number of weight metrics. Then whichever one fit best I would use and then proceed to looking at what an age effect, in the absence of a weight effect, would be to see if I can describe one, and if so, what it is. That's my intent here.

The reason why I did this in this way is to try and not have the effect of age confounded by weight and the only weight metric I had, which I couldn't pull out in any other way, was kilograms.

The path, in addition to what I've just indicated for the models that we would consider -- and this is speculative. It will be driven by data, but this is sort of how I see it going and thought it would be useful to share.

First, we would consider adding exponentials if the data supported it. You've seen a two-exponential fit, and as Dr. Sheiner said, it's effectively both descriptions of weight. But the idea is if we should discover that at early ages there appears to be a unique phase of the curves -- it doesn't occur at later ages -- and is not as simple as a single exponential fit, then we would consider adding additional exponentials, a structural model, if you would, of more than one term.

One thing also I haven't shown here is an offset for the age effect. That is, you might not expect

that the age effect would be 0 at birth. Whatever processes are occurring, maturation may begin -- almost certainly did begin -- in utero. So you might want to add a term that would give an offset for the age effect. Again, this is speculative, but not based upon a real data set that I'm currently evaluating.

Finally, we would begin to look at more physiologic covariates. Can you enter covariates such as the percent excreted unchanged, the Km for a given enzyme, the Km ratios across the enzymes for which metabolism of the drug is responsible?

Finally, the approach I've shown is very empirical. Whether or not it will be successful is a question, and if it were unsuccessful, the next step would be to consider models which are more mechanistic.

The first mechanistic model perhaps to be considered would be one that is less than a full-blown PD/PK model but which does incorporate what I'm calling process constants, such as GFR, such as Km and the percent non-renally eliminated.

Finally, if even such mechanistic models were not successful, you might have to go into more of a full-blown physiologically based pharmacokinetic model. The difficulty with that is clear. Usually it's difficult to obtain data to support such a physiology-based model.

Would anyone like to tell me if they think this is reasonable?

DR. VENITZ: Thank you, Gene.

DR. DERENDORF: I have a question for clarification. Are these all lumped together, hepatically cleared drugs, renally cleared drugs, high extraction, low extraction, no difference?

DR. WILLIAMS: Yes. The initial cut would be the raw data is age versus clearance independent of the physiologic mechanism by which drug is excreted or eliminated.

DR. DERENDORF: Well, then I would not agree with the first question that it's logical because I would expect there to be major differences depending on the mechanism of clearance. Obviously, for a renally cleared drug, the enzymes don't matter, and for high extraction drugs, the intrinsic clearance would matter, and so on. So I think to break it down into several subgroups would make a lot of sense.

DR. WILLIAMS: You might expect that as the physiology differs, so will the relationship between clearance and age. But I guess it's dependent upon a few elements. One is to what extent is each one of those different elements not a function of allometry. In other words, if the enzyme maturation and, say, GFR are both

linear functions of weight, then you might expect that this approach would work.

Now, the clear difficulty is at early ages, there's a whole literature, which many of the members of this committee have helped develop, that speaks to the fact that that is sometimes or perhaps oftentimes not the case. So the question is perhaps, how much data do I have that can address that? Specifically, do I have a lot of data at early ages or how much does it vary?

Would you agree that --

DR. DERENDORF: I'm not an expert, but if I recall correctly, glomerular filtration rate in a 2-year-old is almost like an adult. Right? There's no difference. Whereas, clearly the number shows that for a 2-year-old the clearance per body weight is almost twice as high. So there are differences depending on the route of elimination, clearly, because you wouldn't expect a difference for a renally cleared drug.

DR. LEE: Can I add to that? What we're planning to do is look at different drug classes. For example, we will look at a drug class which is purely renally cleared and then try to see what's the relationship between clearance and age. Then we will look at a bunch of drugs, for example, 3A4, purely 3A4, and then see how it's going to change in our clearance versus age. So that will

probably address your question. And we know from the literature that the maturation of different enzymes are very different. I mean, 2D6 may be fast and 3A4 may be slower. This is what we planned. We want to look at different drug classes and build a model perhaps about one drug class at a time, and then finally we have an individual model. Then we will look at a drug that has a combined pathway, maybe a drug with 20 percent 3A4, 40 percent 2D6, and see if the model can actually predict the age effect.

