

Good Morning! I'm Larry Williams from City of Hope in Duarte, California and I'm going to discuss, basically, two topics. The first is dosimetry, so called, and second, is the measurement of radioactivity by planar imaging. This is the first of a set of two talks. There's going to be a second discussion tomorrow morning at the same time, where Ken Coral from the University of Michigan will discuss three dimensional imaging to try to measure radioactivity. I assume you would understand then, that measurement of radioactivity is necessary for us to make the absorbed dose estimates. Here is a picture of City of Hope. We're, a cancer hospital in the San Gabriel valley, about 25 miles from Los Angeles, to the northeast, and about 90% of our patients are cancer patients. Now, the motivation for this work is the first thing I want to discuss. Why do we want to discuss

internally emitter therapy? The basic reason we, at City of Hope got involved, was that the patient may develop multiple metastatic sites and that we want to treat those sites and we realized, initially, that all these sites may not be imageable. External beam therapy is, probably, not possible, at least for most of them and, likewise, Brachytherapy. Now, what happens to these patients? Typically, there is a survival curve. I've shown here the colorectal cancer patient survival curve. If the patient can survive up to a period of time, on the order of approximately six years, they probably have an indefinite survival. But what may occur over the first, say, five to six years is that multiple metastatic sites arise. Typically, in colorectal cancer such sites occur in the pelvis, abdomen and liver. And the treatment of those sites is usually limited to surgery and, of course, if there is more than a

certain maximum number, the surgeon will not commit to a procedure. So, what we want to do, then, is treat those patients using some sort of targeted radiopharmaceutical and today, that's usually called radioimmunotherapy, because the pharmaceutical is generally going to be an antibody protein. Generally, at least in the 1980's, these antibodies were animal-derived proteins. Today, they are engineered using recombinant DNA technology. We can also use stable liposomes to try to target multiple tumor sites. We will have a different label, depending on whether the agent is intended for initial imaging or therapy. We will discuss that as we go through. Now, there are two basic reasons, historically, for estimating absorbed dose. And I want to emphasize, that this word here is correctly given as "estimating." Dosimetry is...is basically a contradiction in terms. There is no

dosimetry in nuclear medicine and I'll mention, later on, that there's essentially no dosimetry in external beam therapy either. Generally the dosimetry we're interested in is not on the surface of the skin of the patient or in a body cavity. We're interested in a dose inside a normal organ and, in particular, in a tumor tissue. Historically the first motivation for dose estimation would be what I call a legal or scientific requirement. What we're saying here is that we are going to submit a document called an IND, Investigational New Drug document to the Food and Drug Administration. In that document, you're going to have to show some set of dose estimate. Typically we use the so-called MIRD phantom, Medical Internal Radiation Dosimetry phantom usually for an adult; either a male or female. The second type of absorbed dose estimation is for determining toxicity

in therapy in a clinical trial. In this case, what we're discussing is a specific patient. This

is the fundamental change that's occurred in dose estimation in the last five to ten years. So, we've gone from a phantom, if you like, to a specific individual. In the patient-specific case, we're going to have to use some kind of anatomical data along with the nuclear data. We cannot live with just nuclear data in this context because we have to know something about the geometry of this patient and the fundamental thing we have to know is the size of the normal tissues as well as the size of the tumor sites. And that we can only really obtain using CT or MRI. We will call these two types of estimate the phantom and patient-specific types respectively. Usually we refer to a MIRD-type phantom. These phantoms are inside a computer and they're defined by mathematical

formulas. And the standard program today, is Mike Stabin's MIRDOSE3. Dr Stabin has a new **OLINDA** program which is about to come out. . There are about six phantoms available at the moment. Shown below we have the patient specific dose estimations and these are, typically, done now in the context of radioimmunotherapy or RIT. I wanted to say at the outset, what the possible dose estimation errors are. This topic is almost never discussed in these calculations. Let us start out with the activity, which I'm going to discuss later. The activity (A) measurements are uncertain, we estimate, to about plus or minus 30% using the geometric mean method. That's what GM stands for, the Geometric Mean Method. This technique was developed by Jim Sorenson and Steve Thomas about 25 years ago. We have a newer method, which I'm going to describe later, called CAMI,

