FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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1 P R O C E E D I N G S

2 (1:04 p.m.)

3 DR. SANTANA: If everyone could please take
4 their seats and we'll go ahead and get started.
5 This is the first meeting of the Pediatric
6 Subcommittee on oncology drugs. This subcommittee was
7 formed in the hopes of providing focused advice to the FDA
8 regarding issues in pediatric oncology, and this is the
9 first time that we officially meet. Am I correct, Steve?
10 DR. HIRSCHFELD: Correct.
11 DR. SANTANA: So, it's quite an honor for all
12 of us who are in this room today to have the inaugural
13 meeting.
14 Those are my opening remarks. We'll go ahead
15 and get started. Everyone around the table, please
16 introduce yourself by your name, your affiliation, and your
17 area of expertise using one of the microphones. If we
18 could get started on the left-hand side with Frank.
19 DR. BALIS: I'm Frank Balis at the Pediatric
20 Oncology Branch of the National Cancer Institute and by
21 training a pediatric oncologist also interested in
22 pharmacology.
23 DR. SMITH: Malcolm Smith at the Cancer Therapy
24 Evaluation Program and a pediatric oncologist.
25 DR. BURGER: Peter Burger. I'm a

1 neuropathologist at Johns Hopkins.

2 DR. GOLUB: I'm Todd Golub from the Department

3 of Pediatric Oncology at the Dana-Farber and also Director

4 of the Cancer Genomics Program at the Whitehead Genome

5 Center.

6 DR. COHN: I'm Sue Cohn. I'm a pediatric

7 oncologist at Children's Memorial Hospital in Chicago.

8 DR. PARHAM: I'm David Parham. I'm a pediatric

9 pathologist at Arkansas Children's Hospital.

10 DR. BOYETT: James Boyett. I'm a

11 biostatistician from St. Jude Children's Research Hospital.

12 DR. SANTANA: I'm Victor Santana. I'm a

13 pediatric oncologist from St. Jude Children's Research

14 Hospital in Memphis, Tennessee.

15 DR. TEMPLETON-SOMERS: Karen Somers. I'm the

16 Executive Secretary to the Oncologic Drugs Advisory

17 Committee, FDA.

18 DR. FRIEDMAN: I'm Henry Friedman. I'm a

19 pediatric oncologist from the Brain Tumor Center at Duke.

20 I'm interested in both childhood and adult brain tumors.

21 MS. ETTINGER: I'm Alice Ettinger, and I'm a

22 pediatric nurse practitioner from New Brunswick, New

23 Jersey, and the President of the Association of Pediatric

24 Oncology Nurses.

25 DR. FINKELSTEIN: I'm Jerry Finkelstein. I'm a

1 pediatric oncologist from Long Beach, California, and I
2 chair hematology/oncology for the American Academy of
3 Pediatrics.
4 DR. PRZEPIORKA: Donna Przepiorka, cell and
5 gene therapy, Baylor College of Medicine, Houston.
6 DR. SHAPIRO: I'm Alla Shapiro, pediatric
7 oncologist, and work with the FDA Division of Oncology Drug
8 Products.
9 DR. DAGHER: I'm Ramzi Dagher. I'm a pediatric
10 oncologist at the FDA also in the Division of Oncology Drug
11 Products.
12 DR. HIRSCHFELD: Steven Hirschfeld, pediatric
13 oncologist, FDA, Division of Oncology Drug Products.
14 DR. PAZDUR: Richard Pazdur, Division Director,
15 Division of Oncology Drug Products, CDER.
16 DR. REYNOLDS: Pat Reynolds. I'm from
17 Children's Hospital, Los Angeles.
18 DR. SANTANA: Thank you.
19 The next item on the agenda is the conflict of
20 interest. Karen?
21 DR. TEMPLETON-SOMERS: The following
22 announcement addresses the issue of conflict of interest
23 with regard to this meeting and is made a part of the
24 record to preclude even the appearance of such at this
25 meeting.

1 Based on the submitted agenda for the meeting
2 and all financial interests reported by the committee
3 participants, it has been determined that since the issues
4 to be discussed by the subcommittee will not have a unique
5 impact on any particular firm or product, but rather may
6 have widespread implications to all similar products, in
7 accordance with 18 U.S.C. 208(b), general matters waivers
8 have been granted to each special government employee
9 participating in today's meeting.
10 A copy of this waiver statement may be obtained
11 by submitting a written request to the agency's Freedom of
12 Information Office, room 12A-30 of the Parklawn Building.
13 In the event that the discussions involve any
14 other products or firms not already on the agenda for which
15 an FDA participant has a financial interest, the
16 participants are aware of the need to exclude themselves
17 from such involvement and their exclusion will be noted for
18 the record.
19 With respect to all other participants, we ask
20 in the interest of fairness that they address any current
21 or previous financial involvement with any firm whose
22 products they may wish to comment upon.
23 Thank you.
24 DR. SANTANA: Thanks, Karen.
25 We have some time for the open public hearing.

1 Nobody has registered to make any comments, but if there is
2 anybody in the audience that wishes to make any comments,
3 this is the opportunity to do so.
4 (No response.)
5 DR. SANTANA: If there are no comments from the
6 audience, we'll go ahead and get started. Steve Hirschfeld
7 will speak to the group first to try to set the platform of
8 the issues that we're being challenged with this afternoon.
9 I have to notify the committee members and the
10 audience that, unfortunately, Michelle LeBeau is stuck
11 because of airplane problems in Chicago, so her
12 presentation will not occur and we'll just move down the
13 agenda as outlined in your package.
14 Steve?
15 DR. HIRSCHFELD: Thank you. I want to welcome
16 everyone too. This is enormously exciting to initiate a
17 new process, and we hope that with this committee, we can
18 not only advise the FDA but help move the field of
19 pediatric oncology forward in several ways drawing on the
20 expertise of this committee. I'll note that the
21 composition of the committee may change from time to time
22 to address particular issues.
23 But the broad issue at hand for this afternoon
24 is the issue of extrapolating experience from adult
25 oncology data to pediatric data. The background for all of

1 us to be aware of is that in 1994 the FDA issued a
2 regulation which was known as the 1994 Pediatric Rule, and
3 that established the regulatory principle of extrapolating
4 adult efficacy data to pediatric populations if the disease
5 and the mode of action of the drug treating that disease
6 are sufficiently similar.
7 In 1998, that rule was amended so it became a
8 mandate. So, if the conditions of the 1994 Pediatric Rule
9 are met, then it is imperative that the development program
10 of a drug for adults include pediatric studies.
11 What we'd like to examine today is the
12 application of this rule to pediatric oncology. At first
13 glance, that might seem difficult because we were all
14 trained -- and most of the people at the table are trained
15 as pediatric oncologists, although not everyone -- that
16 pediatric tumors are different than adult tumors, and the
17 applicability of a rule which would ask people to do
18 studies on the basis of similarities between adult and
19 pediatric tumors might seem not to apply at all. But there
20 has been in the recent past, and we anticipate in the near
21 and continuing future, data which asks us, I think, to
22 reexamine our assumptions and our thinking about
23 categorizing tumors and describing tumors.
24 What we will do for the rest of the afternoon
25 is, first of all, we have a series of very distinguished

