effective in positron emission tomography (PET) imaging of the myocardium under rest or physiological stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease (CAD)?"

I think we'll again follow the vote, your vote and your comments.

Dr. Herscovitch.

DR. HERSCOVITCH: Yes, and I think I've made all the comments that I have to make. Thank you.

DR. TATUM: I would also say yes, mainly because I do think the data does show it's safe, and it's quite effective. But in addition, there's been a lot of discussion of gold standard, and it's probably the most likely candidate for now for giving us something that's quantitative, which is a badly needed tool in the approved arena for other reasons. So I would definitely support it.

DR. KONSTAM: Yes.

MS. BEAMAN: Yes.

MR. HAMMES: Yes.

DR. HERTZBERG: Yes.

DR. TULCHINSKY: Yes.

DR. CHOYKE: I'd just like to be a little more wordy. I think I'm a little hesitant about the data,

frankly, because I saw it all over the place, ranging from 99 percent to 50 percent correlations. But even in that range, it seems like we definitely have some kind of correlation, that it is a meaningful agent. It may very well be that the gold standards that are used in the test are just not adequate to measure this, and that's supported I think by the animal data, or what we hear of the animal data. It's certainly a harmless agent.

So for those reasons, I'm voting yes.

DR. MALCOLM: My answer is yes, and I completely agree with Pete's comment.

DR. RAMSEY: Yes.

DR. PONTO: Yes.

DR. AMENDOLA: Yes.

DR. ZIESSMAN: Yes.

DR. LINKS: Yes.

MR. MADOO: We have a total agreement on the committee, 12-0.

One other comment. Dr. Love, when we leave, are you comfortable with us keeping our materials on the desk in a locked room, or --

DR. LOVE: Yes.

MR. MADOO: Okay. That's probably relevant to people. You don't have to tote your stuff.

DR. LOVE: All of these data are publicly

available.

DR. RAMSEY: Any other questions or comments?

(No response.)

DR. RAMSEY: Okay. I want to thank the presenters all for coming in. I know sometimes it's hard to get here. I really appreciate your coming and sharing your information. I want to thank all of you for participating.

We will begin tomorrow sharp at 8:00 in this room, where we will have the presentations regarding nitrogen N-13. Am I right? No. Presentations on water O-15 beginning at 8:00 tomorrow morning. So I'll see you here. Thank you all.

(Whereupon, at 4:40 p.m., the meeting was recessed, to reconvene on Tuesday, June 29th, at 8:00 a.m.)

- B -

- C -

- E -

- F -

- G -

- H -

- J -

- K -

- L -

- M -

- N -

- O -

- P -

- Q -

- R -

- S -

- T -

- W -

- X -

- Y -

- Z -