for CT-Assisted Matrix Inversion. CAMI yields errors on the order of about 10% in the same context. A tilda is the integral of "A" over time and that's uncertain to about, 10% due to the integration problems. You have to model, in other words, A as a function of time and then integrate it. Finally, we have the S factor. Remember, dose is going to be $S \times A \text{ tilda}$. That's a matrix equation and S is uncertain because of the geometry. Now, the dominant error in dose estimation is actually due to uncertainty in S. We found out, in specific patients, S errors can be on the order of two to three-fold. This is because the patient simply doesn't have tissue sizes, for example in the cases of liver or spleen, kidneys, that are the same as in the context of the MIRD phantoms. Next, let's go to the definition of absorbed dose. I'm going to take a few potshots here at absorbed dose,

because I always like to do that. Absorbed dose is not a pleasant concept to deal with. You know 100 ergs per gram as a centigrade, or rad. You should remember also, for particulate radiation, which is the one we're going to discuss, basically, alpha and beta rays; that the absorbed dose is proportional to the tissue uptake in percentage injected activity per gram. This is because all the radiation, the alpha, and the beta, will be absorbed locally. An obvious problem with absorbed dose is the amount of dose depends on the volume, or mass, of the target you select. To illustrate using temperatures. A centigrade or a rad is about 2.6 micro-degrees in a water phantom. Remember, measuring temperature change is one of the classic ways of measuring radiation dose. If, however, we limited our consideration to a single mAb monoclonal antibody molecule and we

imagine a single ionization there. Let's say the energy deposited (E) is 32 electron volts. If you do that calculation, you get about 24 degrees Kelvin and the equivalent dose at the molecular site is 10 megarads. Thus,, depending on where we're looking in the phantom

or looking in the tissue, we can see very different effects due to what is occurring. And so, you're a little bit puzzled about what to do with radiation dose. I also wish to point out that the limit of ΔE over Δm , has no clear meaning. This is because the limit depends upon where I shrink the mass to zero. Thus, dose is not readily defined in a differential sense. So because of these spatial problems, at least with dose, the user is often forced to employ what is called a quality factor. In other words, we have to go to units of sieverts rather than gray and this can be quite an appreciable enhancement. The Q

factor may be ten or twenty-fold, in order to get the effective dose in sieverts. One thing I'll point out here is that you should probably show any reviewer both your calculated dose in centigray, as well as your effective dose in sieverts and explain how you've gone from one to the other. A second limitation on the use of absorbed dose is the one I mentioned earlier. We generally can't measure the quantity of interest. So, we're in a sort of metaphysical situation here, because we can make these estimates, but in general, there cannot be any kind of direct measurements. Now, the same thing is true throughout therapy physics and I call that the Physicist's Curse. The physicist has invented dose and is cursed to try to estimate it. These same estimates have to be made by our colleagues in Brachytherapy and external beam, because no one can put dosimeters into the interesting

points inside the patient. Thus all radiation therapy methods depend on measurements made, at most, at a few peripheral points. In our business, radioimmunotherapy, the activity distribution compounds this problem. Let us first consider the standard MIRD format in this analytic process. One determines, first, the activity in the tissue of interest at various times, t . We integrate this, A of t over time to form *Atilda*, the cumulated activity and this is often done through some sort of computer model. And finally we convert *Atilda* to dose by multiplying by a matrix, typically called S . Now this S can be phantom-dependent or it can be voxel-based. And I'm going to discuss later a voxel-based methodology for that. Now, there are generally available methods to determine absorbed dose, given *Atilda*, the integrated activity. There are two standard programs,

the older BASIC Language program and the MIRDose 3 program available, free of charge. Both use phantoms, of course. I would recommend you use one of these programs if you deal with regulatory agencies because the regulatory reviewer will be familiar with the method and the phantoms. In these phantoms, though, you realize that the kidneys and the lungs are both a single organ system. Thus, when we do a calculation in these phantoms, the two kidneys are together as one entity and the two lungs are together as one entity. That fact becomes a problem, as we'll see later, when we deal with specific patients. One reason is that in humans, at least, the right kidney and the liver are usually in intimate contact, so that the right kidney has a different radiation dose, than that estimated for the left kidney. In our patient-specific work, we've had to split the two