1 expert speakers who will discuss with us some of the
2 upcoming or established techniques for describing tumors.
3 Following that, we will have then a discussion here on the
4 committee and draw on the counsel of our expert panelists
5 to see if we can generate some principles on how we might
6 think about linking tumors or linking tumor types. Then we
7 will go into some specific examples to see at the end of
8 the day if we could have a list of at least some types of
9 tumors which we feel could be linked between adults and
10 pediatrics. Then last would be to discuss trial designs.
11 Now, we all recognize -- certainly I do -- that
12 an agenda of this sort could probably take several months
13 to complete thoroughly, and we only have a few hours. Many
14 of the people have to leave earlier rather than later. So,
15 we will use the judgment and experience of our chair to
16 guide us through those parts of the agenda which we are
17 able to address and we can then reconvene with the same or
18 somewhat modified group at a later date to examine those
19 issues which merit further discussion, and if there are
20 issues which do not merit discussion, then we would
21 appreciate advice on that also.
22 Dr. Santana.
23 DR. SANTANA: Thanks, Steve, for outlining the
24 central issues that we are going to be challenged with this
25 afternoon.

1 With that, we'll go ahead and start with our
2 first speaker. It will be Todd Golub from the Dana-Farber.
3 DR. HIRSCHFELD: I'll just hog the mike here
4 for a moment during this scene change here and tell you
5 that it's a particular pleasure to welcome Dr. Golub
6 because Dr. Golub has been at the forefront of using DNA
7 microarrays to describe tumors. Dr. Golub is a pediatric
8 hematologist/oncologist trained at the Dana-Farber, but he
9 has extended his interests to using not only molecular
10 arrays, but I think new types of informatics and new types
11 of thinking and he's going to share with us some of his
12 thoughts and perspective.
13 As I noted this morning, when I opened up the
14 most recent issue of Science last night, his name caught my
15 eye and he was featured in a review on the use of DNA
16 microarrays to describe tumor types. He's done some, I
17 think, very interesting and exciting work, particularly in
18 the areas of leukemias.
19 DR. GOLUB: Well, thank you for that very kind
20 introduction.
21 What I'd like to do is to quickly go through
22 with you what I think are some of the early experiments
23 from our lab and some perspectives that we've gained in
24 these very early days of using DNA microarrays for
25 expression profiling as an adjunct -- not a replacement

1 for, but an adjunct -- to other existing strategies for
2 cancer classification to try to highlight what I think are
3 some of the current bottlenecks which are likely to be
4 solved and what are likely to be some bottlenecks for the
5 future that I think are relevant for the discussion here.
6 I think the general questions that we're
7 interested in addressing with this type of technology are
8 the following two. That is, given an individual tumor --
9 particularly, let's say, a child with a seemingly rare
10 tumor -- what other tumor type is this most like? I think
11 that that's one type of question one could ask.
12 But I think it's worth mentioning at the outset
13 that the molecular similarities of a tumor to another do
14 not necessarily include information regarding likelihood of
15 response to therapy, which I think is a slightly different
16 question that one might address in a slightly different way
17 and perhaps is more germane to this particular committee.
18 That is listed in number 2, to ask the question, is tumor X
19 likely to respond to therapy Y regardless of its
20 pathogenesis or the age of the patient?
21 And those are really two different analytical
22 questions.
23 There are, as I'm sure many of you are aware,
24 several currently available strategies for doing whole
25 genome or approaching whole genome approaches to expression

1 profiling where one measures the expression level of
2 thousands of genes simultaneously on some kind of a solid
3 support. There are several commercially available arrays
4 available now. Our lot lab happens to use those that are
5 made by Affymatrix, but this is a very dynamically changing
6 field and I think it's quite certain that the landscape for
7 the technology itself for generating the raw data in this
8 area will look very significantly different a few years
9 from now when we should expect to have whole human genome
10 arrays available for all genes in the human genome and to
11 have them affordable.
12 I think that does pose a new challenge in terms
13 of reproducing these studies and extending studies that are
14 done in the year 2000 and repeating those studies, let's
15 say, next year by other investigators when the technology
16 platform itself is so rapidly evolving that it becomes
17 nearly impossible to repeat the exact same experiment
18 entirely because the technology itself is slightly changed.
19 The experiments that we've done primarily have
20 focused on oligonucleotide arrays that contain probes for
21 6,000 or 7,000 known human genes, but again I think it's
22 likely that whole genome arrays are going to be available
23 in the near future.
24 One word about methods for preparing RNA. The
25 amount of starting material that one needs from these

1 tumors is decreasing rapidly. Now we routinely use, on
2 average, 10 micrograms of total RNA from these fresh frozen
3 tumors. I'll come back to this again at the end. I think
4 the availability of appropriately stored, that is, frozen,
5 material with clinical annotation that is long-term
6 clinical follow-up is really rapidly becoming the
7 bottleneck in doing these sorts of studies, not the
8 technology itself but rather the availability of clinically
9 annotated tissue that is suitable for these types of
10 studies. Paraffin fixed, embedded tissues are not usable
11 for these types of arrays.
12 In terms of reproducibility, I don't want to go
13 into the details of this, but suffice it to say that the
14 amount of biological variability that one sees from patient
15 to patient or sample to sample far outweighs the amount of
16 technical variability that one sees at the level of a
17 microarray itself. So, I think while I'm all for the
18 development of more technically reproducible arrays for the
19 future, I think the challenge for the field is how to
20 account for the tremendous amount of biological diversity
21 that occurs in these types of human studies.
22 But for the most part, if you take a single
23 sample and put it on two different arrays, most genes are
24 measured within about twofold of each other, expression
25 levels within about twofold of each other.