DR. SADEE: Do you consider changes between males and females and the various sexual developments and so on? If you talk about maturation of enzymes, which sounds a little fuzzy of a term, but males and females are probably very different, but that may also depend on the age. I don't know.

DR. KEARNS: Actually with respect to drug metabolism, they're not very different at all. There are a few examples of substrates for P450s that during adolescence differ a bit and it probably has to do with the things that make for differences in linear growth more than sexual maturation. But for the most part, it's pretty boring, boys and girls, before puberty.

DR. SHEINER: If you go back to that picture, the one with the graph that we had the problem with, if I

just connected the dots, I'd have a function defined by line segments of that y axis value, the relative clearance, versus age. And everybody would be completely clear that I had totally explained all the data with my function, and consequently there's no way to partition out the effect of age from the effect of something else in your case that is a function of age, which is weight. So the fact that you could partition out, means you made some kind of very powerful assumption that allowed you to take this function of the x axis and see it as a separate contributor to this curve which is practically connecting the dots. So that's the point I'm making.

It's nice that you started with this one because here we all know there's only one variable age. We don't know anything about weight, not the real weight. So you've got perfect what's called multi-colinearity or you've got a perfect problem that the one substitutes for the other. The value from your table can be translated back exactly into the ages and the other way around.

So this is what's called, you know, an ill-posed inverse problem or an unidentifiable model. It depends on what field you're in. And the only way you can get something out of those -- and I'm going to get to the key question here in a minute.

But the only way you can get something out of

those, if you're trying to learn about these different effects, is you have to make some very powerful assumptions, some assumption that allows you to separate. Here, the assumption you made is the exponentiality.

So I could say, if I didn't know anything about this, if you have a solid basis in physics for that exponential equation, something at the level of theory that's as powerful as physics, that says each of these has to influence and the only way it can influence the spread of these points is through a rising exponential, then I'll believe that what you sort out of the two effects is right because that's the key piece of information that you've added that you told me essentially everybody knows this is true. But if you say, well, I just -- the exponential because it kind of went up and then it went over, you know, then there's no reason to believe you've got it sorted out right now.

I don't want to criticize this picture because you were clear this was an example, but you're going to have a similar problem with the real data. That is to say, there's going to be very high correlation between age and weight. So you got an almost ill-posed problem. You got an almost unidentifiable model.

So if your goal is to sort out the independent effects of things we can measure like size -- even that's a

surrogate for something else -- and what we will all agree is an unknown age-related something called maturation or something like that that we don't measure when we measure renal function, that we don't measure when we measure these other things, if your idea is to sort that out and then look at the shape of that thing, we're going to have a lot of trouble believing it even when you're not as bad a situation as this because of that high colinearity.

So I told you I'd get to the question. So my question is, what's the question? What do you really want to learn? If you want a predictive equation, you could do anything. I'm not being facetious. If you want a predictive equation and you're not going to interfere with the system, you're not going to deliberately change people's ages or weights or whatever, you can just let it come as it falls, and you find some general predictive equation for clearance of all drugs as a function of a few easily measurable things, that would be completely valid as long as you don't go in and mess up the system, even though it doesn't give you an understanding necessarily of what the causes are.

But on the other hand, if you say no, I want a predictive equation for a whole new drug, then you're interfering because you're not sampling from the same world.

So I guess my question is, what's your question?

DR. WILLIAMS: First of all, I would say if it does turn out as you're saying and you do have this high colinearity and this difficulty, it seems to me that would be good news because it means that you have the ability to describe the relationship between the ratio and the age as only a function of weight. If the data is well described by small or perhaps a single parameter, that would be fantastic.

