1 helium gas and rubidium in such a fashion that the helium
2 gas can be promoted to be very magnetically active, 100,000
3 times stronger signal than you might get otherwise.
4 This, I will show you at the end is where we are
5 today in small animals, at 50 millisecond temporal
6 resolution, 100 micron spatial resolution.
7 [Slide.]
8 Much of that has been, as I say, due to Larry's
9 development of ventilatory apparatus here. This is a little
10 valve that lets us give the animal a pulse of gas, control
11 the breathing amplitude, the breathing duration, how long
12 the animal holds its breath, how long the animal inhales,
13 how long the animal exhales.
14 We can mix helium, oxygen, nitrogen, keep the
15 animal anesthetized for quite long periods of time.
16 [Slide.]
17 This is the polarizer. It was manufactured by a
18 little company in the Research Triangle called MITI.
19 Nicomed has recently, last July, bought the company, and it
20 is moving towards clinical trials.
21 [Slide.]
22 This is a guinea pig in which we have delayed the
23 acquisition for 100 milliseconds from the onset, and you can
24 see the gas going into the smaller airways, 300
25 milliseconds, it has gone a little bit further, and 500

1 milliseconds, it has gone even further.

2 Now, now we are talking about functional

3 microscopy.

4 [Slide.]

5 There are some physics, interesting physics. I

6 suspect very few of you in this room really care about the

7 interesting physics, but I am going to show it to you

8 anyway.

9 The gas moves around a lot, so to me, as a

10 physicist, that was a neat challenge. The typical diffusion

11 coefficient which imposes the spatial resolution limit on

12 much of what we do is 2.5 times 10^{-5} cm^2/second. That means

13 during the time it takes to encode the signal, water protons

14 might move this RMS distance. It might be 10, 15 microns.

15 But if the gas has 1 cm^2 diffusion coefficient, 1

16 cm_2 per second, it is going to move a lot further during the

17 encoding time, so we became very concerned about that early

18 on.

19 [Slide.]

20 I had the pleasure of some wonderful, really

21 extraordinarily bright graduate students. I am just hopeful

22 that they would never learn how little I know. This is work

23 that was done by Josette Chen, a recent one of our

24 graduates. David referred to the problems of spatial

25 encoding. This just shows the graphics of the radio

1 frequency pulses and the various gradients that are applied
2 to make an image.
3 Typically, an image is acquired at some time, an
4 echo time that is distant from the initial excitation. We
5 excite and then we acquire a signal someplace out there.
6 That signal is always decaying exponentially and our
7 acquisition time is TE and T2*, some metric that is a
8 physical property of the gas.
9 Typically, in a clinical system, the time from
10 here to the time for when you capture the signal is on the
11 order of 5 or 10 milliseconds, but with the hyperpolarized
12 gas, the signal will decay so terribly rapidly that you have
13 got to reduce that a lot.
14 Josette has been able to reduce that down to
15 something on the order of--well, Josette and one of my
16 engineers, Sally Gualt, have been able to reduce that down
17 to about 100 microseconds, and with that, we are able to
18 acquire images such as this.
19 This is an animal breathing the hyperpolarized
20 gas, a guinea pig, and we have modified, we put a little
21 gradient in here. This indicates that we are putting a
22 magnetic field on that varies across the animal for a few
23 milliseconds, about 3 or 4 milliseconds in here, and the two
24 images that will follow will show with this gradient and
25 without this gradient.

1 David alluded to the pulse sequence, the staining
2 properties. Basically, the spins are moving in a magnetic
3 field, and without that gradient, they stay, the signal
4 persists, but with that magnetic field gradient on, you see
5 that the large airways disappear, and they disappear because
6 the gas molecules can move so freely in the large airways,
7 but you note that the signal in the smaller airways
8 persists. This can be a very powerful metric for us in
9 measuring the microstructure of the airways.
10 [Slide.]
11 This is from Josette's recent work. This appeared
12 in our journal, the MR Journal, about a month ago. This
13 just shows that the diffusion coefficient in the large
14 airways is very, very large, and we were told by our
15 colleagues, actually a Nobel Laureate told us that we would
16 not be able to get below about 300 or 400 microns because of
17 the diffusion.
18 [Slide.]
19 What that Nobel Laureate missed was the fact that
20 the diffusion of the gas in free space is very high up here
21 in the large airways, but the Nobel Laureate was a
22 physicist, not a biologist, and he missed the fact that the
23 alveoli constrain the motion of the spins, so the gas signal
24 persists, and it is gas trapped in these areas here. This
25 is conventional histology.

at

1 This is in a control system. These are
2 conventional optical micrographs, of course, and this is in
3 an animal that has been treated to generate a model of
4 emphysema. This is an elastase-induced injury.
5 [Slide.]
6 So, we have begun working towards getting higher
7 resolution. This is a 100 micron by 100 micron by 400
8 micron slice with a hyperpolarized gas. This is a perfectly
9 matched proton image at the same level, this in a Fisher 344
10 rat, and you can see structural detail approaching that of
11 the alveoli.
12 [Slide.]
13 If you blow it up a little bit, you see these
14 defects down here in the treated animals, the spatial
15 resolution, the marker shows you the 1 millimeter scale, and
16 what we are really looking at is signal decay because the
17 compliance of the lung is no longer sufficient to adequately
18 ventilate that area.
19 [Slide.]
20 This is part of a 3-dimensional array. As Dave
21 has alluded, it is 512 by 512 by 128 slices. I can't show
22 you all of those slices on a slide. These are six
23 individual ones showing you the relatively high resolution.
24 [Slide.]
25 There is a perfectly matched proton set where we

at

1 can go back and do the cardiac imaging, as well, and then if
2 you want to look at it in some further detail, it is very
3 nearly isotropic, and this is an animal imaged at held
4 breath. The whole image acquisition took about 15 minutes,
5 but we could stroboscopically acquire the image always at
6 held breath.

7 We are paging from the front to the back, and we
8 are going through the individual 300 to 400 micron slices
9 here. You can see structural detail defining some of the
10 lobes of the airway, and now we have thrown this into a high
11 end silicon graphics workstation, sort of the same thing
12 they use for terminator, and we are creating a 3-dimensional
13 volume-rendered image, and you can see some structural
14 detail back here. The rat apparently does not have the
15 sublobular structure, yet we see it, and it is really a
16 consequence of the function that is defining that sublobular
17 structure back in here.

18 I will emphasize that this is a living, breathing
19 animal. One of my students now is working on taking this 3-
20 dimensional dataset and moving on to 4 dimensions. You will
21 see another 3-dimensional set in a minute where the third
22 dimension is time.

23 What we eventually would like to have is three
24 dimensions of space and one dimension of time, so one could
25 zoom around inside the animal as the animal is breathing, of

at

1 course, giving you a great deal of structural and functional
2 information.
3 This is work from another one of my students,
4 Magalee Villeone [phonetic], who is now at the University of
5 Leone. She was doing her Ph.D. with us, and these are six
6 images from a 16-slice dataset.
7 [Slide.]
8 The single slice is at a single level, and the
9 third dimension is time, so that now each of these things
10 represents a 50-millisecond time frame, and we have in-plane
11 resolution of 100 microns.
12 What is crucial here is we have the challenge, not
13 just of spatial resolution, but animals breathe a lot faster
14 than we do, their hearts beat, and all those sorts of
15 details.
16 I guess the word I heard earlier, I am an alpha
17 geek. We were talking about this earlier. I am an alpha
18 geek. I like making the toys, and it is really challenging
19 when you have both space and time that you have to wrestle
20 with.
21 [Slide.]
22 This is allowing us now to start make regional
23 functional measurements which we are doing in toxicology
24 studies, as well as in some physiology studies.
25 [Slide.]

at

1 I am going to close with some examples similar to
2 those that David had on MR histology. Histology is the
3 structure of tissue according to Webster. David has already
4 pointed out the unique benefits of MR histology over
5 conventional optical techniques, and he has shown this very
6 elegant example that he has executed, comparing the
7 sensitivity of MR to that of other stains.
8 [Slide.]
9 I will show you a few other examples. This is the
10 visible mouse. We have started a very extensive program now
11 for the molecular biologists where we are cataloging,
12 putting on line a web-based archive of all of the major
13 mouse models.
14 This is the mouse stained. Now we are not
15 requiring the endogenous stain. David has alluded to this.
16 We can talk about the biophysics of the water and how it is
17 tied up in the tissue, and how it enables us to distinguish
18 soft tissue contrast.
19 We are talking yet one other possibility. This
20 animal has been fixed, perfused with gadolinium in such a
21 fashion that we can diffentially fill the structures.
22 [Slide.]
23 These are six slices from 1,000 slices of the
24 entire mouse scanned isotropically at 100 micron spatial
25 resolution.

1 [Slide.]

2 Since the resolution is isotropic, we can slice
3 and dice, and pare and peel. If you will order today, I
4 will get you a free set of Genzing steak knives--I am not
5 trying to sell anything here, of course--and we can see
6 along any plane the same spatial resolution because we have
7 this isotropic image.

8 [Slide.]

9 It is non-destructive, so we can take the same
10 specimen. It is just fixed in formalin now. It is fixed in
11 formalin with a little bit of the special barbecue sauce we
12 make in the lab, but it is a formalin-fixed specimen.

13 We can scan it again. That initial dataset was
14 done at 2 tesla. This is now done by 50 micron. You can
15 see a great deal of structural detail in the kidneys and
16 vascular detail in the muscles back here, as well.

17 [Slide.]

18 And volume rendered.

19 [Slide.]

20 Now, we have taken an organ out and taken the
21 brain in this case and scanned it 40 by 40 microns, and we
22 can begin to see structural detail down to cellular layers.
23 I have cored this specimen and scanned just a 5-millimeter
24 cored specimen at 10 microns here on the left, and you can
25 begin to see structure at the same detail that one might

at

1 expect from an optical microscope.

2 [Slide.]

3 All of this is moving forward in what we are

4 calling web-based phenotyping. We believe there are a

5 number of markets. Our first market that we are looking at,

6 a toxicology market, we are looking at environmental impact

7 market, and we are looking at application for the molecular

8 biology community.

9 This is our whole visible mouse web site that we

10 are beginning to assemble, where we will have for each of

11 these animals, a full isotropic dataset of at least 100

12 microns resolution and quite probably up to 50 microns.

13 Our limit really isn't the scanning anymore, our

14 limit is what can the web deliver, and if we try to deliver

15 this whole dataset to a desktop, it swamps the desktop.

16 So, we believe that there will be some

17 opportunities here to create a better use of the web with

18 more interactive data. We can isolate individual organs.

19 In this case, the kidney has been scanned at 25 microns.

20 We can acquire these datasets now with a great

21 deal of spatial resolution, we think more than an adequate

22 degree of resolution. What David has suggested is our

23 problem is now getting the information dispersed and to the

24 broader community, and that is our next challenge.

25 With that, I will stop, I hope almost on time.

1 Thank you.

2 DR. DOULL: Thank you.

3 I think we should start off by thanking all of our

4 speakers. You have done an incredibly great job of bringing

5 us up to date in an area that will be fundamental to what

6 this committee does and what we plan.

7 **Subcommittee Discussion**

8 DR. DOULL: Dr. Johnson, you make me feel old

9 somehow. I recall a meeting a long time ago when Bill

10 Waddell, who was a toxicology expert in radioautography, and

11 I forget where the meeting was at, but there was a big

12 celebration because Bill was able to get resolution of

13 radioautography down to the silver crystal business and how

14 great that was at the time.

15 In your system, you amplified some of your scans.

16 What happens, does that limit your resolution?

17 DR. JOHNSON: The amplification can be done. You

18 can talk about amplification several ways. The most recent

19 development which I found amusing, to say the least, that

20 whole mouse that you saw there, we fix perfused him truly

21 with 15 or 20 cents worth of chemistry, and the

22 amplification of signal that we got, which then translates

23 to amplification of spatial resolution or shortening of

24 time, however you want to play it, was about 20- to 50-fold,

25 20 to 50X.

1 Now, you can put this in context with the rest of
2 the technical developments that have been underway in MR for
3 the last 15, 20 years. The major way to get higher spatial
4 resolution, to get more signal and then get higher spatial
5 resolution in MR has been the use of stronger and stronger
6 magnets.

7 The clinical machine started out at 0.15 tesla,
8 they stabilized at 1.5 tesla. There are a dozen or so sites
9 in the U.S. now scanning people with 4 tesla systems.

10 As you go from a 1.5 tesla to a 4 tesla magnet,
11 the dollar figure goes up by about a million dollars, so you
12 are investing about a million dollars. We got the same
13 signal gain, we got, oh, my goodness, we got 15 times more
14 signal gain with a trick of our barbecue sauce with
15 literally 15 or 20 cents worth of chemistry.

16 So, just like David has got all the latitude in
17 the world. He can take a specimen and slice it, and stain
18 it with all sorts of histochemicals. We said maybe we could
19 do that with MR chemicals, as well.

20 So, the chemistry trick is the trick, and it is a
21 pretty useful one. It is going to bring us into a real
22 application of these technologies, not in a year, but now,
23 today, we are doing several neurotox studies with David, and
24 we will make this accessible over the web within the next
25 six months. It will be routine.