1 Now, in thinking about how one could use gene
2 expression profiling for cancer classification, we've
3 thought about this in two separate pieces: one which we
4 refer to as class discovery in which you might take, for
5 example, a group of tumors, let's say, small, round, blue
6 cell tumors of childhood, which historically have not
7 previously been well separated, and use gene expression
8 profiling to divide these into discrete subsets that were
9 previously not recognized.
10 That's quite different from saying I know about
11 the existence of several different subclasses of tumors,
12 but now I have a diagnostic dilemma, for example. I have a
13 particular tumor and I want to know to which of the
14 available six subtypes of small, round, blue cell tumors
15 that have been recognized as being bona fide subtypes does
16 this one sample belong. That's what we refer to as class
17 prediction.
18 I'll go through a couple of proof of concept
19 experiments of that.
20 Our first study relates to the distinction of
21 acute lymphoblastic leukemia from acute myeloid leukemia
22 which, of course, in this day and age is quite feasible
23 using the benefit of several decades of biological research
24 into the distinction of ALL from AML using a combination of
25 immunohistochemistry, flow cytometry, and cytogenetics to

1 make this distinction, but to try to model the notion of
2 taking what are quite similar tumors at the light
3 microscopic level and trying to distinguish them on the
4 basis of molecular genetics, without any presupposition as
5 to what the molecular distinctions were, we chose this for
6 proof of concept experiments.
7 I won't go through in detail how the algorithm
8 works to do this prediction except to make the point that
9 all of the studies that we've done so far, not only in
10 pediatric oncology but in adult oncology using more common
11 tumors, having sufficient numbers of appropriately
12 clinically annotated and appropriately frozen tumors is the
13 problem. So, this brings up quite a tremendous statistical
14 problem of how to squeeze as much information as possible
15 out of a limited number of samples without overtraining a
16 model to recognize the difference between, let's say, two
17 subsets in a particular study that you may be conducting
18 with a limited number of samples but with very little
19 applicability to samples outside of your particular study.
20 For this, we've used a method referred to as
21 cross validation in which one assembles all of the patient
22 samples. In this case, these were 38 bone marrow patient
23 samples, pre-treatment diagnostic bone marrow samples from
24 childhood ALL patients or AML patients. In fact, the AML
25 patients were a mixture of childhood and adult patients.

1 I should say that we were unable to
2 distinguished the childhood from adult AML patients in this
3 study, although the study was not specifically designed to
4 pull out those differences. We were unable to separate
5 them on the basis of gene expression profiling.
6 So, we had these 38 samples for which we
7 measured the expression profile at 6,800 known genes using
8 these oligonucleotide arrays, and then in this process of
9 cross validation, you leave one of the samples out, using
10 it as a test case of one, and now build a model to
11 recognize the difference between these two subtypes, in
12 this case ALL versus AML, but clearly this could be any two
13 subtypes of cancer that you would want to consider. Then
14 we used those 37 samples to make a model to recognize this
15 distinction and then used that to predict the class of the
16 withheld sample. In this case, is it ALL or is it AML?
17 You keep track of whether you got that right, returned that
18 withheld sample back to the mix, randomly withhold another
19 one, until you've gone through this loop 38 times and keep
20 track of what your cumulative error rate is.
21 Of course, if you had an infinite number of
22 samples, you would simply build a model with one data set
23 and then validate it with an independent test set, but I
24 think this is a reasonable strategy for trying to make the
25 most of limited amounts of data.

1 When we did that for this distinction, again we
2 had 38 samples. We also set an a priori confidence
3 threshold so that we were able to say the model is able to
4 make a high confidence prediction of one of the two
5 classes, in this case ALL or AML, but we also wanted a
6 method that could recognize a low confidence call and
7 actually have a model fail to produce a call if the data
8 were uncertain. In this case, there were 36 high
9 confidence predictions that were made. All of them were
10 correct with respect to the ALL/AML distinction using
11 immunophenotyping and morphologic analysis as the gold
12 standard for making this diagnosis.
13 In this particular case, we did have access to
14 an additional data set of samples, in this case 34 samples,
15 that were used as an independent test of this gene
16 expression based diagnostic method. Again, of 29 high
17 confidence predictions made, all 29 were correct with
18 respect to this distinction.
19 So, again, I don't believe that the world needs
20 a chip based diagnoser of acute leukemias, but I think this
21 does suggest that there's sufficient information content in
22 these diagnostic samples to find these patterns, at least
23 in this case, and to use these in a general sort of way.
24 Now, if we turn to the other side of the coin
25 now saying, well, let's suppose we didn't know about this

1 distinction of ALL from AML in the beginning and we just
2 considered these as a group of 38 acute leukemia patients
3 and we cluster these in what's referred to as unsupervised
4 learning as opposed to supervised learning, which we did
5 before in the class prediction, we just said cluster
6 yourselves into, in this case, four groups according to
7 your gene expression patterns along these 6,800 genes.
8 What you can see here is that the samples
9 segregated on the basis of gene expression into an AML
10 cluster, as shown in blue. All but one of the AML samples
11 fell into one cluster. All of the T-cell ALLs, shown in
12 green, fell into one cluster, and the pre B ALLs were
13 divided among two clusters, again suggesting that had this
14 ALL/AML distinction not been previously known, it would
15 have emerged through this type of unsupervised learning
16 approach. So, I think there's reason for optimism that
17 when applied to tumor types for which there is not the
18 wealth of molecular understanding, as there is for the
19 acute leukemias, that similar robust patterns may emerge.
20 Now, it's quite possible that some of those
21 distinctions may be more subtle than a lymphoid versus
22 myeloid distinction, and I think it's going to take some
23 time to sort that out.
24 I will mention some additional unpublished data
25 that does also suggest that this looks promising. For

1 example, these happen to be adult patients with diffuse
2 large cell lymphoma, a collaboration with Margaret Shipp
3 and John Aster at the Dana-Farber and Brigham and Women's
4 Hospital in Boston.
5 We asked the question: Can gene expression
6 patterns be used to predict outcome of patients given
7 standard chemotherapy, in this case a CHOP-based regimen
8 for diffuse large cell lymphoma? This is somewhat similar
9 to the NCI/Stanford effort in lymphoma outcome prediction
10 that appeared in Nature earlier this year, although in this
11 case we took, obviously, a different set of patients,
12 different arrays, and took a supervised learning approach
13 to say can we train a model to recognize the difference
14 between patients with a good outcome and patients with a
15 bad outcome, make a predictor that tries to predict this
16 outcome, testing in the same cross validation, leave one
17 out type of strategy.
18 And the results are shown here where for 58
19 patients with a new diagnosis of diffuse large cell
20 lymphoma, those patients who were predicted to have a good
21 prognosis are shown at the top and those predicted to have
22 a bad prognosis actually did have a poor prognosis. The p
23 value here, which didn't show up, is .0003. So, I think
24 this is encouraging.
25 I should mention also that we're able to make

1 this distinction. This appears to be somewhat different
2 than the NCI/Stanford diffuse large cell lymphoma outcome
3 prediction study that's been previously reported, I think
4 highlighting the fact that it really is a good idea to have
5 multiple institutions, multiple investigators tackling
6 these large problems. Even though they are expensive
7 studies to do, I think there's tremendous value in having
8 multiple approaches to the same problem coming at them with
9 different technologies and different analytical methods.
10 We've done similar studies in collaboration
11 with Scott Pomeroy, which I'll mention, in brain tumor
12 outcome. I know there's going to be more discussion about
13 this later this afternoon. But in particular for
14 medulloblastoma, this is a group of 75 childhood
15 medulloblastoma patients where again we tried to predict
16 survival in these patients who received standard treatment
17 at a number of centers. As you can see here, the ability
18 to predict survival was very significant, with a p value
19 that's about 10 to the minus 5th.
20 So, again, I think that this suggests that
21 there is real structure that emerges if you ask the right
22 question, in this case supervised, directed question, what
23 is the difference between patients who do well, given a
24 particular treatment, and those who do not.
25 Now, again, this is slightly different from