kidneys in our analyses. And I imagine later, the MIRD people will do the same. Beside organ-sized S values, there are voxel-based calculations, where now S becomes local. In other words, we go down to a voxel on the size of, say, a few millimeters on an edge; something like the resolution of a nuclear medicine image. There are also point source kernels, where S is entirely local. Ultimately, you can do a complete Monte Carlo analysis

and then you dispense completely with S . In other words, you find the actual tracks of beta rays and alpha rays that go between source and target organ. If we assume a geometry for S based on the standard phantoms available in MIRDOSE 3 we have to, in general, adjust the A_{tilda} value obtained from a patient or a volunteer. And this is because there's going to be differences between the patient and the phantom. So, here are

the general corrections we would make to the MIRDOSE3 program. We can correct A_{tilda} to allow substitution into the program. This is in the Type 1 estimate; where we're using the program's own phantoms. In addition, we can use the S value from the MIRDOSE3 program to allow Patient-specific dose estimates. This is what I call a Type 2 estimate. So, in general there will be two types of corrections. The first type is a correction to A_{tilda} , or if you like the activity and the other is to the S value. I want to point out things about anatomic imaging. CT or MRI images are probably more appropriate for organ mass determination than is nuclear imaging. Nuclear images are diffuse and their size, their absolute size, is difficult to measure. Moreover nuclear images are not used by our colleagues in medical or radiation oncology, something to keep in

mind. So, when you talk to someone who works in, say, radiation oncology, their immediate interest is not in a nuclear image, but in an anatomic image. Here, we have increased signal intensity and as a result a very sharp edge to the tissue. In conclusion regarding the two types of dose estimation, we can recall that both types require corrections to the data sets to make the computations self-consistent. In the first case, we have to make changes in the A_{tilda} values and, in the second case, we have to, to lowest order, change the S value. I recommend, also, that dose estimators use anatomic information, that is CT or MRI data, to make these corrections. I mentioned earlier, that the corrections can be two to three-fold for a typical patient. Here's how you would correct the activity for use in the MIRDOSE phantom. The patient may have a different

ratio of the size of the organ to the total body mass, than does the phantom, in which case, you then, simply take the ratio of m , the organ mass *divided* by the total mass of the body of the MIRD phantom in the numerator divided by that same ratio for the patient in the denominator. So, here again, m is the organ mass and M is the total body mass. We're assuming the standard phantom, so we're making, for example, an argument to the FDA. Now, in the other case, if we're going to use the MIRDOSE3 program and we're going to talk about non-penetrating radiation, which is, typically, what we deal with in RIT. In this second context we are going to correct that S value by, simply, the ratio of m in the MIRD phantom for that organ divided by the mass of that organ in the patient. Again, the little m is the organ mass and the subscript np implies non-penetrating. So, we're talking

about betas, typically, although occasionally, people will deal with alpha therapy. Now, what are the variations in patient's organ size? I'm going to show you some data obtained from our lymphoma patients using CT scan images. We have 15 consecutive patients that we recently analyzed. We're looking at the spleen and this is the whole body mass. In the figure, we have ten males and five females. For the males, this is the MIRD phantom value. Now, you can see, there's quite a bit of scatter in the patient data for the spleen. A significant fraction have values that are quite a bit higher than the

MIRD value- typically about a factor of two. Notice the one patient who has a very low splenic mass. And for females, you also see a similar variation. Here's the female standard MIRD value and here are the values measured clinically, again by CT. So, this

is the kind of variation you can find in a group of potential therapy patients. This is why I earlier referred to the S correction as being two or three-fold. Now, admittedly, some of these people are going to have disease in the spleen and that's why it's enlarged. Others have had therapy which has proved effective, or perhaps they have a smaller spleen. In the next slide are shown kidney variations which were slightly smaller, but still extensive. . In essence, there's a wide variation in organ masses compared to the standard MIRD phantom. Again, these are consecutive lymphoma patients. So, here's our corrections for dose estimates for Type 1 or phantom based calculations. The S, by definition, is correct, but we have to change the *Atilda* by these m over M ratios. For patient (Type II) calculations, we'll use the MIRD S value, only if we can change it by the ratio of m