1 DR. MacGREGOR: Can you address the general issue
2 of resolution in normal formalin-fixed tissue? I think one
3 of the suggestions David made was that it might be fruitful
4 to think about going to archived tissues and serving the
5 ability of this technology to see previously characterized
6 lesions.
7 DR. JOHNSON: Yes, it is quite possible. We are
8 doing studies right now with formalin-fixed specimens. We
9 have published a number of things with specimens that have
10 been in formalin for 15, 20 years. One of my students a
11 couple of years ago did a study of the change in the MR
12 properties, the stains, if you will, in cardiac tissues,
13 looking at old infarcts versus scar tissues.
14 It is entirely possible to do. We are doing it
15 routinely. There are some tradeoffs in time and spatial
16 resolution, but we can get on the order of 30 or 40 microns
17 with a 12-hour scan. Twelve hours is too long.
18 There are two technologies that will drop that by
19 a factor of 4 to 5. One is using better RF receivers. We
20 are collaborating with Dupont right now and using high
21 temperature superconductors, and that we have demonstrated
22 gives us a 5X improvement in signal to noise.
23 Then, there is the very real possibility of
24 acquiring five or six specimens simultaneously, you can scan
25 five specimens at the same time. It's an engineering

1 problem. It is not really that overwhelming an engineering
2 problem, it's mostly dollars right now.
3 So, we will, we are able to do formalin-fixed
4 specimens from previous studies. We have a collaboration
5 with the Armed Forces Institute of Pathology, looking at
6 some of their specimens, as well.
7 DR. MacGREGOR: But you can enhance the resolution
8 by adding gadolinium after the fixation in some way, or you
9 haven't played with it?
10 DR. JOHNSON: Ten years ago, 15 years ago I made
11 the mistake of estimating what the spatial resolution limit
12 was going to be along with some of my colleagues, and the
13 spatial resolution limit 10 years ago, it was fundamentally
14 going to be limited at a millimeter by a millimeter by a
15 millimeter.
16 So, I don't say things can't be done. It is a
17 matter of the technology of histologic preparation, and one
18 could, for example, take these specimens and apply what
19 probably a chemist knows right now, says, oh, yeah, that's
20 easy. If I want to get gadolinium into that tissue, I just
21 do an isotonic solution of such and such.
22 I think it is quite possible. Do I know how to do
23 it? No, but I think it is quite possible that we can take
24 previously fixed specimens and alter their contrast and
25 amplify the signal using gadolinium or some other relaxation

1 agent. I just don't know how to do that yet, but I am not
2 dead yet. I have got a lot of things to work on. That is
3 another good one.

4 DR. REYNOLDS: Maybe referring to my previous
5 question, and questioning the application of the microscopy
6 component of this, not just imaging. It is hard for me to
7 understand what a 4 tesla magnet would equate to in the
8 human setting in terms of resolution.

9 Secondly, are there examples where the preclinical
10 microscopy has built a bridge to, or served to extend our
11 ability to measure these kinds of endpoints in humans?

12 DR. JOHNSON: Yes. The 4 tesla system--let me
13 address your first question-- how does the field strength
14 address the resolution issue. Basically, the resolution
15 does not go up with the magnetic field. The resolution is
16 really driven by some other details of the gradient.

17 The reason people go to higher and higher magnetic
18 field is as you crank the resolution down, the signal gets
19 weaker. If you have a pixel of oxyl, which is a million
20 times smaller than one in a clinical setting, the signal you
21 get from it is a million times weaker.

22 So, you have to do everything you can to amplify
23 that signal, and that is why people have gone to 4 tesla.
24 At 4 tesla, the signal strength is about--well, it's almost
25 linear, so it's about 2 1/2 times what it is at 1 1/2 tesla.

at

1 People have pushed it and gotten something on the
2 order of 300 microns, 300 by 300 by 300 microns is
3 achievable in vivo. Some folks at Duke and some people at
4 the University of Minnesota have also done that.
5 The second question was have there been examples
6 where the small animal studies have been moved on to large
7 animals. Yes, many, many examples. For example, the
8 hyperpolarized gas images that I showed you, we showed the
9 first hyperpolarized gas images in small animals in 1995.
10 By the end of '95, and published in the first part of '96,
11 we had human images.
12 Unlike Mr. Clinton, I did actually inhale the gas,
13 but only a couple times, and that has moved on to clinical
14 studies. They are knocking at your door, the FDA's door
15 right now to move on with that.
16 We have done some studies with glycine antagonists
17 with a number of the pharmaceutical companies, looking at
18 those as mediators of stroke, and they have moved, based
19 upon the MR microscopy data, to their preclinical studies,
20 primarily based upon the decisions they were able to get
21 from the small animal measurements that we have one.
22 Marcus Rudin, as I have suggested, has done
23 numerous studies where they have been the director of the
24 direction that Novartis took based upon those small animal
25 studies. So, MRI is now a very common tool for the

1 pharmaceutical industry. I get a call, I probably get
2 somebody from the industry visiting once or twice a month.
3 DR. LESTER: I just thought maybe if you would
4 address it in terms of the resolution, the possibility also
5 of surface coils.
6 DR. JOHNSON: There are so many games that can be
7 played to increase the spatial resolution. David alludes to
8 one of them where you build a specialized antenna that is
9 placed sufficiently close to that which you are imaging, so
10 that you capture the signal very carefully.
11 We did some of that with actually implanting coils
12 in an animal, and the coils could persist for 18, 20 months.
13 We have done tox studies in bromobenzene models, in liver
14 models, and mercuric chloride models where we can image in
15 vivo at something like 50 or 60 microns.
16 So, we just don't have enough time to go through
17 all of the possibilities here.
18 DR. MacGREGOR: Just to get this in perspective
19 for me, using what you consider now the optimum existing
20 technology, what scan time would it take, for example, to
21 get 40 micron resolution of a rat kidney?
22 DR. JOHNSON: In an unfixed rat kidney, we can do
23 that in probably eight hours.
24 DR. MacGREGOR: Or I would say even fixed, I mean
25 using an optimum gadolinium fixation to get that kind of

1 resolution, what is the most efficiently you could do it?

2 DR. JOHNSON: It is two hours, two to three hours

3 today. Within six months, with our high-temperature

4 superconducting coils, we have one more coil design that is

5 underway right now, we expect to drop that to under an hour.

6 So, it is two to three hours right now, and we can drop it

7 to under an hour within the next six months.

8 If you multiplex, do several coils simultaneously,

9 the effective time, you could do four coils, four specimens

10 simultaneously, so it's 15 minutes. We can overwhelm you,

11 we can swamp you with data. You will be inundated with

12 images.

13 DR. DOULL: Since we have all four of our

14 speakers, Dr. Collins and Dr. Frank, Dr. Lester, and Dr.

15 Johnson, let me ask the subcommittee, let's go back to Dr.

16 MacGregor's charge at the beginning.

17 What we have is the problem of converting what is

18 really gee whiz science, in my viewpoint, it is incredibly

19 impressive and very sophisticated and very elegant, what

20 this committee I think is going to have to deal with is how

21 do we convert that into a real world working tool?

22 One of the things that this committee can do, that

23 will facilitate the transition, we would like to get this to

24 the point, you know, where it is usable and where a lot of

25 people know about it, a lot of people understand it and

1 appreciate it, and are moving towards utilizing it somehow
2 in their preclinical testing, and we would like to get it
3 into the tox area and into the efficacy area, so it really
4 gets built in and utilized in a fashion.

5 Right now it's, I would say, still pretty much gee
6 whiz science, and we somehow need to facilitate that
7 transition. Let me ask the committee about questions.

8 Jack.

9 DR. DEAN: John, to follow up with the question
10 you were framing, is the limitation in the application of
11 the technology to the analysis that you might do in a
12 company to look at toxicity or pharmacology, and ask the
13 experts, is the limitation the availability of the equipment
14 to do it with? It sounds like a lot of this is very
15 specialized equipment that they have built themselves.

16 Is the equipment commercially available for the
17 sort of animal work that we are talking about here, or is
18 the limitation the number of animals or the amount of time
19 that it is going to take to do this kind of thing?

20 Costs, difficulty, availability, all those things,
21 because I suspect you are not going to be borrowing these
22 units from the clinical practice.

23 DR. DOULL: I suspect some of us are going to go
24 to Duke, to look at it at least.

25 Dr. Frank.

1 DR. FRANK: There certainly is an element of
2 hardware and software availability, as well as the
3 intellectual capacity to make the best application of that,
4 and specifically with regard to the small animal PET
5 scanners, they are currently under construction by a
6 commercial supplier, and they have a backlog measured I
7 think more in years than in months.
8 So, there certainly is some access to hardware
9 issues, and what can be done about that, I don't quite know,
10 but certainly the increased visibility and interest that
11 will result from the subcommittee's activities, I think
12 would marginally contribute to expanding that production if
13 they know that they are going to have a product which is
14 useful.
15 That can't really be separated from the
16 development of new tracers and the development of people to
17 apply those, as well, and if I can take this opportunity,
18 then, to address another part of your question, how can we
19 move from gee whiz science to actually making this happen.
20 In the back of my handout I have listed a number
21 of references in the Parkinson's disease area. This is a
22 real life scenario in which a great deal of validation work
23 already has been done down to the point of looking at
24 longitudinal course of disease, determining confounding
25 factors, and looking at potential interaction between the

1 therapeutic agents and the imaging agents.

2 So, I would like to make sure that we don't come
3 away from this with the impression that this is a future
4 event. These are things which are happening now. The
5 pharmaceutical industry, the companies which have the
6 intellect and have had the clinical problems needing answers
7 are actually using this now.

8 So, as we expand in the next few years, the need
9 for additional hardware and additional people able to use it
10 will be increasing.

11 DR. JOHNSON: Can I voice one answer to that
12 question, as well?

13 DR. DOULL: Sure.

14 DR. JOHNSON: How do we get it from gee whiz
15 science into the real world? That is I enjoy the other half
16 of my life. I have this sort of dichotomy. As Director of
17 the Physics Section in the hospital, my first job in 1974
18 was to install this new toy. People had no idea what it
19 would do. It was the second CT scanner in the United
20 States.

21 In 1983, we had the first high-field MRI system,
22 and we are currently doing some stuff similarly with 3D.
23 There is a huge barrier between the technology and getting
24 it into the clinical arena. At least in this situation in
25 the hospital, you have got all the radiologists, you have

1 got them corralled. You can get them all in one place, and
2 they have radiology meetings that allow the dissemination.
3 The challenge that we have here is probably
4 gathering the tox and pathology community into a single
5 arena, so that we can share the information. The equipment
6 is, yes, it is specialized, but if you say to me go out and
7 buy the toys necessary, and make it happen from commercial
8 systems, I can modify a commercial system and make it work
9 within, oh, four months, and most of the pharmaceutical
10 industry has now grabbed onto the idea of MR pretty well.
11 Making it MR microscopy and making it toxicologically
12 relevant, it is mostly an information transfer.
13 What this committee could, in fact, do is
14 orchestrate a meeting sort of like this, but with a larger
15 population of industry in attendance, so that we had the
16 opportunity to hammer out some standards.
17 What the radiology community has done, about two
18 years go, the American College of Radiology formed a
19 committee that is headed by Dr. Hillman at the University of
20 Virginia. It is called ACRIN, the American College of
21 Radiology Imaging Network.
22 The goal of that committee is to facilitate
23 multicenter trials with the statistical backup that is
24 necessary and the necessary pooling of data in single--you
25 can use the web wonderful, wonderful ways to pool data.

1 So, with guidance from a committee like this, you
2 could orchestrate a similar organization that would pool
3 data and define protocols, so that we could exploit the web
4 in a very fun and creative fashion.
5 DR. CAVAGNARO: In terms of discussing the
6 introduction of these technologies, I think it is fairly
7 staged, and it is based upon whether or not the current
8 technologies that we have are able to be able to answer the
9 questions.
10 I think it was mentioned by Dr. Frank, as well,
11 when to use this, and you wouldn't use it all the time, et
12 cetera. So, I think we have to be careful not to expect a
13 generic application for all cases.
14 I think you will find, as was just stated, those
15 companies that have a question it needed to answer, and
16 couldn't answer it any other way, are the leaders in terms
17 of utilizing these various technologies.
18 I think for those of us who have been in the
19 biotechnology field for many years, many of these novel
20 technologies have been used, unvalidated if you will,
21 because they were the only technologies that could answer
22 questions.
23 So, I think over the years, we probably have not
24 paid attention to whether or not the various methodologies,
25 new animal models, new assays were "validated." We didn't

1 quite worry about that, but rather we worried about the
2 science, you know, the studies themselves, if they supported
3 in terms of answering the question.
4 So, I think the technologies again will be
5 introduced when it is found that there is a question that
6 cannot be answered by current technologies, and those will
7 lead the introduction, and they will champion the
8 introduction into those areas, as was mentioned with
9 Parkinson's.
10 I mean there was a real need there, and so those
11 are the leaders, and then it will evolve.
12 DR. DOULL: That is probably an opportunity for
13 closer collaboration between industry and academia and
14 regulatory agencies, because they are going to have the
15 equipment to do some of this, and in order to teach our
16 students is why we are going to have to go where the
17 equipment is undoubtedly.
18 When Bruce Ames introduced the Ames test, it
19 certainly didn't require a million dollars worth of
20 equipment. It required microbiological strain and that was
21 about it. This is going to be a lot more expensive, a lot
22 more complex.
23 If it isn't coordinated, I think it is going to be
24 very difficult to do. In a sense perhaps the main function
25 of this committee is to look at the forest rather than the

1 trees. If we bogged down in the trees and in the specific
2 advantages of each of these techniques, then, we may lose
3 sight of the overall goal, which is to enhance our ability
4 to use the science in doing better diagnosis and doing
5 better prediction about adverse effects, doing better
6 efficacy studies, and ultimately, to do better regulation.
7 Jack.
8 DR. REYNOLDS: One of the things--and it may be a
9 different answer for PET, as well as for the microscopy--but
10 what, in general, is the format and structure of the data
11 that would be gathered?
12 I think that both on the regulatory side, but
13 especially on the industry side, we need to be cognizant of
14 the ability to document the gee whiz or the observations
15 that we make. We need to have those data in a format where
16 they could be verified both by our internal folks, but also
17 people that we submit these to.
18 Also, there has to be a mechanism whereby there
19 could be independent reviews of these data. So, I guess
20 with PET, there may be a different answer than with
21 microscopy, but I think we need to think about the format of
22 the data, how much data, and do industry have to look at
23 particular types of ways to structure the data, and do the
24 FDA have to prepare themselves to receive these data or to
25 analyze these data?