1 saying how are different types of brain tumors, for
2 example, related to each other. You won't be able to read
3 this. It doesn't really matter. But, for example, as part
4 of this project, we've taken examples of a number of
5 different types of brain tumors, medulloblastomas,
6 oligodendrogliomas, glioblastoma multiforme, PNETs, CNS
7 rhabdoid tumors, and clustered them now in an unsupervised
8 way to ask the question how do these different tumors
9 relate to each other. I think there's going to be useful
10 and important information gained there regarding the
11 pathogenesis and cell of origin of these tumors. I'm not
12 certain that this type of unsupervised approach will really
13 get at the question of what treatment are these patients
14 most likely to respond to. I think that remains to be
15 shown.
16 It is worth saying that with these
17 medulloblastomas, if we simply cluster the samples but,
18 say, into two groups in a completely unsupervised way, that
19 distinction of group 1 from group 2 that emerges on the
20 basis of unsupervised gene expression profiling has nothing
21 whatsoever to do with prognosis or response to therapy.
22 That only emerged when we asked that specific question in a
23 supervised fashion.
24 Now, finally, I just wanted to mention one
25 additional set of experiments. I think it does get perhaps

1 get a little bit closer to what we'd be like to be able to
2 do, which is to say, given a given patient's tumor, there
3 are several therapeutic options. Which of them are most
4 likely to be effective in this particular patient? We've
5 tried to model this type of exercise using a well-known
6 panel of cell lines called the NCI 60 cell lines, which are
7 60 diverse human cancer cell lines to which the sensitivity
8 to thousands of chemical compounds has been previously
9 determined. But we measured the gene expression profile
10 again of 6,800 genes in these 60 cell lines and asked the
11 question, are these gene expression profiles in the
12 untreated cells -- that is before they see any drug, are
13 they predictive of response or sensitivity to these
14 chemical compounds?
15 I won't go through the details of again how
16 this prediction model works, but the results are shown here
17 for a group of 232 compounds in these 60 samples. In this
18 case, we were trying to predict is a given cell line
19 sensitive or resistant to each of these 232 compounds.
20 What you can see in gray is the result of a coin flip. If
21 you simply guessed whether a sample was sensitive or
22 resistant, which is really the best that you can do with
23 currently available information, you would get this right
24 about 50 percent of the time, occasionally do better,
25 occasionally do worse.

1 However, if we look at the prediction of
2 sensitivity versus resistance based on gene expression
3 profiling, you can see that this distribution is markedly
4 shifted to the right, and the difference between these two
5 distributions is highly significant.
6 Now, clearly the response and sensitivity of
7 all cell lines to all drugs was not highly predictable, but
8 for a significant subset they were. Again, I personally
9 don't think that pushing the cell line studies, in terms of
10 understanding direct extension of these prediction studies
11 to the clinical setting, is likely to be that helpful, but
12 I think it does suggest that there's sufficient information
13 content in the resting gene expression profile of untreated
14 cells to allow one to predict, at least for a subset of
15 drugs and a subset of samples, what the likelihood of
16 response is going to be. I think these are the types of
17 studies that we should be thinking about going forward,
18 building into early phase clinical trials molecular
19 predictors of response.
20 So, I think what we can look forward to in the
21 future on the technical side, as I mentioned, are whole
22 human genome arrays that are cheaper and widely available
23 in the academic community, the availability of better
24 analysis tools which at the moment are still somewhat
25 rudimentary and are not easily deployable throughout the

1 community, better signal amplification methods so that less
2 patient material is needed for these studies. I think what
3 is going to remain, however, is the issue of sample
4 availability. You'd like to do these studies with hundreds
5 of samples with follow-up information, and that is not
6 going to help. I think as institutions start to recognize
7 the value of these samples, more prospective banking of
8 tumor samples and accumulation of clinical data will occur.
9 But doing this retrospectively I think is going to remain
10 somewhat of a challenge for the year ahead.
11 Again, I think in the short term, that focusing
12 on trying to develop molecular predictors of response to
13 treatment is going to be very worthwhile. Even if this
14 doesn't necessarily provide direct insight into the
15 pathogenesis of the development of these tumor or the cell
16 of origin or the oncogenes involved in them, it's quite
17 possible that one could obtain patterns that are predictive
18 of response.
19 Then, of course, the longer term goal would be
20 to use these whole genome approaches not only to define
21 patterns but to get more at the fundamental basis of the
22 development of the tumors and to design magic bullet drugs
23 that get precisely at the critical players involved in
24 transformation. But I don't think that that's the only
25 strategy for using this type of approach.

1 I think I'll stop there.
2 DR. SANTANA: Thank you. That was very
3 informative.
4 I think we do have some time for a few
5 questions. So, we'll go ahead and take those now. Steve.
6 DR. HIRSCHFELD: What would be the interaction
7 between a new drug with a new mechanism of action, which
8 you can't compare to previous history, and a DNA microarray
9 in terms of questions you might ask or information you
10 might learn?
11 DR. GOLUB: Well, I think one strategy would be
12 to develop a compendium of gene expression responses to
13 known drugs of known mechanisms of action, to develop
14 signatures of those drug responses so that when faced with
15 a new compound, one could ask which of those signatures, if
16 you will, is the response downstream of this new compound
17 most similar to as to give you a hint as to what mechanism
18 of action it may be. There's some suggestion that may be
19 feasible, at least in yeast. I don't think that's been
20 quite developed yet for human experiments.
21 DR. SANTANA: As a follow-up to that, in that
22 slide that you showed where they're flipping a coin versus
23 looking at the gene expression and its predictability, if
24 you were to look at that data in a different way, rather
25 than saying response to a specific drug but response to a

1 class of drugs, would that give you additional information
2 so that when a new drug comes in, you would consider it in
3 the context of how that drug fits into the class rather
4 than the specific response?
5 DR. GOLUB: That's a good question. We haven't
6 looked at the data in that way. I think this particular
7 data set is a bit challenging because while it's 60 cell
8 lines, it's about 7 or 8 examples of cells from multiple
9 tissues of origin. As you know, there are correlations
10 between drug response and cell of origin, particularly
11 whether you're breast versus leukemia. So, we specifically
12 designed this predictor to not be confused by this lineage
13 distinction, but I think to do the types of studies that
14 you're alluding to, you'd like to have a broader panel
15 within a tumor type of interest.
16 DR. PRZEPIORKA: Two questions that we'll be
17 discussing, identity and predictability to response or
18 prognostication. My question is in trying to extrapolate
19 from adults to pediatric patients, has this technique been
20 applied to any tumors such as AML or ALL to see whether or
21 not adult ALLs are, in fact, like pediatric ALLs and should
22 be treated the same way or can be used to base our
23 determination on which pediatric patients should be
24 studied?
25 DR. GOLUB: That is something that we're