But to get to your later question, perhaps you can educate me some more. It's not so clear to me if you had the situation that you're defining where you did have this high amount of colinearity and you then parsed out your drugs as a function of all of the things that you can look at, metabolic route, percent renally eliminated unchanged, et cetera, and you found that you could not identify covariates which interfered with that relationship, then wouldn't it be legitimate to extend it to the new drug?

DR. SHEINER: That would certainly be an empirical basis on which you would guess that a new one would look just like the other ones because you had a whole bunch that all looked the same and you hadn't chosen them for that purpose. I agree it wouldn't be a mechanistic

basis. That's why I said sort of a whole new drug class. Somebody might say, sure, you know, you've been right 85 times out of 90 so far, but you've never looked at one like this before. So that's the problem. That's what I'm saying.

I agree with you, it's good news if they all look the same because it gives you more faith that the new one, even though we know it's a little bit different, will also look the same. But that's just counting how many times have I been right out of how many times I've tried.

So is that your goal?

DR. WILLIAMS: Yes, that would be the goal.

I'm new to this area, but from my read of the literature, I think it's unlikely that we would see that at young ages. Now, the question is the quality of my data. Do I have a lot of data at young ages? Because I would expect that that's where they will separate from a simple function of weight.

DR. JUSKO: Don't you at each age have data from many children where there's a distribution of weights at each age?

DR. WILLIAMS: Yes.

DR. JUSKO: So if you do have that, then you have the ability to discern the separate effects of age and weight. So I don't understand Lew's --

DR. WILLIAMS: Yes. Our data set will be an improvement of that. But if the colinearity is -- if they're very highly correlated --

DR. JUSKO: Certainly they're highly correlated, but there are factors in addition to age that control weight that you would be able to discern through this kind of analysis.

What do you select as the upper limit in age or weight to reach the maximum? Because for many physiological functions, the graph will look like this for a certain age range, but reach a maximum at about 18, and then as we all know, we steadily deteriorate until we reach some lower level.

(Laughter.)

DR. JUSKO: So a more insightful empirical function may be more of a U-shaped type of --

DR. WILLIAMS: I didn't grapple with that here obviously. What I did is I just fixed it to 1. But yes, it's a question. I guess what I would do is I would try and look at as great a wealth of adult data as I can to see if there is an age relationship, and if so, where's the maximum I suppose. But you're right. That's something that will have to be worked through.

DR. SHEINER: Bill, I think you're right except I'm not sure what you get out -- so if I've got different

ages and I've got a lot of weights at different ages, then it's quite true that if I want to say there is some sort of sum of these two effects that's operating, then if it were only weight, then I should be able to go across age and find it at the same weight. Everybody had the same clearance. And if I didn't, then I'd have to explain that by age. Is that sort of where you're -- yes.

DR. JUSKO: Age is likely to be the strongest determinant, but then we have to bring in genetics and diet and the rest as additional determinants of weight.

DR. SHEINER: Yes. I think Bill is completely right, that having independent variability in age and weight will help. It's just how much of that do you need to feel comfortable about what you get out. And strange things like Simpson's paradox can happen where, as you move from age to age, the regression within each age versus weight could be actually opposite the direction that it was when you do the whole thing. These sorts of things happen. So it's just a matter of what the data contain.

I guess one of the things that bothers me is that with kids it's going to be a very, very strong relationship; whereas, with adults we expect a small age effect -- the deterioration that Bill is talking about -- and a large weight effect.

But again, for predictive purposes, it doesn't

make any difference. If you're not going to do anything different the next time, then your data has got all the information. I suppose what you're saying is an interesting result here would be if there was a relatively simple equation that predicted most of what you see across lots of drugs.

DR. WILLIAMS: Yes. I anticipated that I would get the reaction that I believe Hartmut is expressing, which is this is sort of naivete to expect that it would go that way and that it's probably very important to incorporate physiologic covariates. But one of the things that drove me to think about it in this way is it made sense to operate on parsimony and start simple and see what the data set would support.

DR. DERENDORF: But you want to use anything that you already know. So if you know that you have gentamicin, you can use glomerular filtration rate as a pretty good estimate. So if you know what the physiological value is for that, you should use that and not ignore it.