1 There is probably not a simple answer, but just
2 some general, I guess, guidelines that this committee can be
3 thinking about by building that infrastructure at the same
4 time we build the science going from the gee whiz to the
5 pragmatic.
6 DR. JOHNSON: Again, the radiology community
7 provides a model that we can follow. We have had the same
8 evolution in data formats. We had Siemens and G.E. and
9 Phillips for years, and you couldn't get a Siemens machine
10 talking to a Phillips machine if your life depended upon it.
11 But over the last six years or so, people have
12 come to a realization that there probably will be a couple
13 of each machines in each hospital, so the DICOM standard of
14 image data has evolved.
15 It is possible right now for us to put the PET
16 images, the MR images, it is possible for us to settle one
17 some standards pretty easily. It needs a committee meeting
18 that says are we going to settle on these standards, sure,
19 and I would suggest that is probably not a big decision
20 process.
21 You point out, though, one of the more interesting
22 phenomena that if you generate a 10-24 cubed array, do you
23 just leave that 10-24 cubed array on the web? If you do,
24 how do people interact with it?
25 Again, the radiology community is wrestling with

1 this. I alluded to the fact that we can flood David and his
2 colleagues with images. We are trying, and I think there
3 will be a couple other attempts right now to just
4 standardize the interactivity and the space.

5 If you are going to do brains, for example, the
6 people that have been doing the brain imaging project
7 throughout the U.S. have come up with the standard space,
8 and we can define a similar standard space for the rat, for
9 the rat brain, for the rat kidney, and then we can define
10 standard interfaces that again take place over the web.

11 It can be made available to the FDA trivially,
12 truly trivially. You have downloaded a web browser, and
13 there is a database for your access. We can talk, perhaps
14 off-line, how you might want to try and play with that. We
15 have data they can get to right now.

16 I can go plug that personal computer in if a
17 bandwidth line here, I can pull up 3-D datasets from our
18 archive. Again, I emphasize this web stuff. I couldn't get
19 what the web was really about. My children kept telling me,
20 and I couldn't get it.

21 But now when you get a real application, you have
22 terabytes of data that you would like to get to, and you
23 would like pharmaceutical A, B, and C manufacturers to pool
24 their data, and they are ecstatic to do that incidently.

25 You just need a central repository where everybody

at

1 has the same image sets to look at, and the technology
2 exists right now, it is being used for distributing Gone
3 with the Wind and a whole bunch of other image sets that we
4 have just routinely out there, you know, all of that stuff
5 is available right now. We just need to put our images in
6 there instead of a picture of a Chevy van.
7 DR. DOULL: One of the things this committee might
8 be involved in, of course, is establishing some of those
9 ground rules to facilitate this information transfer.
10 Dr. Frank.
11 DR. FRANK: I am grateful for the opportunity to
12 discuss a couple of the other slides which I left out for
13 the sake of brevity today. Although I have spoken on PET
14 today, I am one of the first to acknowledge that magnetic
15 resonance imaging has distinct advantages in certain areas,
16 and cognitive testing is one of these.
17 Just to boil it down, it is a matter of temporal
18 resolution. In order to do a functional PET study
19 generally, we would have to ask the subject being studied to
20 conduct that motor task or that memory task for a duration
21 of about 30 seconds in order to collect adequate data to get
22 the image for PET, whereas, you have about a 10-fold
23 improvement in temporal resolution with magnetic resonance
24 imaging, so they only have to hold that thought, to hold
25 that memory for about three seconds in order to collect the

1 magnetic resonance imaging image.

2 Therefore, especially, for cognitive imaging,

3 there is a clear advantage to MRI over PET, and that is just

4 one example of how we should not advocate any particular

5 technology in general, but make sure that we choose the best

6 technology for a particular problem, and that means you have

7 to have a clear understanding first of what the problem is.

8 So, I think starting on a case-by-case basis,

9 identifying problems for which there are not other good

10 solutions, and then looking for the best solution among the

11 imaging technologies would be the way to go.

12 Shifting gears, if I could take off my hat as the

13 immediate past President of SNIDD, and put on my hat as a

14 clinical pharmacologist working for Sanofi Synthelabo, I

15 think I can answer what I understood to be another of your

16 questions, and that is, I would be making a mistake if I

17 went to the FDA with a fully-cooked dossier tied up in a

18 neat ribbon and asked them for approval if I knew inside the

19 package there was some high-tech methodology which they

20 hadn't seen before.

21 I should certainly avail myself of the pre-IND

22 meeting, end of Phase II meeting, for example, and take

23 every opportunity to ensure that FDA agreed with my

24 conclusions, not just the efficacy conclusions, but the

25 applicability of that particular technology, and for each

at

1 company to do that for each drug and each technology would
2 be a very cumbersome process, and I should think perhaps
3 even more cumbersome for FDA than it is for the sponsors
4 because they have to deal with all these different sources
5 of information.

6 So, maybe there is a great opportunity to help the
7 people in the FDA who ultimately will have to review these
8 dossiers and decide whether or not the data are relevant and
9 persuasive. If there is some way we can help the reviewers
10 to keep up with the science, which for them I guess is an
11 equally difficult task as it is for the rest of us, then,
12 that would be a great leap forward, I think.

13 DR. DOULL: That is a great idea.

14 Dr. Essayan.

15 DR. ESSAYAN: As I sat here, I was asked to come
16 up with a couple of approaches, I actually scribbled down
17 two, and as I have been listening to the discussion,
18 everybody has hit on bits and pieces of them, but the two
19 things that I had thought that we would really need to focus
20 on, one was standardization.

21 It was mentioned earlier that standardization of
22 the lexicon used would be a very important aspect of this,
23 and then standardization of the protocols, and I think we
24 have heard all the other discussants talking about both
25 acquisition of the data, storage, and archiving of the data,

1 as well as standardization of protocols for access of the
2 data.
3 The second major thing that I think we would need
4 to start to focus on would be identification of
5 opportunities based on both the potential drug class, but
6 also on the toxicity class. As Dr. Cavagnaro pointed out,
7 this isn't really the kind of thing that is going to be
8 generally applicable potentially.
9 This is the kind of thing where we are going to
10 have to at least initially identify specific focuses to go
11 after and look at as project examples in order to really
12 move the field, you know, in portions of the front line
13 rather than try to just brute force advance the entire front
14 line.
15 I am afraid that if we try to advance the entire
16 front line all at once, the efforts might be so minorly
17 incremental that the effort would be lost.
18 To expand just briefly on your analogy about
19 forest and trees, I view the standardization as the
20 topographic map of the forest, and that's the only way to
21 really see the differences.
22 DR. DOULL: Thanks. When you were talking about
23 the MRM, you talked about validation of that through
24 pathology, I think, Dave, you talked about that in your
25 presentation.

at

1 In a sense, all those different stains that you
2 did helped to validate that procedure, but as I understand
3 what you are saying, is that one can also validate, MRI can
4 validate PET, and so on, so that the whole thing builds--one
5 of the problems that a committee has, the Pharmaceutical
6 Sciences Committee has, has to deal with validation, how one
7 does that, and its integrity, and so on, and I think I hear
8 you all saying that there is some self-validation within
9 this whole process, and, you know, if you had all this out
10 on the internet where everyone was playing with it, I think
11 there would be some validation going on, some powerful
12 validation within a relatively short time.

13 Other comments from the committee? Joy.

14 DR. CAVAGNARO: In some of the efforts that you
15 are looking at in terms of establishing databases, one
16 challenge to toxicologists has always been looking at normal
17 rodents, doing toxicology in normal rodents versus use of
18 animal models of disease as a more accurate predictor, if
19 you will.

20 That is, using animal models of disease in
21 assessing toxicity in those animal models of disease even
22 though they don't mimic all aspects of disease as patients
23 are generally sick, and not normal individuals.

24 In the past, there has been some reluctance for
25 toxicologists to use animal models of disease again for the

1 interpretation issue, and not quite understanding the
2 disease pathology versus perhaps the added pathology of the
3 agent, and I was just wondering, for the many new
4 technologies, is there also an establishment or a
5 consideration of using disease animal models in establishing
6 a baseline, if you will, so that we can use those better or
7 smarter in assessing toxicity.

8 DR. LESTER: As Dr. Johnson pointed out, there are
9 efforts in terms of going through all of the various
10 transgenic mice and characterizing using MRM, not only MRM,
11 NIH has been interested in microCT scanning or some microPET
12 scanning, so there is that effort.

13 There is another thing, though, that I wanted to
14 bring up and I failed to mention in my talk is the Armed
15 Forces Institute of Pathology are now investing heavily, and
16 they are setting up a magnetic resonance imaging microscopy
17 facility.

18 Part of their rationale is they believe that is
19 the way of the future. They believe that pathology, in
20 general, we recognize pathology can be done using magnetic
21 resonance imaging microscopy across the board, not case by
22 case, but they believe based on the information in large
23 part from what Dr. Johnson and some other labs have
24 collected, it has got the potential of being used across the
25 board.

1 They are going to go ahead now--and I think that
2 this committee should also link with them and connect with
3 them in some way--they are going to go ahead, and they are
4 going to start systematically analyze, and they have the
5 best results in the world in terms of toxicology and
6 pathology, and they are going to start systematically going
7 ahead and doing a lot of these analyses, and some of them
8 will be in collaboration with Dr. Johnson, and some of them
9 will be independent, so I think that is really an excellent
10 opportunity.
11 But I think it also points out the utility of that
12 particular technique for that application, so all of you are
13 correct in saying that these different modes should be
14 connected to specific applications.
15 More specifically in answer to what you asked, I
16 think, yes, it can be done. People are thinking along those
17 lines. I don't think there are enough tools out there yet,
18 and enough toys out there, to really go ahead and do it, but
19 certainly things are looking up.
20 DR. DOULL: Hopefully, we will have an opportunity
21 to come back to this in our discussion. This afternoon we
22 are going to focus on the biomarkers and the other aspects,
23 and then we will have a general discussion, Dr. MacGregor,
24 in which we will come back and hopefully weave some of this
25 together again.

at

1 Why don't we adjourn at this point for lunch, and
2 can we be back at 1 o'clock.
3 [Whereupon, at 12:00 noon, the proceedings were
4 recessed, to be resumed at 1:00 p.m.]

at

1 AFTERNOON PROCEEDINGS

2 [1:00 p.m.]

3 DR. DOULL: I think we will go ahead and get

4 started again. We are pretty close to on time.

5 **Open Public Hearing**

6 At 1 o'clock, we are scheduled for an open public

7 hearing. Kimberly tell me we have no requests for public

8 hearing, but I guess we will offer that opportunity to

9 whoever would like to take advantage, if anybody.

10 [No response.]

11 DR. DOULL: All right. We will then go ahead and

12 the next phase of the program has to do with the biomarkers

13 and recommendations, and that is going to be started out by

14 Dr. Sistare.

15 **Biomarkers**

16 **Frank Sistare, Ph.D.**

17 DR. SISTARE: I was joking with Dr. Doull earlier,

18 saying there was a typo, and I actually had an hour and 25

19 minutes to talk, and not 25 minutes to talk, so you wouldn't

20 pull the cane on me. But I won't.

21 [Slide.]

22 Thank you for giving me this opportunity to speak.

23 I really appreciate this opportunity to appear before the

24 committee, and I am looking forward to feedback and next

25 steps that may be taken.

at

1 My charge was to discuss the concept of moving
2 biomarkers forward, biomarkers in the context of safety
3 monitoring of pharmaceuticals or toxicity biomarkers.
4 [Slide.]
5 When you think of biomarkers, it's biomarkers of
6 exposure, things like DNA adducts, it tells you that toxin
7 has gotten to a certain site, biomarkers of susceptibility,
8 things like genetic polymorphism that will tell you that one
9 population may be more susceptible to toxicity of an agent
10 than another. Then, there is biomarkers of effect or
11 biomarkers of response.
12 I am not going to talk about biomarkers of
13 exposure, I am not going to talk about biomarkers of
14 susceptibility. I would say that the whole issue of
15 biomarkers of susceptibility is something that probably
16 should be encouraged and discussed in some context. It is
17 rapidly evolving.
18 But what I am going to focus on today is
19 biomarkers of effect.
20 [Slide.]
21 Very busy slide, but I felt it important to get a
22 couple issues out here. People think of biomarkers and
23 surrogate endpoints in the context of efficacy, and there is
24 analogies in the safety end, but there is also important
25 differences, as well.