1 planning to do but we have not done yet and, to my
2 knowledge, hasn't been done yet. There's good evidence, as
3 you probably know, from the cytogenetic literature that
4 adult and childhood ALLs are different at the molecular
5 level in terms of the frequency of chromosome
6 translocations. So, I think it's quite likely that there
7 will be gene expression patterns that may be able to
8 distinguish these.
9 Again, I think that it's possible that there
10 may be molecular distinctions between childhood and adult
11 ALL, for example, that aren't necessarily correlated with
12 differential response to therapy, and I think in terms of
13 study design and thinking about that, I think that's going
14 to be one of the challenges because I believe that
15 childhood leukemia that looks more like an adult leukemia
16 isn't necessarily unlikely to respond to conventional
17 childhood treatment.
18 DR. PRZEPIORKA: My other question had to do
19 with your analyses of predictability to response or
20 survival. In those studies, was the p value for a
21 univariate analysis or a multivariate analysis looking at
22 differences that we could pick up clinically at the
23 bedside, as opposed to something that we saw 100 of the
24 exact same kind of patients and exact same kind of tumors,
25 but we could molecularly tell a difference?

1 DR. GOLUB: This was a univariate analysis,
2 what I showed. That p value was looking at this alone for
3 all patients. In the case of the lymphomas, when we
4 incorporated the International Prognostic Index, that
5 current conglomeration of existing clinical prognostic
6 factors for diffuse large cell lymphoma, and restricted the
7 analysis only to a single subgroup of high intermediate
8 risk IPI patients, we're still able to see some distinction
9 but, of course, it was less powered because there were few
10 patients in that group.
11 I think that's going to be another challenge.
12 I think it's unlikely that these types of approaches are
13 going to replace existing prognostic factors. The
14 challenge will be how to best combine them with additional,
15 previously described prognostic features.
16 DR. SANTANA: Dr. Balis?
17 DR. BALIS: I think you may have been alluding
18 to this on your last slide, but have you gone back and
19 looked to see, once you've been able to group these tumors,
20 whether the genes that are either more expressed or less
21 expressed between the two groups have any biologic
22 significance to the phenotype that you're looking at?
23 DR. GOLUB: Yes, we're doing that. In some
24 cases, it's quite obvious that they do, and in others it is
25 a bit of a mystery. That is another challenge in terms of

1 taking this to the next step. Certainly in the case of
2 distinguishing lymphoid malignancies from myeloid
3 malignancies, it's quite clear that there are lineage
4 related transcription factors that are expressed in one and
5 not the other, and this makes a lot of biological sense.
6 For some of these outcome predictions, however,
7 the story seems to be much more complicated, perhaps
8 reflecting the fact that there may not be a single
9 mechanism, for example, of drug resistance that explains
10 all of the failures in patients with a poor outcome from
11 lymphoma treatment, for example. But there are actually
12 multiple mechanisms, some which may have immune mediated
13 mechanisms of failure, some which may have intrinsic drug
14 resistance mechanisms of a failure and so on. When those
15 get merged together into a single signature of outcome
16 prediction, the results can be confusing.
17 I think it's quite possible for many projects
18 like this that a signature will have some clinical value
19 long before there's biological understanding to explain why
20 the signature is actually of any clinical value.
21 DR. BOYETT: To follow up on the
22 medulloblastoma, the Pomeroy data, just to make sure I
23 understand the method. You dropped a sample out. You
24 build a gene expression, predict survivor versus not, and
25 you saw how well it did.

1 DR. GOLUB: Right.

2 DR. BOYETT: There were no samples for which
3 there was uncertainty? Because in your early example,
4 while you were 100 percent correct when you predicted, you
5 certainly had in one, I think I remember, about 15 percent
6 uncertain samples.

7 DR. GOLUB: That's right. Again, what the best
8 strategy is for setting that uncertainty threshold I think
9 we still haven't defined optimally. In the medulloblastoma
10 data, that was using no threshold and it was taking all
11 patients.

12 Of course, it's a challenge also. In terms of
13 doing this sort of experiment, you need to assign each
14 patient to either a good outcome or a bad outcome group to
15 train the model, and particularly for tumors that have a
16 late pattern of relapse, that can be challenging and
17 restricts the number of samples that you have.

18 DR. SANTANA: Two last questions. Dr.
19 Finkelstein and then Dr. Reynolds.

20 DR. FINKELSTEIN: I'd like to explore your
21 statement in terms of the genome approach and the classical
22 prognostic factors. I'm a little disturbed, but maybe
23 you're being humble in suggesting that the classical
24 prognostic factors are still going to survive for years
25 when frankly I think we who have used them are looking

1 forward to some advances with the genome approach.
2 Specifically, for example, if you use the P190 BCR-ABL-ALL,
3 is not the same disease in an adult and in a child?
4 DR. GOLUB: I think it probably is and I think
5 children who are BCR/ABL positive are going to respond to
6 STI-571 even though it's been tested in adults only so far,
7 to my knowledge. I think that's a great example of how
8 you'd like to extend adult studies to pediatrics.
9 I think my only cautionary note was that we
10 shouldn't be too fast to throw out existing, albeit
11 imperfect, clinical prognostic factors until these new
12 studies are really validated in multiple clinical trials
13 and are really shown to be robust. I think like any other
14 study, it is possible to have findings that appear to be
15 robust in one study and are difficult to reproduce either
16 for technical reasons or for other reasons in other
17 studies. I think we need to be as patient for these
18 approaches as we have required of studies of clinical
19 prognostic factors.
20 DR. SANTANA: But I think the point is when you
21 revisit history, what happened with cytogenetics or what
22 happened with molecular diagnostics is that not being
23 skeptics, we want the proof and the validation of the
24 system before we move forward.
25 I think Jerry is correct. You shouldn't be too

1 humble. I think this probably, hopefully, will provide
2 further refinement of how we classify patients and
3 ultimately how we treat them.
4 DR. REYNOLDS: I just wanted to comment that
5 what you're looking at there, as you've mentioned, is
6 overall prognosis or overall outcome, which is a multitude
7 of factors. One of the issues at hand here is really
8 response to drugs, which is difficult to look at. The
9 problem is that if you're thinking about phase II studies
10 of single agents, most of those are carried out in
11 recurrent patients where you don't have access to the
12 material before they got treated.
13 However, there seems to be an opportunity here
14 within stuff that may have been collected by the Pediatric
15 Oncology Group and maybe one of the POG people could
16 comment. But they did phase II windows and presumably
17 those up-front patients had stored in the tumor bank
18 material. So, perhaps someone could look at response
19 correlation between gene profiling and those phase II
20 window patients that were stored relative to those single
21 agents, which might be very interesting.
22 DR. GOLUB: I think those are precisely the
23 type of studies that need to be done.
24 Now, if I could just follow up briefly on Dr.
25 Finkelstein's point again. I think the type of studies