DR. KEARNS: Just two comments, one to speak in support of doing this in the context of getting you in the ball park because I think it clearly has the ability to do that. You're right in that for very young infants and perhaps even up to 6 or 8 months of age, it's not an issue

of weight for much of the maturation. Probably post-conceptional age falls out as a way to best predict these things because you do come to the field with a little bit of activity depending upon when you come to the field. That's clear.

But from a practical standpoint, I was sharing at the break our experiences in doing a study with a drug that was 100 percent renally cleared. This drug was studied under that list of 72 who've been given exclusivity, and they got their 6 months of extended marketing exclusivity and had a big party and everyone was happy.

But in going back in time and looking at those studies, we were able to simulate the results of the trial before we enrolled one patient, as you might believe you could do. We made an argument that we thought was reasonably passionate, but perhaps not sufficiently so, that the trial that was done needed only to contain children in the first 3 months of life, that everything else could be predicted. We were sent away believing that, indeed, some revelation would occur. We could use the knowledge that we had to simplify and improve and streamline the process only to find out that we were wrong, that ultimately we were expected to fill in all the pieces of the puzzle of the barnyard despite knowing that it

indeed contained animals of identity that was known. At the end of it all, there was a lot of time, effort, and money spent for no good reason. No good reason.

So for all the pimples on an approach like this mathematically, this has the ability to improve the design of pediatric studies if, within the halls of this wonderful agency, it would just be used to do so.

DR. WILLIAMS: I guess, Larry, that helps justify my detail.

(Laughter.)

DR. LESKO: I was just going to comment on what is the question. Actually Greg's comments are discouraging to what I was going to say.

(Laughter.)

DR. LESKO: Nevertheless, when Lewis asked the question about what is the question, it would seem what we want to know is not necessarily the empirical relationship we're talking about, but rather the more mechanistic one where you can look at a drug and it would be a whole new drug, but look at it not as a whole new drug in a therapeutic class per se but a whole new drug with certain attributes of processes of elimination, cytochrome enzymes, what we know about Bmax and Km's of those enzymes, and based on that information and based upon the analysis of a pediatric database, know where there are breakpoints in the

age groups and perhaps do a limited study that might bracket age groups, and then you can fill in the blanks in between based on some model to say I know this from these relationships between routes of elimination and age. I might do some limited studies, but then cover age groups I haven't actually studied in terms of extrapolating that information. It's kind of what you were saying in terms of knowing something in the first 3 months and then using that to predict the rest of the puzzle, but it just struck me that if there's a difficulty in doing that with a drug renally excreted, the difficulty becomes magnitudes more for a drug that is out the enzyme system.

But nevertheless, that's our noble mission here to try to look at the database. Maybe we just need more examples of this using data we already have as opposed to something new. I don't know, but I think where we want to go eventually is to take attributes of a drug and be able to make better predictions and maybe even excuse pediatric studies from being conducted if we're confident enough that we can predict clearance in those age groups.

DR. KEARNS: And the other thing -- and what I'm about to say is not mine. I really owe this to Steve Spielberg who began preaching this some time ago -- is that if you can define a breakpoint, if they really exist, then it's possible to design your trial in such a way to enrich

it so that you can get the most information out of the least numbers of subjects studied. That's okay because in the process, we don't compromise the end game result, and we also don't put children in trials just for the sake of confirmatory purpose.

Parents always want to know, especially for a nontherapeutic trial, they say, explain to me again why this is important. As an investigator, you really have to be able to tell them that. If they're convinced, you have a child on your study and you have good data. If they're not convinced, maybe you shouldn't be either.

DR. KARLSSON: Maybe in addition to what you presented here, your analysis, if you looked at it, could also settle the debate that was before the break regarding what about variability in elimination capacity with age. Does it actually decrease? Does it increase? Is that dependent on the elimination pathway, et cetera?

DR. WILLIAMS: Yes.

DR. FLOCKHART: I guess I'm back to what's the question. It seems to me, Larry, that you gave a different answer to the question.