MIRD divided by m of the patient. In this context, *Atilda*, by definition is correct. It is important to look at the record of MIRD calculations that have been published. I went through the first 12 MIRD reports, which go back into the 1970's. Only two of them, actually use explicit correction for the mass of the source organs and the whole body. This was in Report 1 and Report 2, which are listed and, in these cases, the authors had autopsy data. These go back to the early seventies, so that the CT data, I think, was not available,. For the next ten reports, it was unclear if any corrections were made, for organ mass or the whole body mass. So, these results may not be self-consistent and I want to point that out to you. In other words, the patient, as they presented in the clinic, may look considerably different from the phantom. If their organs are larger in size relative to the

total body of the patient, then the distribution of the radioactivity is going to be different than if that patient had the geometry of the standard MIRD phantom. We have to keep that in mind. Now we'll switch to our second topic, which is determining activity in a patient's normal tissues and tumor. There are two philosophies here. You can do this either two dimensionally or you can do the calculation three dimensionally. The latter topic will be discussed tomorrow by Professor Ken Coral, from the University of Michigan, iHe will describe quantitative SPECT and, also, to some degree, the use of standard uptake values from PET to try to determine activity. I want to point out, and he's going to point out tomorrow, that using PET for antibodies or radioimmunotherapy, is not trivial. That's because it's difficult for us to find PET radiolabels that are appropriate for

these proteins. There are only two radiolabels that are used seriously now and both iodine-124 and copper-64 suffer from certain difficulties. The primary difficulty is their positron emission is relatively low, that is, most of their decays are not positron decays. So, I'm going to emphasize today a discussion of two dimensional methods of activity measurement.. As an aside, it may be possible to get some samples directly via surgery. . In particular, blood samples should be obtained for a patient undergoing radionuclide therapy. I'm going to concentrate on single camera projections, using either the geometric mean or the single projection as our fundamental ways of determining activity in the

patient. And then, I'm also going to discuss our new method CAMI, CT Assisted Matrix Inversion. This is a technique which tries to reconstruct the activity inside the patient,

giving the benefit of CT data, as well as the nuclear data. Now, nuclear imaging is logical. If you like, it's the astronomy of the internal universe. If you can see objects from two or more sides of the patient, you can do a geometric mean. You may have, however, a situation where the tissue is imaged only from one side of the patient and you have to live with that.. Now, you can also have this situation, which we all worry about. The object is imaged from no sides of the patient. By imaged here, I'm talking about nuclear imaging. With CAMI, we have a technique for trying to get around that because the object is, presumably, imaged using the CT scanner. Here's the fundamental geometry as given in the slide. We will talk about rays passing through the patient and these .have a finite cross section, so they are really voxels going through the patient. So, as you go

along the voxel through the patient, there is a sequential set of unknown activity densities. That's your problem. There's one of These unknowns per organ. . We call this the function a , the linear activity density. Its units are in micro curies per cm or becquerels per cm, so that when you pass the voxel through the tissue, the unknown is "how many micro curies per cm does that tissue have?" In the simplest calculations we've done with the CAMI method, we have assumed that the tissue has only one such parameter. You don't have to make that assumption. Now, each tissue in the CT, of course, has its characteristic length, as well as its characteristic activity density. It's this density that we're going to seek to determine. Here's what it looks like if, let's say, this is the anterior side of the patient and posterior; I'm imagining a situation where you have three different

activity densities. You have tissue y , thickness l , which is maybe the tissue of most interest and another background or posterior tissue, thickness x . So, if you add together x and y and l , you get the total thickness at that line level or that voxel level going through the patient. One very simple case arises for single projections. In the case of a superficial lesion, for example, if the patient has melanoma, you can measure activity directly. You get the activity in the various tumor sites. This is the number of counts, which is N , divided by an efficiency, and then a Δt , the time of the counting. What we are saying here is that we can actually measure the amount of activity in a superficial lesion directly. There is no attenuation whatsoever. As far as I know, this has only been done once clinically. It was done by Dan Macy, when he was at UC Davis and was able to

measure in an individual patient, the activity in a number of melanoma lesions. So, this type of superficial quantitation has been performed, but, typically is very rare. Now, assuming the more usual case of a tissue at depth then the attenuation must be considered explicitly. As given on the slide, the number of counts per unit time N divided by Δt , is given by an efficiency factor times the activity times this multiplicative factor, which includes two exponential terms.. Now, the geometric mean method, which was developed by Steve Thomas and Jim Sorenson in the 1970's, assumes that you can get two opposing projections; one from anterior a and one from posterior p and you take the square root of their product N values to lead to the resultant equation. Beside the efficiency factor and Δt , it has the activity (A) on the right hand side. You can, then, calculate backwards