1 that are going to be most exciting would be, for example,
2 in the case of STI-571, the BCR-ABL kinase inhibitor for
3 CML. If one could develop a gene expression signature of
4 ABL kinase activity in a tumor cell, independent of whether
5 you happen to have CML or BCR-ABL-ALL or activation of some
6 other kinase pathway that mimics that same signature, that
7 would provide I think, while not statistical certainty, at
8 least some rationale for study design for who should be the
9 next non-CML patients to receive this experimental agent,
10 and I think that type of study design would make a lot of
11 sense.
12 DR. SANTANA: Todd, thank you very much for a
13 very exciting and challenging talk.
14 Let's go ahead with the next item on the
15 agenda. David Parham from the University of Arkansas will
16 give his perspectives on the use of histology for diagnosis
17 and classification.
18 DR. HIRSCHFELD: While there's a scene change,
19 I'll just comment that when we first invited Dr. Parham, he
20 said why do you want me? I'm just a pathologist. And we
21 said, well, that's first of all why we would want you, and
22 second of all, we wanted you in particular because of the
23 body of work and your reputation for clear thinking.
24 That's what we're looking forward to in the discussion now.
25 DR. PARHAM: Well, thank you very much for

1 asking me. A lot of what I'm going to say is not going to
2 be anything new, I'm sure, to the majority of the audience.
3 I think of this more as a brief recap in relationship to
4 the topic at hand and also a brief summary of my own views
5 and perspective on the topic of histologic diagnosis and
6 its relationship to outcome.
7 It's hard for a pathologist to talk without a
8 pointer, so they're finding one. Here we go.
9 What I'm briefly going to cover are these five
10 aspects of histologic diagnosis. First, how a diagnosis is
11 made, the standard parameters of clinical diagnosis as it
12 is traditionally done by pathologists. Second, the role
13 for pattern recognition, which is the major factor in
14 making a histologic diagnosis. Thirdly, resemblance of
15 tumor cells to normal cells, which is the theoretic basis
16 for tumor classification, handed down to us over 100 years
17 ago. I'm going to briefly talk about cost and availability
18 of various modules used to make diagnosis, and then finally
19 I'll talk about the major topic at hand, which is how
20 pediatric tumors and adult tumors relate from a histologic
21 classification standpoint.
22 My first topic is standard parameters of
23 diagnosis. Pathologists do not make diagnoses in a void.
24 I have had pathologists who said they did and they always
25 wind up either with egg on their face making mistakes or

1 actually disobeying their own rules. In fact, we may try
2 to initially look at things from an unbiased viewpoint,
3 that is, just looking at a slide, but before you put your
4 name on a piece of paper that you have to sign for
5 posterity, you should always look at these things. The
6 clinical features of the lesion; primary sites, which is so
7 important in distinguishing small cell tumors; patterns of
8 metastases, and particularly with bone and brain tumors,
9 radiographic patterns of disease.
10 We also do a careful gross examination, and
11 gross examination is tantamount to histologic diagnosis
12 because, for one thing, we select the tissues we look at
13 through a gross examination. And if we select the wrong
14 areas in a variegated tumor, then it's going to be more
15 difficult to make a diagnosis. So, careful gross
16 examination and observation is really the basis for
17 histologic examination.
18 Then we get to histologic appearance or
19 microscopic appearance which is based on observation of the
20 histologic patterns. That is, how do cells relate to each
21 other and form a framework of a pattern? Secondly, the
22 individual cells, the cytologic features of individual
23 cells, which is important not only for diagnosis, but also
24 for prognostication using histology.
25 This being done, we then rely on a series of

1 ancillary techniques for diagnosis which particularly in
2 the past 20 years have largely included
3 immunohistochemistry and electron microscopy. Electron
4 microscopy has played a descendent role with the ascent of
5 immunohistochemistry. I'll talk briefly about that. Then
6 as has been alluded to, more and more we're looking at
7 cytogenetics and molecular pathology.
8 Now, the first of the topics, when we look at
9 how we make a diagnosis by using standard histology, is
10 pattern recognition. Pattern recognition is a hard thing
11 to quantitate. I think this is largely a function of the
12 right side of the brain, and particularly in medical
13 school, it's apparent that some people who have made
14 straight A's during premed hit the wall when they come to
15 pathology because they're unable to do this using logic and
16 mathematical reasoning. So, it's a certain breed of
17 physicians I think that go into pathology because this is a
18 talent that you're more or less born with. I don't think
19 it's easy to acquire this. I think you're born with this.
20 This is a talent, much as if you're born with a talent for
21 music or art.
22 Now, when we look at birds feeding in the
23 winter -- and this is a picture I took during one of the
24 rare snows we had in Arkansas. This particular bird was
25 very easy to diagnosis, if you will, as a slate-colored

1 junco. In fact, if one wants to rely on a compendium or an
2 encyclopedia to help one diagnose things in the bird world,
3 we use mainly this major text by Dr. Roger Tory Peterson,
4 and you can look up the features of a slate-colored junco
5 here. We see, by these various arrows, the key points that
6 one would observe. In spite of the fact that you have
7 these key points, it's very easy to distinguish a junco
8 from other birds in general.
9 Now, if we got a fleeting glimpse of a junco,
10 as can happen with a tumor -- sometimes we get so little
11 material or such bad material, it can be difficult -- it
12 might be difficult to make a diagnosis of junco. But if we
13 get a good view of a junco, usually it's easy to know what
14 it is.
15 Now, here's a sparrow. Probably most people
16 can recognize this as a sparrow but only those that are
17 familiar with bird watching would recognize this as a
18 white-throated sparrow. It has particularly certain
19 features on the head. So, you have to get a good look at
20 the head to see these bands. You have to see the white
21 throat and this yellow spot here in front of the eye.
22 Now, we also have these bird watching manuals
23 in pathology.
24 (Laughter.)
25 DR. PARHAM: We're privilege to have in the

1 audience and on the panel here the Roger Tory Peterson of
2 brain tumors, Dr. Peter Burger. So, whenever I see a brain
3 tumor that I need to make a diagnose on and am having
4 problems, I look at his book. As a matter of fact, it's
5 getting quite dog-eared now because I take it with me down
6 to the frozen section room regularly.
7 So, when I see a tumor like this, it's much
8 like looking at a slate-colored junco because I see these
9 reddish globs, and combined with the pattern of low
10 cellularity, I recognize it as a pilocytic astrocytoma.
11 Indeed, you can go to Dr. Burger's book and find this
12 little photograph of pilocytic astrocytoma with the
13 Rosenthal fibers, and it's not a very difficult thing for
14 the majority of pathologists to recognize Rosenthal fibers.
15 That's one of the things we learn as a first-year pathology
16 resident.
17 Now, here's a particular case that I pulled
18 from my files because I remember this tumor from St. Jude
19 as being one that even Dr. Burger's colleague, Dr. Vogel,
20 could not diagnose. So, I wanted to find an example of a
21 sparrow, if you will, a rare sparrow. This one was so
22 rare, Dr. Vogel could not put a name on it. I think he
23 called it, Peter, a PNET.
24 In fact, I'm sure Dr. Burger could make a
25 diagnosis of this tumor. Now, here's a picture of a