Greg, I think if the playing field is so big and has very significant error within it, I've got to ask the question, what's the point of asking where it is on the playing field. I can't tell by looking at the playing

field whether the ball is in the goal or is at the centerpoint. If it's a very vague thing from doing this kind of activity before, I'm not sure knowing it's on the playing field is a valuable exercise.

On the other hand, I guess we're all biased as scientists towards believing that a more mechanistic, physiologically based approach would work better. But I have to say that that real hypothesis even in adults has not been really hard core tested. We don't really know that.

So this becomes, therefore, a testable hypothesis. Each time you add a new drug, you're testing the idea, and if it turns out even between the ages of 1 and 16 that things fit, that would be a tremendously valuable thing to know that we kind of got gratis, we got free as we went along.

The error is the key, though, because it's very variable.

DR. KARLSSON: Are these 72 studies intravenous studies, or are you going to mix IV with oral studies? If so, how do you handle bioavailability issues?

DR. WILLIAMS: Until I look at the actual data, what drugs are available and pick them, I won't know that answer. In other words, how do I choose among the 72? Perhaps the easiest way to start would be to look at IV

drugs, but on the other hand, perhaps you would have a willingness to accept drugs whose metabolic route is well defined and is thought to be largely one process. So the 72 will be a mix, but which ones I choose to look at first and how I develop it is something that we have to consider.

DR. CAPPARELLI: I would just like to echo what Mats was referring to, that the oral component is going to be huge, especially in the younger age groups, and everything that's been said before about some of the formulation issues. So I think that it's going to take careful selection. I'm excited to see this direction, and I lean on the mechanistic fence of things, starting off with what we know and building on it. I think renally eliminated drugs make a lot of sense from the standpoint of what we know about renal function, how we can measure it or how we can, at least, estimate it in different pediatric populations and relate it.

But you start getting into drugs where there are bioavailability issues in adults, it's going to go all over the map, and you're going to have the additional confounding issue if you've got active transport or gut metabolism. And those may not parallel what's going on in the liver.

So, again, trying to simplify it and at least starting it at points that I think you'll have buy-in and

belief in the model I think is very important.

DR. SHEINER: How variable will be the way in which the clearance was determined in the individual children across these studies?

DR. WILLIAMS: I guess fundamentally you can separate into sparse and dense, and we're likely to see both of those. But beyond that, how studies are conducted, sampling times, populations, numbers, probably a wide range.

DR. DERENDORF: Just to clarify, because I was under the assumption from the beginning it was only IV data. Now you're saying that there was some oral data. So they were the ratios of the oral clearances between kids and adults that you showed in that very first table?

DR. WILLIAMS: My recollection of -- oh, this is perhaps unfortuitous. This is slide 4, not data IV.

(Laughter.)

DR. WILLIAMS: So the answer to the question is yes. Certainly some of these or perhaps all of them are. I did not separate this out into oral versus IV.

Now, when we actually perform this on the FDA database, of course, we will have the luxury of choosing the order in which we consider the drugs. Obviously, there's an advantage, especially given Dr. Capparelli's comments, of beginning with the simplest case which would

be IV drugs.

DR. DERENDORF: The probability of getting anything useful out of it then is very low in my opinion. I think you have too many things that are lumped together here.

I'm amazed at the ratios, that they come out to be so close to 1 in that figure there. If oral bioavailability is included there, it's almost hard to believe.

DR. LESKO: But in our own data set, we can control for that. We can select drugs, as we said, taking care of those differences. We would combine drugs in different ways that take those similarities into account, whether they're IV or oral, and not mix them. He's working with a published data set, but I think your question and issue would be resolved if we picked from the data set appropriately that we have within the FDA. Isn't that right? Am I misunderstanding?

DR. DERENDORF: If you stick to high bioavailability drugs where there is not a big difference and where we don't expect a big difference, but if you have high extraction drugs in the group, you would really get numbers all over the place.

DR. LESKO: But I think one of the plans would be to look at different ways of categorizing the drugs that

we're looking at to see if that makes a difference or not.