from equality to determine A . You have to know some factors. You have to know the thickness l of the emitting source and you have to know something about x and y , those two attenuating thicknesses on the anterior and the posterior side. So, given that you can get two projections, you can solve for A , the unknown activity and the term $x + y + l$, is the total thickness of the patient at that cross section. Notice the assumptions I've made. I've assumed there's no activity in this slab, thickness y and likewise, no activity in this slab, thickness x . There's only activity in this orange region, in the middle. And that was the assumption made by the two inventors of the method. If you have activities in either or both of these overlying tissues then the method fails. There's a revised version of the textbook by Phelps and, Sorenson with Simon Cherry as their co-author: "Physics in

Nuclear Medicine". In this edition, Jim Sorenson points out that if you have two sources within this space, the calculation is ambiguous. You cannot separately determine the activity in each of the two or more sources. The geometric mean only works if you have a single source and that you know the geometry of the source. Because of this limitation, we were motivated to develop a new method. This is work that was done in the middle 1990 but has had little clinical application. I would like to discuss this novel technique which we have called CAMI. This is a short version of CT Assisted Matrix Inversion. It's probably the only new method in this field for quite some time. In the CAMI method, we look at the counts along a voxel again, and now we admit that there can be several different tissues along that voxel. We integrate them from the front to the back of the

patient and here are our unknowns, $a_{sub j}$. We include a buildup factor, because we were a little concerned about scatter here. We thus include a buildup factor and attenuation factor. We do this integration, as I say, from front to back of the patient. We can solve this problem if we take some of these factors out of the integral and we did that for the activity by saying that it's not a function of thickness x , in other words, it's a constant in a given tissue. Likewise we assumed the buildup factor was a constant. Then, you can do the integrations and obtain this matrix equation. The equality involves a matrix and a vector, where you notice the unknowns now are an unknown vector of activity densities. Finally, you simply invert this matrix and get the set, or best set, of activity densities along the various tissues of interest. Now, how do we get this picture in the first place?

We have to have a CT scan. Thus, we're not limiting ourselves here, to just nuclear images. That's very important to understand. So, in a way, what we were doing in the middle 1990s was anticipating hybrid scanners. At the time we invented the method, there were no hybrid scanners. So, we were trying to think of ways that we can use the CT to make these overlapping activity corrections. We used one of Jeff Segal's ideas here also - to have a build up factor in this computation. Cf here, is the camera efficiency. This CAMI analysis has been published in Medical Physics and we're happy, by the way, to share this algorithm with anyone. It's not a trivial algorithm to implement, though, in a clinical context. Here's the line integral explicitly, going from front to back of the patient. This is the counts. And here is our set of unknowns, the $a_{sub j}$'s. The problem is over

determined, because we can pick any number of rays passing through the patient, so then

we find the best fit to the set of activity values. And we demonstrated the absolute accuracy of this work in two kinds of phantoms. The first one was a phantom that looked like this, which I call the crude phantom. The crude phantom had a plastic box, in which we put these three cylindrical organs. These are shown as circles in cross-section. The main problem we have to deal with in a patient is looking at liver, spleen and kidney in a background of activity. So, there're four unknowns here. You can look at this phantom from two projections. I will call these view number 1 and view number 2. The point is; view number 1 is the simple view. Here the organs tend to separate. In view number 2, they are all superimposed. In view number 1 we observe the three pseudo organs in

a simple way where we can segregate them geometrically. Here are the three estimated activity results. The estimated error of the CAMI calculation from the least square fitting, for the liver, for example was about 2%. The actual measured was quite a bit bigger, 14%, but the geometric mean error was much larger being 32%. For the pseudo kidney corresponding values were 14% estimated, and 9% measured by CAMI. No result could be obtained by the geometric mean method since we could not clearly separate it from the liver. For the spleen, you can see the values. And for the whole body, we could get a value for the CAMI method, but not for the geometric mean. The whole body is the background radiation level in the phantom. In view 2, the organs tend to superimpose upon each other, so we couldn't do a geometric mean computation. Here are the CAMI

results. The liver estimated error is about 2% and 14% was measured. In the case of the kidney, 13% estimated and 5% measured. For spleen, 2% and 9% were the respective values. Finally, for the residual body, 7% and 12% were the estimated and measured activity errors. Thus, we were able to get estimates with the CAMI method with errors on the order of 5% to 15% throughout. In many cases, the geometric mean couldn't be applied or it gave large errors. Following these results, we then converted to an anthropomorphic phantom. Professor Ken Coral was kind enough to loan us his phantom from the University of Michigan. This object has fillable organs. The phantom itself, however cannot be filled. So, we were limited to placing activities inside the liver, pancreas and the kidneys. These are the CT scans across the phantom. And these are the