1 You can think of it a very broad sense, in terms
2 of a research use, you can think of a pharmacodynamic
3 endpoint or a toxicodynamic endpoint, an indicator that the
4 drug is affecting its intended target or it is affecting an
5 unintended tissue site in an unintended way.
6 Then, in terms of increasing components of
7 certainty that one develops as you go down a spectrum, a
8 biomarker for efficacy assists with some acceptable level of
9 uncertainty in assessing clinical improvement or that the
10 disease is regressing.
11 What we ultimately want is a desired clinical
12 effect and proof that we have actually mitigated or cured
13 the disease, that there is clear improvement. There has
14 been with FDAMA initiative, and there has been examples of
15 fast-track drugs where surrogate endpoints for efficacy can
16 be used as proof of drug approvability reliably, so these
17 are endpoints that reliably predict for the desired clinical
18 effect.
19 As I mentioned, sometimes with these fast-track
20 drugs, valid data below that endpoint sometimes will be
21 allowed to occur in Phase IV.
22 Now, on the other end of the spectrum, the
23 toxicodynamic endpoint indicating that a drug is affecting
24 an unintended tissue site, ultimately, there could be some
25 prohibitive toxicity where the defined risk exceeds expected

at

1 benefit that may result in approvability of a drug.

2 There are safety or toxicity biomarkers that can

3 assist--and I stress in a weight of evidence approach--to

4 prevent the onset or to monitor progression of drug

5 toxicity, and I think a lot of the angst in the field, and I

6 think a lot of the angst in between industry and regulators

7 is that there is a fear that biomarkers will evolve and be

8 viewed as surrogate endpoints for safety, predicting that a

9 toxicity occurs and then it is essentially a validatable

10 endpoint for what would be a prohibitive toxicity and

11 prevent approval of a drug.

12 But we are not talking today about surrogate

13 endpoints, we are talking about safety or toxicity

14 biomarkers where there is always going to probably be some

15 level of uncertainty. There may not be 100 percent

16 concordance in all cases, but they will have value in the

17 assessment of a drug's toxicity potential.

18 [Slide.]

19 Now, within that spectrum of biomarkers of effect

20 for safety, we can talk about early biomarkers of effect and

21 late biomarkers of effect, and there is a progression in

22 time, and there is there going to be a progression in the

23 complexity of the biology that the biomarker is going to

24 reflect.

25 Early on, an early biomarker of response is

1 probably one that is going to give you a very big signal.
2 It's the perturbation of a system at homeostasis, and you
3 are looking at that early response.
4 A lot of the gene expression of microarray
5 technology is focused on those early biomarkers of effect.
6 It is good in the sense you would get a good signal, you get
7 a big signal, but with the complexity of the biology, the
8 difficulty is in the linking of those effects to the
9 ultimate toxicity that is seen.
10 There is going to be a lot of responses and to
11 sort which ones are contributing to toxicity and which ones
12 are pharmacological responses, those are the kinds of
13 difficulties that focusing on early biomarkers of effect
14 will have.
15 Now, late biomarkers of effect, if you look too
16 late, you are at a point where you have got irreversible
17 toxicity, and the biomarker of effect isn't going to help
18 you. I think if you want a practical later biomarker of
19 effect to have some practical utility, you kind of need to
20 be in this range here where maybe you have escaped a lot of
21 the complexity of the early biology, and you are down here
22 before irreversible toxicity, and you are at a reversible
23 stage, so you can catch it.
24 [Slide.]
25 This is a quote, which talks about biomarkers as

1 an essential bridge, a bridge between basic and mechanistic
2 research and effective public policy. "If more simple cost
3 effective biomarkers existed, cost effective public policy
4 could be readily formulated and the effect of management of
5 many toxins could be achieved. The singular drawback in
6 using biomarkers, the necessary biomarkers simply do not
7 exist." This is an old quote.

8 [Slide.]

9 In terms of bridging, as well, as was pointed out
10 several times today, for a biomarker to be practical, it has
11 to be accessible and has to be accessible across species and
12 ultimately be applicable to the human situation.

13 Now, when we think of sources of accessible
14 biomarkers, things that come to mind are the circulating
15 blood elements, those cells that are circulating around.
16 You can look at circular RNA, you can look at proteins
17 expressed in those cells, and you can even look at changes
18 in DNA, like mutations, and things like that.

19 Accessible clinical biopsies, readily accessible
20 clinical biopsies, for example, the skin. If you are
21 interested in asking whether something is relevant across
22 species, you could look at changes in human skin with very
23 small biopsies.

24 Then, there are the serum components. Proteins
25 are potentially lipid products that are up-regulated and

at

1 secreted, and as Jim referred to earlier, tissue-specific
2 proteins that may be released when membrane integrity is
3 compromised, and then there are components of other body
4 fluids - bronchial lavage fluid, the urine. These are all
5 rich sources of potential biomarkers.
6 [Slide.]
7 Now, what are the indications that maybe we could
8 all profit from more and better biomarkers, that could link
9 exposure to toxicity?
10 Well, we can point to the fact that biomarkers of
11 toxicity haven't really changed much in the last 40 years,
12 and Jim elucidated to this point very early on this morning.
13 Like I say, we look at serum chemistry, we look at host
14 responses, we look at changes in body weight. These are all
15 sort of gross biomarkers that we have been using in the last
16 40 years.
17 We can point to attrition of pharmaceuticals from
18 clinical phases of development and say why did this happen,
19 and it is not always going to be because we didn't know
20 early on that there weren't biomarkers, but I think in some
21 cases we can point to that.
22 We can point to removal of approved drugs from the
23 marketplace. Again, I am not saying that every drug that
24 has been removed from the marketplace would have been
25 prevented from a biomarker, but here is an example perhaps

at

1 where those biomarkers of susceptibility could have played a
2 role, where we have susceptible populations and small
3 percentages of people that could be affected that one might
4 not pick in a clinical trial.
5 Another one is questioned relevance of certain
6 animal findings, and we see this an awful lot in the
7 regulatory end of things - do we have something that we can
8 answer that question as to whether these findings in the
9 animals are relevant or irrelevant to the human condition.
10 There is a perception oftentimes of
11 inconsistencies across drug review divisions, and that stems
12 a lot of times from the inability or the science just isn't
13 there to totally justify one decision or another in all
14 cases.
15 Many times drugs are placed on clinical hold for
16 reasons, because of preclinical or nonclinical findings that
17 one could not look and tell whether it is going to happen in
18 the clinic or not, and there is also questions relevant in
19 certain animal models or whole models are being used in the
20 industry isn't totally agreeable to the use of some of these
21 models.
22 [Slide.]
23 General considerations. Focus on biomarkers
24 mechanistically related to pathogenesis of insidious
25 toxicities, and just by its very nature, the term

1 "insidious," it is sneaky, it sneaks up on you, you can't
2 see it coming. So, one would think of a biomarker to help
3 cast some light on the approach of those toxicities we could
4 benefit from.
5 Choose toxicities of interest to both regulators
6 and sponsors to encourage partnering in terms of the kinds
7 of areas for future collaboration to advance the field of
8 biomarkers, and to choose practical biomarker strategy that
9 allows, like I say, extrapolation between animals and man.
10 [Slide.]
11 Now, what I am going to do is slightly different
12 from earlier presentations. I am going to propose as
13 examples, these are just examples of four areas of research
14 that we are currently involved in, in the regulatory
15 laboratories, where we are focusing on the potential for
16 biomarkers, and I think that we could all benefit from
17 expanding and collaborating with partners in industry, NIH,
18 and academia.
19 One is further evaluation of troponin T as a
20 biomarker for insidious cardiac toxicity. That is an
21 example of a biomarker that one could point to as an example
22 of tissue integrity.
23 Skin photocarcinogenicity tissue biomarkers.
24 Example, where a model that is being used now, there is some
25 skepticism across industry, I am not saying all elements,

1 but there is some skepticism that the hairless mouse model
2 might not be the most relevant model for determining that a
3 drug has photocarcinogenic potential or not. This may be a
4 way of nailing down that question of relevance.
5 Drug-induced vasculitis, an example of potentially
6 both inducible and a tissue integrity biomarker example,
7 again where there is issues of relevant animal findings to
8 man, and very difficult to answer, to address, because of
9 the lack of biomarkers.
10 Then, there is the very real issue to all of us,
11 and that is drug-induced hepatotoxicity.
12 [Slide.]
13 Now, this is just data that you can get out of the
14 Federal Register that lists a number of drugs that have been
15 withdrawn for reasons of safety, and I list five drugs that
16 have appeared since 1969, that there was some element of
17 liver toxicity.
18 [Slide.]
19 Now, there are complementary initiatives going on
20 to look at biomarkers. I noticed Denise Robinson is in the
21 audience, working toward fostering an ILSI collaboration as
22 a biomarker initiative.
23 The focus of that is on early biomarkers of
24 hepatotoxicity, renal toxicity, and genotoxicity, and I
25 think that initiative is really evolving toward, at least

at

1 early on in evaluation of gene expression, microarray
2 technologies.
3 There is another group, and I see Roger Ulrich in
4 the audience or I did see him earlier--there he is, he is
5 still over there--there is U.S.-European Community
6 Consortium or Society, I am not sure which is the exact word
7 to put up there, on toxicology.
8 Again, I think it is fair to say that the initial
9 focus at least is on gene expression and microarray, and I
10 think are what are going to be considered early biomarkers
11 of effect.
12 Then, very recently there has been an NIEHS
13 biomarker partnership initiative, which just had their first
14 meeting a month ago. Again, the initial discussions were
15 also focused on early biomarkers effect or the microarray
16 technology. That really grew out of a meeting that occurred
17 in April that was co-sponsored by the NIH and the FDA to
18 call for a partnering initiative to focus on biomarkers.
19 The initial focus was on biomarkers of efficacy,
20 and I think Jim has been really instrumental in bringing to
21 this group the concept that we really ought to bring in
22 biomarkers of safety and toxicity, as well. I believe that
23 this partnership is an outgrowth of that.
24 So, these are ongoing initiatives that we need to
25 tune in to and be cognizant of, and really mesh well with if

at

1 we are going to not be duplicative.

2 [Slide.]

3 Now, where is an example of troponin T as a

4 promising biomarker of drug-induced cardiotoxicity. This is

5 data that is coming out of Gene Herman's lab in my division.

6 Over here we have just serum troponin T concentrations in

7 the serum and as a function of the cumulative dose of

8 doxorubicin that is given.

9 As you can see, there is a dose-dependent increase

10 in release of troponin in the serum, and there is a very

11 nice correlation when you look at the histopathology. You

12 see an increase in histopathology scoring that can be done

13 blindly, as well. So, it really points to the value of the

14 toxicity that can be occurring very insidiously with

15 doxorubicin.

16 The history of doxorubicin is it wasn't picked up-

17 -this is going back a number of years--it was picked up

18 clinically after a certain lifetime exposure, and there is

19 still labeling to that effect, but it is being used now

20 clinically by some investigators who are treating childhood

21 malignancies, doxorubicin is, and there is concern as to

22 them developing heart failure later in life, and they need a

23 way to monitor that therapy, and they are using it.

24 On the other hand, there have been cases where

25 sponsors have brought drugs in for review, and when asked to

at

1 monitor troponin levels, there has been expressed angst in
2 the fact that troponin hasn't been validated, and we don't
3 know the specificity, we don't know the sensitivity, and
4 they are all very good points.

5 So, I think it is an example of a biomarker with a
6 lot of potential that may not be being fully utilized
7 because of some element of a evaluation that still needs to
8 be done with this biomarker.

9 [Slide.]

10 So, one proposal might be--it is sort of an
11 initial start into looking at the effort that needs to go in
12 to getting the level of comfort up with use of troponin T,
13 is just looking at the sensitivity and specificity and
14 establish what are the limitations on predictivity.

15 Notice that I do say evaluation, and not
16 validation, because there is probably always going to be
17 some element of uncertainty, and we need to evaluate what
18 are the limitations - what is the robustness, the
19 reproducibility, the dynamic range, the T one-half of the
20 troponin T in the serum, and relate this to dose, exposure,
21 and time, look across species, look across strains, across
22 gender, variations which are known to occur, and relate that
23 to the gold standard, the histopath observations.

24 It is just one potential way of approaching that
25 issue.

at

1 [Slide.]

2 The next example. Are there skin biomarkers that
3 can predict pharmaceutical photocarcinogenicity risk across
4 species? There, the goal may be to evaluate the predictive
5 ability of conserved molecular biomarkers of response to a
6 photocarcinogen in combination with UV light exposures to
7 targeted skin cells using NC2, immunohistochemistry, the
8 question being are these findings in mouse models relevant
9 to humans.

10 The tumor response in the hairless mouse model, as
11 I have indicated already, has been called into question, and
12 whether expanded use of that model is appropriate is a
13 question that we could potentially address using biomarkers.

14 [Slide.]

15 Now, here is just one example looking at apoptotic
16 cell generation as a function of treatment with UV light and
17 a photocarcinogen as compared to a control with either a low
18 level of UV light alone or with drug alone, and you can see
19 an increase in apoptotic bodies and apoptotic cells that
20 occurs.

21 So, there is a whole lot more that needs to go
22 into that, but here is an example of potentially a biomarker
23 that could give you some evidence. You can also see some
24 evidence of some proliferation changes that are different
25 there, as well, and we are looking at proliferation markers,

at

1 as well.

2 [Slide.]

3 Now, the issue of drug-induced vasculitis. Say a
4 sponsor has a drug which yields a mesenteric vasculitis that
5 is seen on histopath and causes death in the rat study. The
6 company is not seeing clinical efficacy at a certain dose,
7 and they want to increase the dose to meet or exceed the rat
8 AUC at the MTD.

9 There is an impasse between the Review Division
10 and the sponsor because there is really no way of
11 monitoring, to monitor for these rat findings in the clinic.
12 Histopath is showing earlier injury to the rat. Vascular
13 endothelial and smooth muscles cells is something we have
14 been able to see very early on as a function of time, so we
15 are focusing on that, and the injury that we are seeing in
16 endothelial cells suggests that there may be a biomarker
17 response, and we are approaching this by use of looking at
18 proteins that might be up-regulated and released early on.