DR. DERENDORF: Well, the question changes completely. Initially it was a question of how do metabolism and clearance develop, and now we have included bioavailability. We have formulation issues. We have transporter issues. We have intestinal metabolism, I mean, a whole bunch of things that happen all lumped in one number. And I think the chance of filtering out anything that teaches us something is very, very slim. We'll get some kind of an average curve and we can fit a line through it, but what does it mean?

DR. KEARNS: But, Hartmut, if I told you that the data set that they had had over 300 patients intensively studied with midazolam, half of them on oral, half on IV, from ages of 6 months to 16 years, all of a sudden it becomes a little more interesting. And that's in their data set. So there is some gold in there to be mined. But your point is well taken in that it's not something to be done in a reckless way not paying attention to all the assumptions and limitations.

DR. DERENDORF: Again, I think where I'm coming from is to utilize anything that we already know, and the physiological information about blood flow, for example, is something that doesn't vary that much. That should be included in the data analysis. It should focus on

intrinsic clearance as the number to correlate with. I think then it makes much more sense.

Then you have a chance that you can identify maturation rates for the various enzymatic pathways that you then can use to extrapolate for new compounds. Once you know that for a new compound which is the breakdown of different pathways, you already know how the rate of maturation occurs and you can make good predictions without any study.

DR. WILLIAMS: If you're right -- and I initially tended to think that way too, but like I said, this is new to me -- then we will get there because what will happen is the simple models will fail.

DR. LESKO: Gene, do you know the size of these studies, just speaking about the small to large of the pediatric studies in the database? What's the typical n in these studies in terms of getting an estimate of precision of the pharmacokinetic measurements?

DR. WILLIAMS: I really don't.

DR. LESKO: Greg, what do you do? Or, Ed, what's the typical size of a PK study in a pediatric population in your experience in terms of a single age group or all the groups?

DR. CAPPARELLI: When you say all the age groups, that incorporates a little bit of gray as you get

further on down and looking at degree of maturation at birth. Some of those studies get to be very large.

Typically most of the stuff that one sees may not be optimal, but rarely do you see anything less than 50. Most of it is in the 100 to 200 range if it's incorporated into the safety trial.

But the driving force isn't often the optimal PK component. It's really the other aspects of the study. So again, the precision issue really comes near the cut-points which I think was brought up earlier. There is often a lack of information where the action is, unfortunately.

So having a large data set that has three patients under the age of 2, and you get this spread that's here, here, and here, and then trying to make some sense that no, nothing is going on down there or there's something very dramatic going on down there really is based on the belief of who's looking at the graph rather than any real aspect of the data.

DR. KEARNS: Larry, for the phase II things done under most of the written requests that I've seen, it's about 24 subjects to 36.

Some of it's -- I need to pick my words right because we're on tape, but it's interesting some of the ways the designs are done. For instance, if we had a drug

whose metabolism we knew or believed changed greatly in the first 3 months of life, you might see a written request that asks the sponsor to include 24 infants from the age of birth to a year and that the infants should be equally distributed across the age spectrum, so there should be at least 3 infants or 4 infants in the first month of life. And oh, by the way, you can study babies all the way down to 800 grams. Now, the chance of coming out of that at the end of the day with a revelation of therapeutic utility is slim to none.

But unless my experience is somewhat not representative, this is happening every day under the context of negotiating a written request for drugs studied under the Best Pharmaceuticals for Children's Act, which is why I believe that until we put some of this bit of science and ingenuity into the action plan, we're really not serving the intent of the people who put that act together or, even worse really, the children as we try to make a fact out of fancy many times.

DR. VENITZ: Any other comments, questions, or further discussion?

DR. WILLIAMS: Are there data sources anyone here can recommend?

DR. VENITZ: Dr. Sheiner.

DR. SHEINER: At the risk of stupefying Mary,

are you going to go back to the original data, the measurements of concentrations versus time, or were you thinking to use those clearances?

DR. WILLIAMS: The notion is that we would just go back to the clearances.

DR. SHEINER: Okay. And those clearances will be some, you know, from 15 samples after a single dose and a nice area under the curve.