1 similar tumor. I believe this happens to be a rather rare
2 and unusual tumor in children that has a lot of
3 morphologies, an atypical taratoid rhabdoid tumor, which
4 had not even been described when we sent that tumor to Dr.
5 Vogel. I don't know if you saw that one or not, Peter.
6 I'm not going to lay any blame on you.
7 The big difference between tumors and birds is
8 that when I see a sparrow I can't identify, I can't call up
9 Dr. Peterson. Unfortunately, he's dead now anyway. I
10 could shoot the sparrow I suppose and send it to Dr.
11 Peterson. But there's a big difference with brain tumors,
12 and that is if I see an unusual tumor, I usually do send it
13 to Dr. Burger. So, we have a captive audience, if you
14 will, of experts who are willing to look at birds that we
15 as bird-watching pathologists cannot identify.
16 In fact, this has formed the basis for
17 pathology review in pediatric groups like the Pediatric
18 Oncology Group, Children's Cancer Group, Intergroup Rhabdo
19 Study, the National Wilms Tumor Study, and the European
20 groups like SIOP and CWS. All of these have had Roger Tory
21 Petersons who have actually look at every single tumor
22 entered on these studies. So, we don't rely on people who
23 are not well-versed in these things when it comes to these
24 big studies.
25 The next principle in diagnosis is the

1 resemblance of tumor cells to normal cells. This comes
2 from an old concept espoused by Dr. Virchow in the mid-
3 1800s. I don't know if the Latin is correct, but it
4 basically means that tumor cells come from normal cells.
5 Prior to that time in the mid-1800s, it was felt that tumor
6 cells actually were derived from some ill-defined blastema,
7 which was not even cells at all but which sort of spit out
8 cells. Dr. Virchow said all cells have to come from a
9 parent cell. So, the theory would be then that every tumor
10 cell at some point was a normal cell. This works quite
11 well in a number of tumors and has formed the traditional
12 way of classification of tumors using pathology.
13 Here's an example of embryonal muscle tissue.
14 You see how it condenses into these strap cells, which are
15 called myotubes. Because of this remarkable resemblance --
16 here is an embryonal rhabdomyosarcoma -- we see that we can
17 classify this as a tumor of embryonic muscle based on this
18 principle derived from Dr. Virchow.
19 Even the ancillary methods that we use as
20 pathologists are based on this concept. Here's an example
21 of normal muscle, as seen by an electron microscope, with
22 these condensations known as Z-bands and these alternating
23 thick and thin filaments. And here's the same thing in a
24 rhabdomyosarcoma, showing a bit disorganized, but still
25 thick and thin filaments and Z-bands.

1 More recently we have immunohistochemistry
2 which is based on a similar preposition, that is, that
3 tumor proteins in normal cells are also expressed in the
4 tumor cells. A muscle cell has all sorts of unique
5 proteins like desmin, actin, and myoD, and these are all
6 expressed in rhabdomyosarcoma. So, one can use this type
7 of staining to identify proteins to determine whether it in
8 fact is a muscle cell, albeit a malignant muscle cell.
9 Now, one of the limitations of standard
10 histology and standard classification is the fact that
11 sometimes we can't identify where tumor cells come from or
12 even in fact exactly what they are. Here's an example of a
13 tumor which, by pattern recognition, is another one of
14 these things that first-year pathology residents get right,
15 and that is an alveolar rhabdomyosarcoma. It also has
16 these very characteristic crystals by electron microscopy,
17 these crystalloid structures. But in fact we still have
18 not determined where these tumor cells come from. What is
19 the normal cell? What is the normal counterpart? So, Dr.
20 Virchow's theorem does not work in this tumor and it still
21 has resisted attempts to figure out where the cell comes
22 from.
23 Here's another problem we run into,
24 particularly with using immunohistochemistry, and that is
25 bi-phenotypic tumors. Here's an example of an

1 ectomesenchymoma, and we're showing with a brown stain that
2 this tumor is expressing desmin, which is a muscle protein,
3 and we're showing with this light brown stain here, as well
4 as these rosettes, that this tumor also expresses neural
5 features. So, it's a tumor showing both neural and
6 myogenic features. So, where does it come from? A nerve
7 cell or a muscle cell? We can't really say using standard
8 histology, even the tools of histology.
9 So, I think the advent of these arrays and the
10 newer things with genetic studies and molecular studies are
11 going to help us with issues like this where we either
12 don't know where the tumor cells come from when we're
13 trying to describe new entities and when we're trying to
14 understand things that don't seem to follow standard
15 histologic rules.
16 Now, I'd like to touch on briefly cost and
17 availability, which is something that Dr. Golub alluded to.
18 I think one thing I've learned being in Arkansas is that
19 there are certain things you can easily get and certain
20 things which are very difficult to obtain when we're trying
21 to make a diagnosis. So, based on my own personal
22 experience, I've constructed a hierarchy of diagnostic
23 techniques to which hospitals have available to them.
24 Every hospital does routine histology. The majority of
25 them have immunostains. EM is now limited to only centers

1 that are large enough to support the declining volume of
2 cases. There's only one cytogenetics laboratory in the
3 State of Arkansas, and that happens to be the one that I
4 run. And then now even less of this is the molecular
5 testing. In fact, we don't have any available molecular
6 test in the State of Arkansas for childhood tumors. We
7 have to send it off to someplace like Nebraska. Lastly,
8 the newest technology is the least available, that of gene
9 arrays.
10 Now, let's look at relative costs based on
11 catalog prices listed in the Mayo Clinic Pathology Catalog
12 and the Clonitech catalog. Histology is $200 with the
13 interpretation. This is even including my salary here.
14 (Laughter.)
15 DR. PARHAM: Immunostains are 82 bucks.
16 Electron microscopy, 590 bucks. Cytogenetics, $725 for a
17 solid tumor, $970 for a lymph node. For one genetic study
18 -- and this happens to be immunoglobulin gene rearrangement
19 -- you pay $235. So, you basically have $235 per gene.
20 The cost of an array from Clonitech ranges from $600 to
21 $1,400 per array. Now, I know that these are changing
22 values according to marketplace rules, and that's what
23 we're basing it on, marketplace rules. So, it could go up
24 and it could go down.
25 Now, another thing to consider is turnaround