19 [Slide.]

20 Here is an example of a drug that appears in the
21 literature. This was actually presented in a session of the
22 SOT last spring, a drug being developed by Novartis, PDI-
23 747, for inflammatory skin diseases. It is a PDI-IV
24 inhibitor, and they got vasculitis findings in every single
25 species that they looked at.

1 In some cases, the safety margin was very poor.
2 In other cases, it was at about the dose that was being
3 projected to be used in the clinic. Every single species
4 they found vasculitis, and they didn't find it--there was no
5 species they looked at that they didn't see it, and the
6 conclusion from that poster was that the drug development
7 was abandoned because of the poor safety margin and also
8 because there was no biomarkers that could be used in man.
9 Now, this is sort of maybe an easy call, but what
10 if you have positive findings in the mouse or the rat, and
11 you don't have it in the monkey, the rabbit, and the dog,
12 what do you do then, or what if the safety margin isn't
13 quite like this, but there is a margin of 4 or 3, and what
14 do you do.
15 These are not hypothetical situations I am talking
16 about.
17 [Slide.]
18 So, those are some examples where clearly I think
19 there could be improvement if we had more science and we had
20 more data and more hard facts to move forward on. Now, here
21 is an example of technology that is available to us today,
22 an example of a technology that we are exploring currently
23 to see if they can give us a handle on biomarkers,
24 discovering and uncovering biomarkers that could be useful.
25 This is compliments of Oxford Glycosciences, an

1 example of a technology using 2D gels, looking at
2 differential protein expression between treated and
3 untreated. Promising spots on gels can be cut out, and you
4 can actually sequence these things, and these things can be
5 done in a very rigorous format and you can identify because
6 we have these huge databases of sequence that we are
7 expanding on every day.

8 We can identify these proteins just by comparing
9 them to the computer databases we have. They may be new
10 proteins and may be discovering things in some cases, and in
11 other cases, they may be proteins that we already know.

12 They could shed a light on biomarkers that we
13 could then be able to use and monitor preclinically and then
14 clinically.

15 [Slide.]

16 Another example of proteomics technology being
17 developed by Ciphergen, what they call a protein chip. So,
18 you have a capture technology. You can vaporize these
19 proteins and collect molecular weight information and then
20 compare treated and untreated, and not necessarily be able
21 to identify what the protein is, but at least to know that
22 there is a difference there, and then develop a strategy to
23 try to identify that protein.

24 [Slide.]

25 Those might be considered low throughput

at

1 technologies, but once you have identified key biomarkers
2 using that technologies, one could automate these kinds of
3 things, and Jim showed this slide earlier. This is
4 compliments of--just one example--you can pull off the web
5 for Luminex where they have bead technology, and you can use
6 a flow cytometric approach to identify hundreds of proteins
7 and antigens at a time.

8 [Slide.]

9 A question I think we need to ask is, you know,
10 there is clearly going to be a lot of benefit to these
11 things, and there is also a lot of angst about these things,
12 but who should assume the costs of biomarker identification
13 and evaluation, where do we start, and how do we prioritize.

14 Well, the vision that I have, and I think the
15 vision that the committee would share, is that a
16 collaborative effort, defining improved panels of biomarkers
17 for specific activities that cut across species, built into
18 a practical format is something that I think is very real
19 and very achievable.

20 Why I say panels is because of that whole concept
21 of biomarker versus surrogate endpoint where there is again
22 I think intrinsic, some level of uncertainty, but with a
23 number of biomarkers, one can use a weight of evidence
24 approach and make sense out of a signal.

25 [Slide.]

1 I talked a little bit about this already,
2 biomarker evaluation considerations. There is the whole
3 clinical chemistry to the standardization or you can even
4 talk about validation, but that point is the accuracy there
5 or the precision there, is it measuring what you think it is
6 measuring, and then when you go into the nonclinical phase,
7 the evaluation, dose response, identification of the
8 threshold of where action may need to be taken, establishing
9 cause-effect relationship, sensitivity, specificity, and
10 predictivity of the response, and then the question of
11 reversibility and irreversibility can be built into any kind
12 of a study design there.
13 Then, you know once you have got these kinds of
14 knowledge base that you can really develop in a nonclinical
15 phase, to bring those into the clinic and get confirmation
16 is not going to be an easy task, and it is something that we
17 have to very carefully consider.
18 [Slide.]
19 So, to summarize, I have discussed the need for a
20 collaborative research approach that will benefit all
21 partners by identifying useful safety biomarkers to reduce
22 human morbidity and mortality, and potentially affect drug
23 withdrawals from the marketplace, to improve drug
24 development go/no go decisions, to delineate when
25 interspecies differences may be relevant or irrelevant to

1 the human situation, prevent clinical holds and impasses
2 that occur, and to improve regulatory decisionmaking with
3 more and better clinical and nonclinical signals.
4 My training, my thesis adviser, I remember very
5 early on in my career when I had to come up with these
6 exercises of research proposals and how you would approach
7 it. I said, you know, give me some ideas on where to go
8 with this. He said look for areas of discordance in the
9 literature. That is one place where you can get a very
10 fruitful area to develop a research proposal.
11 In a sense, what I have done here is highlighted
12 areas of discordance that I have seen from my vantage point
13 in the laboratory and the regulatory setting between very
14 thorough reviewers and very sure sponsors. On the other
15 hand, that things are relevant, things are irrelevant, and
16 like I say, a lot of times when you have that disagreement
17 or discordance, it is because the science isn't quite there,
18 all the information that you need isn't quite there.
19 I think, like I say, these are some examples where
20 we can improve our information base and move forward.
21 Thank you.
22 DR. DOULL: Thank you, Dr. Sistare.
23 We will move on then to Dr. Morgan.
24 **Biomarkers**
25 **Gwyn Morgan, Ph.D.**

1 DR. MORGAN: A few weeks ago, Dr. MacGregor asked
2 me if I would today briefly describe the activities of the
3 ILSI project, whose name is at the top of this slide.
4 [Slide.]
5 Since I saw my name aside the subject of
6 biomarkers on today's agenda, he has given me the latitude
7 to share some thoughts about biomarkers, too.
8 It is not to say that the two are immediately
9 connected, yet, I think that there will be a time when we
10 will be seeking a bridge. So, very briefly, the ILSI
11 project, which goes by this name, was approved by the ILSI
12 board in January of this year, and has by now achieved
13 subcommittee status.
14 The initial approach taken to addressing this
15 topic was to survey member companies, some 30 or 35
16 companies, of the international scope to determine what
17 might be the interest in this topic and what activities were
18 already underway.
19 From this we developed an agenda and conducted a
20 meeting in August of this year. Initially, the goals of the
21 project were defined as follows, very broadly and
22 generically: as an attempt to advance the scientific basis
23 for the development and application of genomic and proteomic
24 technologies to mechanism-based risk assessment, no direct
25 reference per se to biomarkers, but rather to the

at

1 exploration of how genes and proteins may respond to
2 different types of insult, and what pathological processes
3 and pathways might they be representing.
4 It is an underlying goal of ILSI as an institution
5 and of those people participating in this project, that we
6 should, of course, maintain open communication with the
7 scientific community at large, and that is indeed what the
8 project is and now doing.
9 The second meeting in November involved
10 participation by colleagues from regulatory agencies, Dr.
11 DeGeorge and Dr. MacGregor were present at the last meeting,
12 also from the CPMP, and also representatives from
13 governmental institutions, NIEHS, EPA, and so forth.
14 [Slide.]
15 The survey of member companies revealed a fairly
16 uniform response and that there was at the moment a lack of
17 publicly available databases, a lack of information. There
18 was clearly a need for some--I hate to use the word
19 validation--but at least a standardization of available
20 technologies, a diversity of technologies were being used, a
21 variety of different tools and methods, and there was some
22 consensus that there was a need for us to understand better
23 the nature of these tools and how to interpret the data that
24 may be generated from them.
25 Indeed, I am reminded by Dr. MacGregor's remark

at

1 this morning that I feel a little like Krebs in the early
2 1900's. We may yet be redefining genomic and proteomic
3 responses to toxic insult because we know very little about
4 those relationships at the present time in specific terms.
5 [Slide.]
6 As the project has evolved, it became clear that
7 we should try and focus our effort perhaps on two or three
8 major areas. Two major areas of interest currently are
9 genotoxicity and hepatotoxicity, and there are groups
10 currently developing definite plans for further
11 investigations.
12 The concentration at the moment will be on
13 genomics and the application of genomic technology of
14 various kinds - tackmen, grids, microarrays, and so forth.
15 We have deferred an exploration of nephrotoxicity, but we
16 have early on recognized the need for the establishment of a
17 database, and dialogue and communication has been
18 established by a number of centers at EPA, NIEHS, the
19 European Bioinformatics Institute, as well as the National
20 Center for Bioinformation Technology here at the NIH.
21 Therefore, in broad terms, the project objectives
22 at the moment going forward in these specific areas are to
23 establish a common experimental approach, very easily said,
24 but very difficult to achieve.
25 From that and the work that will be done, we wish

1 to establish a firm foundation for the interpretation of
2 such data. I don't think we clearly understand at the
3 moment how to resolve the very complex patterns of genes
4 expressed on various platforms or indeed the multitude of
5 spots that can be generated on a 2D gel.
6 But by assessing the response to various
7 prototypic and well-known chemicals of known biochemical
8 mechanisms perhaps, with known pathological endpoints, we
9 hope to build up a repertoire of data and knowledge that may
10 be shared initially in a public database, and continue,
11 therefore, this public discussion of how this technology can
12 be put to best use.
13 So, I can dispense with that by simply indicating
14 that the next step in the process is to develop more
15 definitive plans whereby we can conduct some experimental
16 work in a collaborative fashion in a multi-laboratory
17 setting whereby these issues can be addressed and the
18 initial collection of data can be initiated.
19 [Slide.]
20 Therefore, we may indeed be able to establish a
21 toxicity database in the fullness of time with well-
22 established, well understood, if not standardized,
23 methodologies, such that we can rely upon such information
24 as we explore new chemicals in the future and attempt to
25 match the responses elicited by them to patterns that may

1 already exist within the database.

2 It is quite refreshing so far that no company
3 participating in this activity has expressed any grave
4 reservation about proprietary issues, so I think this is a
5 project that is on a firm scientific footing with an
6 eagerness to learn and to build our understanding of what
7 this new technology can yield to us.

8 It is quite possible that in the fullness of time,
9 we will get a better understanding of interactions at the
10 level of genes and proteins that could indeed reveal
11 biomarkers. There are people, of course, who will have
12 different applications for this technology, some for the
13 selection of lead compounds from their discovery groups, and
14 therefore they will use perhaps specific biomarkers of
15 efficacious effect, as well as toxic effect in that
16 selection process.

17 There will be others who are interested more in
18 understanding the mechanisms of toxicity that will aid the
19 process of risk assessment, and in time, we may be able to
20 extend all of this knowledge towards man inasmuch as they
21 will be selected biomarkers, whether they be genomic or
22 proteomic in nature, that will enable us to develop more
23 effectively efficacious and safe medicines in humans.

24 The loop may be completed because we can learn
25 from this human experience what are the more relevant

1 biomarkers that we should be using to assess toxicity in
2 animal species, as well.
3 So, conceptually, those are the goals of the
4 project, and that is a very brief account of the status of
5 the project as it stands today.
6 If I may switch gears and at risk of some
7 redundancy, I found Dr. Sistare's presentation to be so very
8 elegant with some very, very clear definitions of concepts
9 and direction, I may be in jeopardy here, nevertheless, I
10 thought I might just share a few reflections on the issue of
11 biomarkers and their utility, both in drug discovery and in
12 development.
13 [Slide.]
14 Many have already reflected on the fact that what
15 we are doing presently is emphasizing very heavily our
16 efforts on hazard identification. In the future, perhaps
17 with the aid of biomarkers, we will be looking more at
18 hazard characterization, understanding mechanisms, and more
19 precise relationships between effect and exposure at the
20 target site of toxicity.
21 Currently, we are somewhat limited in using apical
22 tests that are distant markers of effect, whereas, in the
23 future we may by possibly the assistance of genomic and
24 proteomic methods be able to explore mechanisms at the
25 cellular and molecular level, and create more definitive

1 biomarkers, or at least obtain hints or clues as to what
2 biomarkers might be of utility in the clinical setting if we
3 can authenticate their relationship to a fundamental
4 mechanism of toxicity.
5 Currently, dose metrics that I have chosen for
6 risk assessment purposes are not always closely aligned with
7 pharmacodynamic or biological responses. In the future,
8 this situation is bound to improve with a better
9 understanding of mechanism, and biomarkers might well be a
10 way of rationalizing the selection of dose metrics that will
11 provide a more robust cross-species extrapolation for risk
12 assessment, and so forth.
13 Today, we are forced on occasion to question the
14 predictive value of animal data. I think that in the
15 future, the utility of the use of biomarkers and a better
16 risk assessment will improve this relationship.
17 Indeed, I would contend that perhaps the use of
18 biomarkers to assess efficacy and safety in humans may
19 enable us to predict the response of one human to another
20 rather better than we are able to do today.
21 So, I don't think the fault lies entirely with the
22 animal.
23 [Slide.]
24 I mentioned before the utility of biomarkers in
25 the discovery and development of new pharmaceuticals. I

1 would like to lay less stress on cost savings and time
2 savings, but rather more on the quality of what biomarkers
3 could bring to us. In particular in the selection of
4 superior leads for development, nobody wants to waste time
5 and money deliberately, and thereby reducing the failure
6 rate in development.