CT scans, now superimposed on the nuclear images. So, these are planar nuclear images with effectively a CT scout view. The CT image was used to generate the regions of interest. Using the CT scan we were able to measure precisely where the liver, the spleen and kidneys were. That's not typically the case for nuclear images. Here are the anterior and the posterior fused CT/nuclear images. Several graphs of the resultant calculations are shown. We got fairly good agreement between the CAMI method, geometric mean and a dose calibrator for the liver. We should point out one of the quirks of our CAMI method. We had to assume some finite amount of activity density in the body background, so the CAMI method did give a body background level of activity, which was totally false, but in the real world, that activity would be there and we would have to calculate it. The

activity attributed to the whole body effectively shows some estimate of noise level. Now, we repeated the calculation with overlapping organs. Here, we have pancreas and right kidney overlapping. You can see, we had better agreement with the dose calibrator

than did the geometric mean for the pancreas. The pancreas calculation for the geometric mean was off by approximately 10 to 15%. We had fairly good agreement with the kidney, where the geometric mean method could not be attempted due to overlap. Finally here are some overall comparisons for the crude phantom between CAMI results and the geometric mean. There's a historical precedent for doing quantitative geometric mean and comparing with phantoms. Van Rensburg, et al published a comparison in 1988, and they gave similar results using the same radionuclide we were using, indium-111.

Indium-111 is the radionuclide of interest for radioimmunotherapy, typically, because yttrium-90 is usually the beta emitter of choice and these two have about the same chemistry. Regarding the various planar uptake methods, we think our method, CAMI is superior to GM. It has an absolute accuracy of somewhere between 10 and 15%. However in the primitive stage, where we had to manually fuse images; it might require four to six hours of a physicist's time to try to perform this CAMI calculation. This has caused some political problems in our division. The physicists didn't like to do it and found it very difficult. The geometric mean, however, is more uncertain and requires these problematic conjugate views. The GM method was much faster, if you can get those views. So I point out here that CAMI is today with, say, separate CT and nuclear

imaging, rather difficult to implement. But in the future, we feel that CAMI may be the method of choice, because with a hybrid device the fusion time will not be appreciable. Now, I want to discuss a patient specific method to try to estimate radiation doses in RIT and other internal emitter patients. We call this system the Radionuclide Treatment Dosimetry System, RTDS. It has been published in Journal of Nuclear Medicine and I should mention that we have a patent on this system. In fact, at medical physics meetings, people don't talk much about patents, but we did get a patent on RTDS. We originally tried to get it through UCLA, but they were not interested. However, City of Hope was, so we went ahead and got one. We're trying to get commercial support for the RTDS system but have not yet been successful. The RTDS structure is shown in this slide.

We have the patient demographics, the image data from nuclear and CT. We have, finally, patient sample data, including blood samples. As outputs, we generate a variety of things, including these fusion images. We include quantitative activity calculations and over here, we have dose modules, which can use either the MIRDOSE 3 program, which is built in or our own voxel source kernel method, which we developed. And we do have modeling built in, as well. We use either ADAPT, which is a USC program, or the one from University of Washington, Saam Mark II. Finally there is a set of radiation absorbed doses, specific to the patient. And here's our image processing module for CT. This is where the regions of interest are drawn. As in the phantom examples shown above, all regions of interest, all organs are defined by CT. We're now projecting the nuclear

images onto the CT, after the scaling and translation and you can see the regions of interest are being drawn from the CT onto the nuclear images. And the user simply picks a set of points, using the CAMI method, to try to reconstruct the activity within those tissues. And because you have the CT data and actual projections, if you pass a ray anywhere through the patient, you know, literally, what tissues that ray is going through.