DR. WILLIAMS: Right. Some of them would probably come from population post hoc and some would come from dense.

DR. SHEINER: Well, you want to think about how you mix those because those posterior Bayes' estimates are funny creatures. They're centrally biased. So they do odd things to regressions when you use them either as the explanatory variable or as the variable to be explained. So you need to think about that.

DR. WILLIAMS: Yes. It seems to me it gets pretty complicated if you don't do that, but would you like to propose an alternative?

DR. SHEINER: Well, if you don't do that, it doesn't get complicated. That complication goes away. If you use the original data, the complication I was just talking about goes away because you're not summarizing the data with a strange estimate. But it does mean that you

have lot longer run times and a lot more modeling to set up and all those nasty things.

I don't know. I would almost be tempted to say, since you're going to use them in subsequent regression and you have lots of data, that you should use unbiased estimates of each individual's clearance which you would get essentially by taking the prior variant system infinity or fitting the trapezoidal rule with three points. I mean, that's bizarre to talk about. But I don't know. I have to think about it. It's not obvious.

DR. WILLIAMS: Perhaps we can discuss this further and I can come to the committee as a whole or perhaps even yourself showing you the actual characteristics of the data set.

DR. VENITZ: With that, I think we're ready to conclude.

DR. WILLIAMS: Actually if I could make a --

DR. VENITZ: You conclude.

(Laughter.)

DR. WILLIAMS: First, a number of the committee members are very active in this area. If you would like to share your data, we would certainly welcome it. As I said, some limitations of our data is we often don't see very young ages and we often don't see probe substrates. So if you'd like to contribute, we sure would welcome that.

Finally, should the very empirical models not be successful, the form that you would use not as far as a full physiologic-based model, but incorporating some of these physiologic covariates into the description of age versus clearance is not entirely clear to us. We've worked on it a little bit, but we don't have any firm conclusions. If anyone would like to contribute here or perhaps even off line how they would see the form of those equations running, we'd be grateful.

DR. SHEINER: Just a quick question about that. Usually PBPK to me means the various compartments connected in various ways and blood flow from the gut going to the liver and things like that. Is there a large collection of physiologic models of clearance?

DR. WILLIAMS: I'm not sure I understand.

DR. SHEINER: Well, I mean GFR and renal clearance. They seem to be linked, and usually people do it linearly. I haven't seen too many what I'd call physiologic models of clearance. That would be a thing where you'd have some model of the uptake mechanism and then the transport and the metabolism. That might be McHale-Smitton or something like that.

DR. WILLIAMS: Well, the ones I'm most familiar with sort of group all those sorts of things into a global parameter, intrinsic clearance.

DR. SHEINER: But you're asking for a model for the intrinsic clearance. Right? Or for the Q times clearance over Q plus clearance, or something like that. Because you're not asking for a model of the drug level.

DR. WILLIAMS: Right.

DR. SHEINER: That's what we usually think of when we say PBPK, models of how do concentrations relate to physiologic processes. But you already decided that you are looking at a physiologic process called clearance, and I'm not aware of an awful lot of physiologic models, except I guess everybody who thinks about it could come up with things they think would be more, let's say, reciprocally related and things that would be more directly related. But other than that, I think -- most of those models are empirical, and even in the middle of a population analysis, there's some little equation that says that clearance is a linear function with an intercept often, which doesn't make any sense, of weight, age, and some measure of renal function or of hepatic function.

DR. VENITZ: Sounds like a topic for another meeting.

DR. WILLIAMS: Thanks, everyone.

DR. VENITZ: Thank you, Gene, and thank you all for hanging in for today's agenda.

We are adjourning the meeting. We are

reconvening tomorrow at 8:30.

(Whereupon, at 4:10 p.m., the subcommittee was recessed, to reconvene at 8:30 a.m., Wednesday, April 23, 2003.)

04/22/03

- B -

- D -

- E -

- F -

- G -

- H -

- I -

- J -

- K -

- L -

- M -

- S -

- T -

- U -

- V -