7 The failure rate in development is costly enough
8 only in terms of animal life, but occasionally also in terms
9 of human discomfort. Enhancing our understanding of the
10 potential for hazard to occur in patients based on our
11 observations in animals would be a significant step forward,
12 and most importantly, to be able to improve our
13 communication of risk.

14 We conduct at the moment empirical assessments of
15 risk, but our communication of risk, I don't believe is as
16 good as it could be. What is the relevance and the
17 significance of the observation made? It may enable us, of
18 course, to exclude patients who may be particularly at risk
19 of a particular kind of adverse effect.

20 So, overall, it would result in improved risk
21 management both before and after the introduction of a new
22 medicine into the marketplace. The bottom line, therefore,
23 is a more cost effective delivery of medicines to patients
24 in need, and that is why I choose to de-stress, if you will,
25 the commercial implications of the scientific benefit of

1 embarking on a project of this kind. Let us not make false
2 promises of less cost. There may well indeed be greater
3 costs, but far greater value.

4 [Slide.]

5 Based on the remarks that I made in relation to
6 the latter slide, I don't think I need repeat the points on
7 this line.

8 [Slide.]

9 A conceptual view of what a biomarker might be and
10 the different kinds of biomarkers that might be applicable
11 and the different kinds of situations. This is a definition
12 I made up last night. I am not saying it is a good one, I
13 am not saying it is a bad one. I am certainly not saying it
14 is one that you should accept.

15 But I am tempted, however, to ask you to consider
16 biomarkers in the broadest possible context, that they may
17 indeed be biomarkers of imminent or impending toxicity, but
18 they are tolerable for that because the pathologic process
19 which they predict may well be mild in nature, nonfatal, and
20 reversible, and therefore, such a biomarker may well have
21 value and utility even in the human patient.

22 It does not have to signal only a benign event or
23 only a highly desirable pharmacologic response. Our current
24 approach to assessing hazard is to use conventional tests.
25 I referred to them earlier as apical tests, and a couple of

1 examples are given there.

2 The more noble assays, such as the genomic and
3 proteomic approaches may enable us to look at the proximal
4 indicators of biological activity, that is, at the molecular
5 level. We may, in turn, be able to relate those to the
6 apical tests and put greater credibility behind the existing
7 tests that we have at our disposal. It does not mean to say
8 that one has to displace the other.

9 Biomarkers of efficacy, we do not utilize
10 sufficiently currently in our toxicology studies in my
11 opinion. As regards the primary pharmacology, the mechanism
12 of action of a drug, we may be able to assess its intrinsic
13 potency and the differences in specie sensitivity, which are
14 very, very important in risk assessment.

15 It is not always the most sensitive species which
16 should be the worst harbinger of risk to man. So,
17 therefore, some understanding of intrinsic potency and
18 species differences in sensitivity could emerge from having
19 such biomarkers to assess efficacy, as well as toxicity.

20 Secondary pharmacology or nonspecific effects at
21 non-target sites are a cause of concern, and in this case,
22 these biomarkers could tell us something more about the
23 specificity and, more importantly, the selectivity of our
24 drug, and might account for unique species differences, so
25 that is a body of biomarkers that tell us something about

1 specificity, selectivity, and specificity would be extremely
2 important and useful in risk assessment.
3 Dr. Sistare made reference I believe to biomarkers
4 of exposure, and I agree with his definition of it, but
5 another biomarker of exposure is an assessment of changes in
6 endogenous metabolism, as well as exogenous products of
7 metabolism resulting from biotransformation of specific
8 compounds. Those, too, can be useful biomarkers.
9 [Slide.]
10 There has already been discussion about methods.
11 I will not dwell on those. They are listed on the righthand
12 side and for my sins, I omitted PET imaging, but on the
13 left, I have indicated those materials that are currently
14 accessible to us.
15 Access is an issue for the application of certain
16 biomarkers because of the requirement perhaps for being able
17 to extract DNA and protein from tissue itself. Although
18 facile in animals because we can conduct necropsies, it may
19 be possible to undertake biopsies in human subjects.
20 Cells are accessible in peripheral blood and we
21 can also use cell culture from different species in order to
22 assess toxic mechanisms and the definition of biomarkers
23 that may be of use.
24 Biofluids, bronchoalveolar lavage, saliva, serum,
25 and urine are sometimes underutilized for the assessment of

1 biological response modifiers.

2 [Slide.]

3 We have a tendency to be preoccupied with the
4 novel and the new, thinking that there is not innovation in
5 what we do currently. That is not always the case, of
6 course, because here are some examples of biomarkers of
7 hazard that are quite conventional, quite easy to assess -
8 testicular text toxicity may be related to changes in serum
9 testosterone. A number of these, of course, are endocrine
10 biomarkers. There are chemokines and cytokines that would
11 equally apply on this list, and most of those can be applied
12 to man.

13 [Slide.]

14 I have a very simplistic cartoon that is a way of
15 indicating how we might be able to study genes and proteins
16 to assess pharmacological, as well as toxicologic responses.
17 As I said before, we might do this at the cellular level in
18 culture and perhaps obtain appropriate cell types in order
19 to make cross-species comparisons.

20 This type of evaluation would apply equally well
21 in vivo and could be a way of studying the response of genes
22 and proteins to various kinds of stressors and toxicants
23 across species.

24 [Slide.]

25 In a very idealized scenario, I have indicated

1 here dose response in animals and man, very simplistically,
2 not necessarily congruent toxicities of identical type, but
3 nevertheless, one could imagine having a genomic imprint of
4 toxicity, and perhaps spectra derived from magnetic
5 resonance spectroscopy of biofluids, such as urine or blood,
6 and thereby defining these patterns in relation to
7 pharmacology, perhaps efficacy or suprapharmacology and
8 toxicity, and having this understanding of these changes
9 across the dose response curve, being able to extrapolate
10 therefore what are the relationships between these events on
11 the dose response curve in animals to similar events on the
12 dose response curve in humans, and what are the
13 relationships between them within the same species.

14 I refer to that as a molecular therapeutic index,
15 the traditional approach of assessing the dose differential
16 or exposure differential between that which causes toxicity
17 and that which causes an efficacious response.

18 That is our approach today and with the adoption
19 of such biomarkers and a more critical assessment of
20 pharmacological and toxicological responses within the
21 species, we might be able to get a more objective assessment
22 of risk than simply extrapolating as Dr. Collins said this
23 morning, extrapolating a single exposure metric between
24 species without reference to its relevance to the biological
25 event.

at

1 [Slide.]

2 Here is one example where we are often faced with
3 a situation where there appears to be a congruent pattern of
4 response across species, pharmacological and toxicological,
5 and yet we recognize in animal species that there is a
6 significant difference in sensitivity for the effects of the
7 drug.

8 In this particular case, although there is a
9 difference in specie sensitivity, the interval between
10 toxicity and biology in terms of exposure or whatever dose
11 metric you choose to use, is approximately the same.

12 So, the question therefore is where does man
13 reside on this spectrum, is man less sensitive than monkey
14 and more sensitive than dog? I think with the aid of
15 biomarkers we could address some of those questions very
16 carefully by exploration in the clinic, and more relevantly,
17 if we were to use the same set of biomarkers that we use to
18 explore these phenomena in animals, and apply as many of
19 those as possible in the clinical situation, as well.

20 [Slide.]

21 Toxicities and dose response relationships between
22 species don't have to be the same for biomarkers to have
23 utility in the exploration of efficacy and safety. In this
24 particular example, the rat is a species that exhibits four
25 biomarkers in response to basic biology, some pharmacology,

1 some endocrine effects, such as prolactin elevation, and
2 finally, a toxicity, let us say, affecting the kidney.
3 In the monkey, the toxicity may be affecting the
4 liver. Each of these have discrete biomarkers. Man is
5 responsive to the pharmacology, but also has a metabolite
6 which is associated with some toxicity in the monkey, so
7 therefore, you might use biomarker 5 arising from monkey to
8 be a sentinel of toxicity for man, whereas, the appearance
9 of biomarker 3 in man would cause you concern inasmuch as
10 elevation of prolactin is associated with mammary
11 hyperplasia and mammary carcinoma.
12 Similarly, biomarker 5 in monkey may tell you that
13 you are on the dose response curve at a comfortable interval
14 below biomarker 6, which is associated with toxicity. It is
15 not integration and the interpretation of biomarkers that I
16 think is a key to successful risk assessment, not always a
17 simple extrapolation of dose or exposure between species to
18 indicate the risk, but an integration of the two.
19 [Slide.]
20 Here is an example from a specific experience that
21 several of us have had recently in the development of
22 thiazolidinediones, insulin sensitizers.
23 Here, I offer you three classes of biomarker which
24 reflect the pharmacological and toxicological effects of
25 these new class of drug in multiple species in a very

1 congruent fashion albeit at different dose levels with
2 differences in species sensitivity.
3 It ranges from the lefthand side, biomarkers of
4 pharmacologic effect. There is, in the normal animal, not
5 only in the diabetic model of diabetes type 2, there is in
6 the normal animal a reduction in free fatty acids and a
7 reduction in insulin, indicators of insulin sensitization.
8 There is also the pathophysiologic effect on fluid
9 retention causing an increase in plasma volume, which is
10 manifest as a reduction in hematocrit. In this particular
11 case, the reduced hematocrit, a simple measure, is a
12 biomarker of increased plasma volume.
13 Increased plasma volume, we know can produce the
14 functional response of cardiac hypertrophy, which one can
15 assess by MRI, a completely noninvasive technique, which has
16 been illustrated very well here today.
17 So, we have categories of biomarkers that tell us
18 something about dose response relationships and the nature
19 of the response elicited, and from that, we can extrapolate
20 across species and use these biomarkers to indicate where we
21 are on the dose response curve, and from that choose the
22 most appropriate metric for cross-species extrapolation.
23 [Slide.]
24 This is not an example related to any particular
25 drug, but imagine the following scenario, where you may have

at

1 comparable pharmacotoxicologic responses between there
2 species, but the multiple of AUC at the no-toxic effect dose
3 in the animal relative to man is 0.4 in the dog, 5 in the
4 rat, and 10 in the mouse.
5 Yet, the dynamic range of effect for each species
6 is about the same, and the therapeutic ratio in each species
7 is the same if you look at the biomarker that is related to
8 the toxic response and the pharmacologic response within the
9 same species.
10 So, rather than AUC being the best metric for
11 extrapolation in this particular case, it may be that the
12 total systemic dose, milligrams per kilogram or milligram
13 per meter-squared might show the closest correlation between
14 effect and exposure in this kind of situation, and the
15 interpretation of biomarkers across the dose response for
16 species used in toxicology and including man eventually is a
17 very good way of getting a better understanding of what is
18 the appropriate way of expressing risk for humans based on
19 animal data.
20 Over time, we hope that the use of biomarkers, of
21 course, will make man independent of the animal data
22 inasmuch as those relationships will be established within
23 the patient population.
24 [Slide.]
25 At the moment, here is another situation where we

1 may have a series of events as you ascend the dose response
2 curve, ranging from pharmacologic activity, relatively
3 benign, perhaps rodent specific effects, evidence of renal
4 toxicity, and at the worst end of the spectrum, CNS toxicity
5 and teratogenicity.

6 What we tend to do at the present time is to take
7 a therapeutic ratio, either based on exposure or dose,
8 whatever is the appropriate way, between toxicity and
9 pharmacology, but we may do this in stages. We may do this
10 at this end of the dose response curve, or here, or here.

11 We tend to be preoccupied with those ratios.

12 [Slide.]

13 Perhaps what we should focus on in the future with
14 the aid of biomarkers is to establish how far below the
15 toxic level are we, what is the interval, what is the
16 margin. That's interval 1. Interval 2 would tell us that
17 we are comfortably below the toxic level, and biomarkers may
18 therefore be a very, very useful signal for telling us where
19 are we in relation to the toxic threshold, how far below it
20 are we, rather than the other way around of trying to
21 calculate multiples that tell us how far above we are the
22 desirable pharmacologic effect.

23 [Slide.]

24 A couple of quick examples to finish. Here is a
25 study done on a favorite compound of mine that I worked on

1 20 years ago, dopaminergic agonist called fenoldopam, which
2 produces some of those famous arterial lesions that Dr.
3 Sistare alluded to in one of his slides.
4 This was an attempt to try and better understand
5 what biomarkers we could apply to the assessment of arterial
6 toxicity. In this particular case, I am showing you the
7 levels of von Willebrand factor, a component of endothelial
8 cells in rats administered this compound.
9 You do find that when administering drug, you have
10 higher levels of von Willebrand factor being produced which
11 decline after a single dose by 24 hours, but what you also
12 notice is that in the control animals there is also an
13 increase of von Willebrand factor.
14 In this particular case, there was a greater
15 increase in von Willebrand factor in the early stages post-
16 dosing when the lesions had not actually appeared. So,
17 there was a temporal disconnect and also a background effect
18 on von Willebrand factor in this case, which makes you
19 wonder whether it was, in fact, released as an acute pro-
20 inflammatory factor and was not a reliable biomarker of
21 endothelial damage.
22 [Slide.]
23 I may have referred earlier to the fact that we
24 may have tissue biomarkers, as well as biomarkers in fluid.
25 We were interested in differentiating the type of cardiac

1 hypertrophy we had with a drug under development, and three
2 models were used here, one that causes volume expansion and
3 increase preload, one which has a trophic effect, which is
4 T3, I believe, volume was minoxidil, and pressure was
5 spontaneous hypertension in the rat.
6 In each case, there is an increase in cardiac
7 weight, a significant increase reflecting hypertrophy.
8 [Slide.]
9 Assessment of left ventricular troponin-T showed
10 us the following pattern of response, a decrease in the
11 volume expanded case, an increase in the trophic case, and
12 an increased left ventricular pressure.
13 This is a predictable response of myocytes when
14 subject to increased stress caused by increased preload and
15 increased venous return, and it was this response which we
16 considered important in the differentiation of the cardiac
17 hypertrophy that we had seen with the drug under
18 development.
19 Hence, a tissue biomarker gives us a very
20 important understanding of a mechanism, and from that we are
21 able to assess what is the relevance of the same
22 pathophysiologic effects then in man.
23 [Slide.]
24 Therefore, I conclude with some questions, perhaps
25 for discussion by members of the committee that they might

at

1 consider. There is a question: When is it best to deploy
2 biomarker in the evaluation of new chemical entities? I
3 will not attempt to answer it, but I think it is a very
4 important answer in the context of how do we make
5 interpretations of these data very early in the discovery
6 development process.