We added a voxel source kernel to RTDS. We call this MAVSK, for Monte Carlo Assisted Voxel Source Kernel. We didn't want to do a true Monte Carlo. What we wanted to do instead, was take a small volume, which is listed here and, simply, follow the beta rays from that volume to do the dose estimate for yttrium-90. Yttrium-90 is probably the standard radionuclide in radioimmunotherapy and it has a range of about 1.1

cm in soft tissue. Therefore, we simply, did the Monte Carlo, but only to adjacent voxels, out to an appropriate distance and we published these values. And here are the resultant dose volume histograms for a patient for a pair of kidneys and you can see that some of the differences here: this is the scatter diagram of the actual histogram. The average values are shown for Y-90 Zevalin, which is used to treat non-Hodgkin's lymphoma. We compare it here with anti CEA antibody against solid tumors. Typically, as I said at the beginning, to treat colorectal cancer. Here is our antibody T84.66. Shown are the results of Dr. Jeff Wong's protocols. Here are some numbers from the IDEC literature for liver dose, splenic dose and red marrow dose. You can compare those to some of our cT84.66 absorbed doses that we've tabulated and published in the tumor, in the liver and in the red

marrow. The dose estimates are comparable. That's really my point here, that the two Y-90 RIT therapies led to about the same numerical value. You probably know that the Zevalin regimen has been very successful in treating non-Hodgkin's lymphoma. The reason being that, at this kind of dose level, 25 centigray per millicurie of Y-90 antibody, you can achieve therapeutic results with a lymphoma. But at 25 centigray per millicurie, you cannot achieve therapeutic results with a solid tumor. So, that is why solid tumor RIT remains experimental and difficult, whereas non-Hodgkin's lymphoma therapy appears to be quite successful. In addition, there's another commercial agent (Bexxar) that's available to treat NHL. Zevalin is based on Y-90 Bexxar is labeled with I-131. Radiation of solid tumors is possible, but, I would say, is much more difficult with

radioimmunotherapy. Now, the limiting toxicity in most of these cases, is the marrow, itself. That's another advantage that the lymphoma patient presents. Often, you don't worry too much about their marrow condition or dose, but in the case of, say, a colorectal cancer patient, we do have to consider that. Now back to where I started in the overall scheme; errors in the absorbed dose estimates. The A value, we think, is uncertain to about 30%, using a geometric mean. If you use our method, the CAMI, we can pull those errors down to around 10 to 15%. Integration of A to form *Atilda* is uncertain to, about plus or minus 10%, due to the modeling uncertainties. This includes both interpolation and extrapolation. *S*, however, is the dominant error we've seen because of patient organ sizes. Factors of two and three-fold easily occur in *S* and this is going to be your major

difficulty in trying to do a patient specific absorbed dose estimate. Here are some references. By the way, if you want any of these slides, or wish to communicate just contact me. I have an e-mail. It's just lwilliams@coh.org. Here's Steve Thomas' original paper on the geometric mean. And here is Jeff Siegel's report for the bone marrow dose estimates. Notice Mike Stabin's MIRDose 3. Included are CAMI and MAVSK references and, of course, our committee. I'm the chairman of the committee in AAPM on radionuclide dose estimates and we had a Primert out on that topic. Finally, the MIRD

committee has published on the methods of quantitation of activity, recently in the "Journal of Nuclear Medicine" . Again, Jeff Siegel was the lead author. Future directions in absorbed dose estimation are difficult to predict. We imagine both types of estimates

will have to be made; either patient or phantom. The phantom will change, probably into more human-appearing forms, by use of CT data sets and the first kind of correction, the correction to *Atilda* will continue to be made. This is ratio of m to total body mass correction. We predict that more Monte Carlo will be done using voxel or point source kernels, instead of actual S matrices. In that event, the correction to the S will not have to be made in Type II computations. Dose volume histograms will become common, just as they are in external beam. Importantly the dose volume histogram will point out something about the dose to parts of the target tissue. In other words we're becoming quite concerned about absorbed dose to parts of the kidney, liver or tumor. Such results can come out of the dose volume histogram, through a method like CAMI, for instance.

And a third type of estimate will be for animals, only. Something you don't often see today, but will be done in the future because we'll be doing some calculations on animal results following animal therapies. Here's my contact information and e-mail number. If you're interested in dose estimation or activity quantification, please contact me and we'll be happy to get you involved in the work of the AAPM test group. Thank you very much.