7 Do they become the badge of honor and the badge of
8 safety, or do they become the stigma that forever will
9 plague that product as it moves through development?

10 What are the implications of an effect on
11 biomarkers whose relevance in predicting hazard to humans is
12 not yet known? There is always an unknown element when you
13 are breaking new ground, and I think that will call for a
14 great deal of intellectual discussion and tolerance and
15 collegial exchange.

16 What is the most effective use of biomarkers in
17 the course of clinical development, is it to be focused on
18 selected populations as in the intense evaluation of small
19 numbers in clinical pharmacology, or is to be more of a
20 survey tool to look for adverse effect in the general
21 population, 1,000 patients?

22 There are cost implications and there are
23 implications of interpretation, as well.

24 As Dr. Sistare said, what steps must be taken to
25 qualify the use of biomarkers to determine the safety of a

at

1 new clinical entity in humans, how long will it take, how
2 much proof do we require that it is valid and useful, and
3 what corroboration of that would be required.

4 I think that would be a very fruitful area of
5 discussion between scientists within the center at FDA and
6 those of us who are engaged in drug discovery from an early
7 stage in the process. It would be a very welcome dialogue
8 and a very useful way of gaining confidence in the value and
9 utility of biomarkers by means of collaboration and
10 corroboration of the observations that we make.

11 Thank you very much for the opportunity to share
12 those ideas.

13 DR. DOULL: Since we made up a little time in our
14 public disclosure, I think we will just go ahead and proceed
15 if that's all right with you, Jack.

16 Dr. Reynolds is going to talk about efficient
17 advancement to clinical trials.

18 **Efficient Advancement to Clinical Trials**

19 **Introduction**

20 **Jack Reynolds, D.V.M.**

21 DR. REYNOLDS: I am going to introduce the topic
22 of early entry into clinical trials to shed some light on
23 what I think can be important for us, what are some of the
24 benefits of early entry into clinical trials.

25 I don't intend to reiterate the importance of all

at

1 the new technologies, but rather to provide you what I think
2 are some of the challenges for early entry.
3 [Slide.]
4 Again, just to reemphasize what one of the
5 committee objectives around some of this is to position new
6 science of the emerging technologies as a basis for
7 regulatory guidance.
8 I think we have the opportunity through this
9 endeavor to facilitate, not only drug discovery, but
10 facilitate drug development, as well, importantly, to reduce
11 the drug development time, and I think a benefit that many
12 of us don't think about is to both retain and build
13 confidence that we, as a regulated industry and regulators,
14 are capable of developing both safe and effective drugs in
15 capturing the benefits of these new technologies.
16 [Slide.]
17 I don't need to go over this in much detail, but I
18 did want to kind of put in perspective what is changing in
19 the drug discovery and development area. A lot of us had
20 heard about genomics, proteomics. We have things we refer
21 to as high throughput screening and combinatorial chemistry.
22 All of that has resulted in a remarkable increase
23 in the number of potentially acceptable new clinical
24 entities for development, and it is important that we focus
25 on those numbers of new clinical entities. In there,

at

1 probably lies a better drug that we can identify by using
2 new technologies than if we were to just go ahead and use
3 the older, more conventional technologies.
4 So, I think we need to take advantage of the
5 increased number of potential new chemical entities and find
6 the best one in that number, large number that we can choose
7 from.
8 I think it is important to realize also that the
9 diseases that we are trying to find treatments or cures for
10 really are in most cases chronic diseases. They require
11 extended development times especially around ways to
12 demonstrate efficacy, but also in just being able to
13 demonstrate effects of the drugs on these chronic diseases.
14 This requires larger clinical trials, which
15 increases both the cost and the time, and in some cases
16 there is even a competition for patients to participate in
17 these clinical trials.
18 Because these are complex disease states that
19 require longer clinical trials, more complex clinical
20 trials, it is one of the main stimuli that we see for
21 consolidation in the pharmaceutical industry that the cost
22 and the resources required to develop drugs for these
23 complex diseases is forever increasing and is almost to the
24 point where many people can't afford to be in the business.
25 [Slide.]

1 So, we do have a burgeoning number of precisely
2 targeted potential therapies and speaking from the industry
3 side, we have to realize that we cannot build our facilities
4 fast enough, we cannot train and hire specialists fast
5 enough, we can't synthesize the requisite material to do
6 these trials fast enough, and we can't expand the clinical
7 trials broad enough to meet this challenge of trying to
8 identify drugs for these diseases.
9 So, I think one of the things this committee is
10 trying to do is to really take full advantage of our
11 improved decisionmaking and enhancing technologies, which I
12 think Dr. Morgan did a very good job of illustrating the
13 potential there, I think we need to take advantage of those
14 new technologies and apply them to evolving new paradigms,
15 so we can make better assessments.
16 [Slide.]
17 So, part of what we would say for new paradigms is
18 that I think that if we were to use the conventional methods
19 of trying to get a potential new chemical entity into
20 clinical development, to try to find data or to generate
21 data in the species of choice there, I think you can see
22 there is horrendous hurdles if we try to do that in a
23 conventional way.
24 So, I think again these new technologies do
25 provide opportunities for efficiency in both time, in terms

1 of the quality of the candidates that we would derive, and I
2 think improve our ways to establish safety.
3 I would also echo what I heard one, if not more,
4 persons say that in many cases we are not talking about
5 improving the cost or reducing the cost of development, but
6 really these three factors here.
7 So, just some of the things, and I think other
8 speakers have touched on them, as well. If we can move into
9 clinical assessments quicker using less resources upfront, I
10 think we can achieve a proof of concept sooner. That is not
11 necessarily a proof of concept that the NCE that we are
12 trying to develop will cure the disease, but at least it has
13 an impact on the mechanism or the receptor or the enzyme
14 that we are trying to target.
15 I think it also allows us a way to keep up with
16 the pace of discovery, to validate some of the models that
17 our discovery folks are using to try to uncover new
18 therapies. One can talk about the ability to go into
19 clinical trials and select new chemical entities based on
20 human data.
21 Some folks have coined the term "clinical
22 discovery" to reflect that. I think importantly, though,
23 what we are intending to do here is to get more beneficial
24 therapies to patients much sooner, and I think that one of
25 the things this committee is trying to do in its partnership

with academia, with industry, and the regulatory agency is to demonstrate our leadership in bringing these new commercial innovations to the patients that need them.

[Slide.]

I think one of the challenges to facilitating early entry into clinical trials is at least from the industry side, it is a multidisciplinary approach. No one major stakeholder in the development enterprise and the pharmaceutical industry really owns this, and all parties have to come to the table, and I think that that is what this committee is trying to emulate in some respects.

But I think the three main areas that we need to discuss and to help understand is what are the appropriate preclinical studies, and especially toxicology studies, that are needed to underpin what we would see as low dose, single dose, or even multiple dose human studies.

I think, as Dr. DeGeorge will talk about, maybe there are things we can do more efficiently to just underpin or underwrite clinical trials in general at a very early stage, and not limit it to single dose or low dose studies.

I think importantly, though, and what Dr. Sheinin will address in a little while, is that we also need to come to an agreement on what are the appropriate drug substance specifications and qualifications for these materials.

If we have to wait for this early entry into

at

1 clinical trials for a complete characterization of the
2 material, as we now do for even IND's, but more importantly
3 as we approach registration stages, this is going to
4 encumber the process and make it virtually impossible to
5 have an efficient early and easy entry into human subjects.
6 So, I think we need to agree on a term that we
7 have thrown out, we need to agree on what would be the
8 characteristics of minimally characterized drug substance.
9 I think also there is considerable confusion on
10 the part of our clinical colleagues, and one of the terms
11 that has been used predominantly in this area is screening
12 IND, but aside from that, I think there is a lack of clarity
13 around really what are the opportunities and some of the
14 things that we can learn from single dose or low dose human
15 studies.
16 I think one of the things that we can do in this
17 committee and its activities is to clarify and articulate
18 the potential value and benefits of an early clinical
19 program, and I think you have seen a lot of that today in
20 terms of noninvasive technologies and in areas of biomarkers
21 where I think there is tremendous opportunity to demonstrate
22 value of these.
23 So, I think we need to work hard to understand the
24 clinical opportunities that can be utilized or that can be
25 developed.

1 I heard someone mention earlier, I think because
2 there are very broad subjects with wide and varying
3 applications, that we need to focus on a number of examples,
4 relatively simple examples hopefully, and communicate those
5 to our stakeholders, so they can use as examples how they
6 can build their own programs.
7 [Slide.]
8 So, again, I would close by saying that one of the
9 objectives of this committee is to evaluate the potential
10 applications of new technology tools for application in
11 nonclinical and early clinical trials, and one of the things
12 we need to do is to come to some agreement or understanding
13 on what are the underpinnings, the preclinical underpinnings
14 especially of those early clinical trials.
15 That is all I have to say.
16 DR. DOULL: Thank you, Dr. Reynolds.
17 Why don't we move on then to Dr. DeGeorge.
18 **Safety Issues**
19 **Joseph DeGeorge, Ph.D.**
20 DR. DeGEORGE: Thank you and I appreciate the
21 opportunity to be here and talk a little bit about trying to
22 facilitate drug development from the regulatory perspective.
23 [Slide.]
24 What I am going to do today is really talk about
25 not so much particular models that you have heard about

1 earlier, but give a more general overview about practices
2 that have been going on within the Center for Drugs, areas
3 where we have spoken out, that we might be able to make some
4 improvements in types of assays, and raising some
5 discussions about where we have made changes already, what
6 has been the result of that, and maybe investigating that,
7 as well, as an area for further investigation or data
8 collection by this committee.

9 [Slide.]

10 What I am going to do is I am going to focus the
11 first part talking about our current practice in the use of
12 single dose studies and screening INDs in early clinical
13 trials, and then I am going to talk about some issues
14 generally related to new toxicology study designs, which I
15 think that this whole committee is thinking about, and then
16 I am going to talk about one area where we made some
17 regulatory policy changes about five years ago and where we
18 don't really have feedback in terms of what the outcome of
19 that has been on the drug development process.

20 [Slide.]

21 The first thing I want to talk about is this
22 notion of single dose toxicology studies to support single
23 dose trials in humans. There are two or three datasets that
24 sort of bring this to mind.

25 The first actually comes from oncology drugs where

1 basically, the studies that support entering into humans are
2 pharmacodynamic studies, that the drug actually does
3 something to a tumor, toxicology studies that mimic the
4 initial clinical protocol by route and mode and frequency of
5 administration, that we, in fact, have in these studies
6 histopathology primarily from one species most of the time,
7 not from two species, and that we often then use the second
8 species as a "safe passage" model.
9 Now, I am really talking mainly about cytotoxic
10 types of drugs, but you can see it is a fairly limited
11 dataset that one collects.
12 [Slide.]
13 With that dataset--and this is again talking about
14 single dose studies--usually, one has to recognize that the
15 clinical trial Phase I study is generally a 1 to 5 dose
16 study anyway, once every 28 days, and what I am talking
17 about is supporting a single dose once every 28 days using
18 this dataset, particularly from single dose studies.
19 We are talking about patients who have advanced
20 stage disease and therefore they are willing to take some of
21 these risks because they have exhausted many of their
22 therapeutic options.
23 Initially, we actually start in these clinical
24 trials with 1/10th of a severely toxic dose that is
25 exhibited in the animal studies if that dose undergoes safe

1 passage in the non-rodent model, then, that becomes the
2 starting dose for the clinical trial in these cancer
3 subjects.
4 Now, with this dataset, with this very limited
5 dataset, pharmacology, single dose toxicology in two
6 species, histopathology in only one species, we have not
7 identified cases where we think at least initial dose is
8 unsafe based on that dataset.
9 Now, granted, one, we are talking about single
10 doses and then repeating a cycle later on after recovery,
11 but we are also talking about areas where there is a
12 significant degree of toxicity that is accepted as part of
13 that clinical development. But that is one area where we
14 think we got information that allowed us to say, yes, we can
15 learn a lot from even single dose studies to support single
16 dose entry into humans.
17 [Slide.]
18 Another area where we collected this kind of data
19 is a totally different area, and that is in antibiotic drugs
20 where they had allowed as part of the historical practice
21 within the FDA, single dose toxicology studies for single
22 dose clinical studies where the major effort was to, in
23 fact, understand bioavailability and whether or not the drug
24 was bioavailable.
25 This was based on a process using very low initial

1 doses in humans compared to the animal studies. We are not
2 talking about severely toxic doses. We are talking about
3 fractions of a no effect level in the animal studies.
4 In this process, again, in these early studies at
5 the very low doses, there were not any experiences of
6 increased adverse events over what would be expected from
7 the more standard development plans.
8 There is also a little bit of indication
9 independent experience, and in these cases where we had that
10 data, there were again no cases where we could point to and
11 say this was unsafe or this was right up next to the level
12 where we might run into trouble in a clinical trial, but we
13 certainly found that safety pharmacology studies in that
14 setting have contributed to the kinds of toxicities that we
15 are overly interested in or importantly interested in, in
16 regard to those single dose exposures in normal volunteers.
17 These are the considerations that affect this
18 issue of single-dose toxicology studies has been kicked
19 about in the literature as well. Monroe and Mehta actually
20 first published on this a proposal to allow single-dose
21 studies to support single-dose clinical trials.
22 There was a commentary by a number of individuals
23 from FDA on this approach and there has been another paper
24 talking about ways in which this may be useful in certain
25 settings. Everyone agreed in principle, at least these

1 individuals all agreed in principle that it was a safe
2 practice, that one could use it, but were not necessarily in
3 total agreement in terms of what kinds of toxicology, safety
4 pharmacology and other information might be necessary to do
5 this in a particular manner.
6 For example, we may have a different view within
7 FDA about what the histopathology dataset should include
8 versus others who had talked about this. One of the
9 important points was that, actually the application, the
10 utility of having single-dose human data is really in the
11 eye of the beholder. Some groups will say, "I can't learn
12 anything from a single-dose study in humans." Other groups
13 will say, "I can learn as much as I need to know following a
14 single-dose from humans to help me make a decision about
15 advancing this product further."
16 We actually, partly as a result of this discussion
17 in the literature, wrote a Federal Register notice that
18 talked about what kinds of single-dose toxicity studies--
19 first of all, it talked about single-dose toxicity studies,
20 in general, but talked about if a single-dose toxicology
21 study was to be the primary toxicologic dataset to support
22 human trials, what that should include. And that was
23 published.
24 Interestingly, the ICH has looked at this issue
25 and, in fact, notes that this single-dose for single-dose,

1 at least at the time that the document was written, was
2 unique to the FDA but I have since come to learn that that
3 is not the case, that now some European countries are, in
4 fact, allowing that as part of the development plans.
5 [Slide.]
6 When we talk about single-dose for single-dose,
7 what are really talking about in terms of a toxicology study
8 design. We are talking about two species, rodent and non-
9 rodent. We are talking about dose ranges that go from the
10 non-toxic up through significant toxicity to try to fully
11 evaluate the toxicology plan with clinical observations,
12 with clinical chemistry or clinical pathology as part of the
13 standard, with gross and microscopic evaluation of all the
14 major organs and, in fact, doing this at two different time
15 points, one at peak effect and one at some later time point
16 to assess, in fact, that recovery has actually occurred in
17 the toxicity insult or at least to get an understanding of
18 whether or not the toxicity is reversible and to what extent
19 it is reversible.
20 If the study is to support pharmacokinetics in
21 humans, which is one of the uses of this data, this study
22 design, then, in fact, the animal studies should include
23 pharmacokinetic assessments as part of that development and
24 testing.
25 Bioavailability data on the product can influence

1 whether or not you need to do multiple routes of
2 administration. If the drug is basically not bioavailable
3 by the oral route or only poorly or only variably
4 bioavailable, it is probably something you need to know
5 about in terms of it toxicologic profile and may necessitate
6 needing the IV route studied as well.
7 It talks about the fact that we would still like
8 to support this further with pharmacodynamic safety studies,
9 or safety pharmacology studies.
10 [Slide.]
11 How has this been used? It has been used in
12 initial clinical trials for single-dose indications. That
13 is clearly a relevant use of this design. It has been used
14 to develop and evaluate new formulations of drug products to
15 try to understand is this a change which is going to improve
16 our product's profile.
17 It has been used in cases where there are
18 difficult drug-synthesis concerns where the amounts of drug
19 available to support one of these single-dose studies,
20 particularly in the non-rodent species, can be considerably
21 less when using a single-dose study design, 14 times less.
22 It can be used as a proof-of-concept. A drug is
23 not going to ever be used for that indication by the IV
24 route, for example. It has poor bioavailability, but
25 someone is interested in knowing whether or not the receptor

1 sites are, in fact, going to be of a nature that they would
2 like to develop, spend the effort, to make a bioavailable
3 drug part of those same receptors.

4 It has been used to support PK studies and it has
5 also been used to support screening INDs. But a screening
6 IND, and I will talk about this more in a moment, is not
7 equivalent to single-dose studies in animals and for single-
8 dose studies in humans. They are different beings.

9 In fact, there is no formal definition of a
10 screening IND. Jack mentioned it, but we have allowed them
11 on a case-by-case basis and I will talk a bit about those in
12 a moment.

13 A screening IND is basically the study of a number
14 of related, pharmacologically related and chemically
15 related, compounds to determine whether or not any one of
16 those has a better human profile to actually facilitate the
17 development of a single one or maybe two of those out of a
18 group.

19 [Slide.]

20 That may be something one can learn from a single-
21 dose study but, as this data shows, clearly, the conduct of
22 our expanded acute toxicology studies is not the same as
23 screening IND studies. For example, in oncology, we get a
24 lot of these expanded acute studies because many of the
25 indications are expanded acute, but we have no screening

1 INDs filed to date, or during this course of time that I
2 looked at, in the Oncology Division.
3 In the Imaging Division, a lot of expanded acute
4 studies have been submitted but they have only received
5 three requests for screening INDs. You can see here that
6 there is a fairly wide range of these expanded acute studies
7 to facilitate early entry into humans. I can assume that
8 these are often for single-dose studies in humans. I don't
9 know the details on whether or not they were part of a
10 larger package or not.
11 But, certainly, they were done across therapeutic
12 areas as have been screening INDs, generally speaking.
13 [Slide.]
14 This looks at the same data in a slightly
15 different manner and that is the total number of expanded
16 acute studies that we had had during this--I think this was
17 a one-year time period--was greater than 260, 38 of these,
18 only, though, outside of the oncology and the imaging area.
19 The single-dose studies, for example, though, for
20 single-dose were, again, primarily in the oncology area
21 although non-oncology, non-imaging, there were still 22 of
22 these studied in various clinical indications.
23 We had 18 proposed INDs, screening INDs, or pre-
24 IND meetings. That is another opportunity to have a
25 discussion before one completes a data package to determine

1 whether or not this is going to be a fruitful approach to
2 drug development. We have had 18 of those, 15 in non-
3 oncology and 12 of those, in fact, were accepted by the
4 agency.

5 So when approached, we have had a reasonable track
6 record in accepting these approaches but, clearly, it does
7 require some discussion.

8 [Slide.]

9 So, to summarize the issue of our experience with
10 screening INDs and this notion of early clinical data to
11 help support larger development plans, one first has to make
12 the point that the single-dose study for single-dose in
13 humans is not a screening IND. They are different concepts,
14 and sometimes this gets confused in discussions.

15 The expanded acute studies for single-dose and
16 single-dose tend to actually be done for oncologic drugs in
17 imaging agents largely because that is often the way they
18 are going to be used clinically in the setting of single-
19 dose weight, maybe never again, maybe a month later if it is
20 oncology.

21 The designs have been accepted and proposed for
22 almost all therapeutic areas within the center. They are
23 broadly used, but this broader use, in fact, has not
24 resulted in any increased adverse events and, although we
25 don't have formal guidance on a screening IND approach, it

1 is largely a case-by-case assessment.

2 There are a few, enough, of these at this point in
3 time that we can handle them through that approach and they
4 have been accepted and allowed.

5 [Slide.]

6 Now to talk about some of the issues--that was one
7 of the topics I was asked to speak about here but I thought
8 it was important to talk about, from the regulatory
9 perspective, what are some of the issues in terms of current
10 toxicology study designs and changing those designs to
11 incorporate some of these newer methods.

12 First of all, one has to understand that the
13 available guidance on specific study designs, even what
14 endpoints are to be looked at, really, largely, are
15 international documents or follow international documents,
16 the OECD guidances. FDA does not put out a specific--at
17 least with the Center for Drugs, does not have specific
18 guidance that says, "These are all the specific endpoints
19 which must be assessed as part of any particular toxicology
20 study."

21 So one could clearly ask the question as to
22 whether or not the study designs which are reasonable for
23 environmental exposures, for pesticides, for various kinds
24 of chemicals, are those the best designs that could be used
25 to facilitate drug development or are there ways that we can

1 customize these protocols that are more focused towards drug
2 development.
3 We do do this in some specific cases when a
4 company comes in during a pre-IND discussion, for example,
5 they can say, "We don't want to do this part of the
6 assessment. We would prefer to do this assessment,
7 instead," and if that assessment, in fact, meets the
8 objectives of the study, we will usually accept that
9 approach.
10 So, in terms of what histopathology, what organ
11 systems, what is being looked at, how it is being looked at,
12 we often have discussions about that. Using some of these
13 newer methods as part of an assessment is probably within
14 the realm of our current experience. But it is important to
15 actually get some agreement before one goes down that path
16 of trying novel approaches.
17 [Slide.]
18 There is another issue in terms of pharmaceutical
19 development that is particularly relevant from the non-
20 clinical aspect and that is that we actually have--I use
21 this word with some trepidation--a tiered regulatory
22 dependency. That is not that you get an answer in this
23 study design and then you have to go on and do this study
24 design and you have to make it true.
25 What I am talking about is we have a tiered

1 dependency on the datasets. For example, if you are talking
2 about reproductive toxicology studies, we get very few
3 studies that address that particular issue specifically,
4 that endpoint, such as teratology.
5 If you are talking about general toxicology
6 endpoints, we get two-week studies, one-month studies,
7 three-month studies, six-month studies and one-year studies
8 in two species. So, clearly, any one of those studies is
9 not the entirety of the dataset for assessing a toxic
10 endpoint.
11 And so, within that framework, one can look at are
12 there ways to fit in some of these novel approaches into
13 that area where we actually have a multiple layer of
14 assessments where we can look across the various study
15 designs.
16 So one has to keep in mind that we can use
17 studies, particularly new methods, as either the
18 supplementation to existing methods that they can partially
19 replace methods where we actually have multiple assessments
20 but not a lot, or are we talking about full replacement and
21 giving up entirely an alternative method.
22 When you consider that, that will actually drive
23 the type of information that we are going to need before we
24 are going to be able to say that this is an appropriate
25 approach.

1 I think we also have to keep in mind, when talking
2 about changing study designs, what are the areas where we
3 would like to focus on. Where is the best value? Are we
4 talking about focussing on areas where we need improvements
5 that our current systems don't seem to be doing as well as
6 they may be; as Frank pointed out, liver toxicity, perhaps
7 you could do better at identifying liver toxicity as
8 clinically relevant than what we currently do.
9 Are we talking about new issues? Are we talking
10 about what kinds of studies or what types of endpoints or
11 how would we assess the potential for injury to pediatric
12 subjects. Are we talking about new study designs? Are we
13 talking about different endpoints that could address this
14 area which is a new issue or photocarcinogenicity testing
15 which is a more novel issue of importance?
16 Or are we talking about looking at the various new
17 tools and saying, "How can we use this tool?" Those are
18 different approaches to how you think about changing designs
19 in current toxicology studies.
20 I have up here the word "validation" and I have to
21 agree with Gwyn on this that I don't like to use that word
22 because I think it is very difficult to actually do
23 validation in toxicology. One can characterize toxicology
24 finding results. It is difficult to figure out what the
25 validation standard is going to be, but we have to recognize

1 we are going to try to validate or characterize to
2 understand the characteristics of the response when we are
3 designing these new studies.
4 Clearly, to address these questions, we need to
5 have cooperative research. FDA does not have the resources
6 to do this. Industry does not have the resources to do this
7 on its own and get the methods widely disseminated and
8 widely used, so it really does require a cooperative effort.
9 [Slide.]
10 Now to the last topic, and that is the notion of
11 where we have actually looked at, what it is necessary for
12 the agency to have in terms of supporting initial clinical
13 trials from a regulatory perspective, not from a toxicology
14 perspective, per se.
15 There are three documents that talk about what
16 kinds of study and what kinds of data need to be available
17 as part of an IND. There is the N3 ICH document on non-
18 clinical testing. There is the Code of Federal Regulations
19 and there is a guidance for industry on the content and
20 format of the investigation of new drug applications for
21 drugs and biologic products, about technology-derived
22 products.
23 [Slide.]
24 The ICH document is an international standard so
25 one has to be very careful how we approach this issue

1 because it is not just FDA, but it is the international
2 regulatory body that has to be able to use these various
3 methods that may or may not be proposed because, otherwise,
4 one can develop a drug for the U.S. and may have to repeat
5 all those studies that one thought one was saving to go
6 market the drug in Europe or in Japan.
7 But, for phase, this document is an international
8 standard. It talks about what is needed primarily for
9 phase I, phase II, phase III. I am going to focus on phase
10 I because that is really the facilitation of the drug entry.
11 It talks about meeting safety pharmacology studies
12 on vital functions; exposure data in animals may or may not
13 be available, it says; local tolerance studies by the
14 relevant route but that could be part of other study
15 designs, assessing genotoxicity in vitro; having acute
16 toxicity data unless that information can be gathered from
17 other data; and having repeat-dose toxicity studies of a
18 minimum of two to four weeks in two mammalian species one of
19 which is non-rodent.
20 But that is pretty general. It doesn't say
21 histopathology. It doesn't rule out MRM.
22 [Slide.]
23 The Code of Federal Regulations is actually even
24 more--I am just going to talk about the non-clinical parts--
25 it is even more general. It just says you have to have