1 time because I think this has an effect on how we make
2 diagnoses. Using histology you can make a diagnosis within
3 24 hours or less. Oftentimes I can make a diagnosis at
4 frozen section at the time of surgery. Immunostains take 1
5 to 2 days. Electron microscopy takes 3 to 5 days.
6 Cytogenetics takes 1 to 2 weeks. To obtain a molecular
7 study from the Mayo Clinic takes 4 days, and gene arrays'
8 turnaround time is not currently defined. At least, I
9 couldn't find any listing of that in the 1998 Mayo Clinic
10 catalog.
11 I'd like to finally talk about the real issue
12 at hand; that is, how adult tumors are like pediatric
13 tumors. In fact, the most common cancers in adults,
14 carcinomas, only comprise 4.5 percent of pediatric tumors.
15 There's a striking, disproportionately small population of
16 the overwhelming bulk of adult tumors represented in
17 pediatric practice.
18 Of this pie, you can even separate it basically
19 into three major tumors, thyroid cancers, melanomas, and
20 hepatocellular carcinomas; lesser numbers of
21 nasopharyngeal, adrenal, gonadal and renal cells cancers.
22 This is just a potpourri of a variety of very rare tumors
23 that sometimes occur in unlucky children because of unknown
24 factors, gene susceptibility, exposure to radiation, et
25 cetera.

1 One thing I would like to talk about briefly
2 that I think is very important when we try to link adults
3 to children is sarcomas. My own special interest is
4 sarcomas. Now, the bulk of childhood sarcomas are
5 rhabdomyosarcomas, which we see in red here. With lesser
6 numbers of these non-rhabdomyosarcomas. This is based on a
7 German tumor registry. In fact, if one looks at the tumor
8 I discussed earlier, alveolar soft part sarcoma, we see how
9 few tumors occur in pediatric age groups compared to older.
10 In fact, for non-rhabdomyosarcomas, usually the peak is
11 somewhere between 20 to 40 years of age.
12 Now, we did perform a study of non-
13 rhabdomyosarcomas in the Pediatric Oncology Group, and I
14 just want to share with you the activity we had in 1992.
15 When you can see these appallingly small numbers of various
16 tumors based on histology -- it would take you decades, if
17 not scores, of years to find enough of any individual
18 histology to ever base a decent statistical analysis. Only
19 22 that year, the bulk of them being malignant nerve sheath
20 tumors. Well, that's not even the bulk. That's a
21 minority. So, these are very rare tumors in children that
22 do occur with increased frequency in adults. So, I think
23 we definitely need to consider, particularly in sarcomas,
24 non-rhabdosarcomas combining these materials.
25 I think in rhabdos you have a good argument too

1 because rhabdos and PNETs both occur in adults. One of the
2 papers that we have in our book alludes to this in adults,
3 PNETs in adults.
4 So, to summarize my talk, number one,
5 histologic diagnosis is part of a synthesis of clinical and
6 pathological data. We do not look at things in a vacuum.
7 We should not as pathologists.
8 Number two, pattern recognition is the major
9 technique used in histologic diagnosis and is a talent.
10 It's a talent that's akin to bird watching.
11 Number three, diagnosis of tumors is based in
12 part and certainly historically to their resemblance to
13 normal cells.
14 Number four, histologic examination is
15 currently -- I have to emphasize "currently" -- the most
16 cost effective, readily available, and time efficient
17 method of diagnosis.
18 Finally, tumor diagnosis in children differs
19 markedly from that of adults. I'm speaking primarily of
20 solid tumors. I don't have the background to discuss
21 hematopoietic tumors. But in some circumstances such as
22 sarcoma, it is the same. I think we certainly could profit
23 combining those tumors that occur rarely in children but
24 more frequently in patients over 20.
25 That's my talk. Thank you.

1 DR. SANTANA: Thanks, David. I think we do
2 have some time for questions.
3 If nobody else has a question, let me see if
4 you can synthesize for me your last comment. So, what
5 you're saying is for the majority of sarcomas that we see
6 in kids, similar histologies are represented in adults
7 although with different incidence rates.
8 DR. PARHAM: Right.
9 DR. SANTANA: But histologically they look the
10 same. Biologically they may be similar too.
11 DR. PARHAM: I agree. I think for two
12 particular categories -- and that is, PNETs and rhabdos --
13 they more commonly occur in children, but they do occur at
14 a much smaller frequency in adults. But they're the same
15 tumor biologically and histologically.
16 Secondly, the other sarcomas that occur in
17 children are much rarer but occur in greater frequency in
18 adults, particularly young adults.
19 DR. SANTANA: Thanks.
20 DR. PAZDUR: Are there any examples where one
21 would have a similar light microscopic appearance between
22 an adult tumor and a childhood tumor and the biological
23 activity is markedly different?
24 DR. PARHAM: That's a very good question and I
25 just completed a study on that. I'm glad you brought that

1 up.

2 I want to emphasize that PNETs, in particular,

3 can look exactly like small cell neuroendocrine carcinomas.

4 I still don't know an absolutely foolproof way to separate

5 them outside of cytogenetics or genetics.

6 DR. PAZDUR: How about within the spectrum of

7 pediatric age groups, if one would take a look at the same

8 tumor and map the biological activity from, for example, a

9 young child to an adolescent? We're talking about

10 pediatrics as a composite group here, and is it possible

11 that even within the pediatric age spectrum there are

12 marked differences in the biological activity?

13 DR. PARHAM: Absolutely, and rhabdomyosarcoma

14 is a good example of this where age is an independent

15 predictor of outcome for histologically identical tumors.

16 We have the same thing with neuroblastoma. Absolutely, age

17 is very key.

18 DR. PAZDUR: Could that be identified on any

19 light microscopic evidence or any immunohistochemistry

20 techniques other than the clinical experience that one

21 would have?

22 DR. PARHAM: No.

23 DR. SANTANA: Well, except for the difference

24 of histologic types, David. You would expect to see more

25 alveolar in the younger age group.

1 DR. PARHAM: Absolutely. You can expect to see
2 certain histologies in certain age groups, but within the
3 class for a given histology like embryonal histology,
4 embryonal rhabdomyosarcoma or neuroblastoma, you cannot
5 reliably differentiate a tumor from an older child and a
6 younger child. Yet, the prognosis is markedly different
7 based on the independent predictor of age which occurs in a
8 number of pediatric tumors.
9 DR. BOYETT: The same is true in ALL as well.
10 DR. PARHAM: That's right. ALL is another one.
11 DR. SANTANA: Malcolm?
12 DR. SMITH: I was just going to emphasize in
13 ALL where in young children you have cases that are, for
14 example, hyperdiploid or tel AML-1 translocations that you
15 don't see once you get past the age of 10 or you see less
16 commonly, even though light microscopically the appearance
17 may be very similar.
18 DR. PARHAM: Particularly in neuroblastoma, I
19 think you can see histologically similar tumors that you
20 can separate out by biological means like n-myc
21 amplification. I think n-myc amplification is more common
22 in older children, but it does occur in babies, but when it
23 occurs, it's still a bad feature. So, there are biologic
24 things but not histologic.
25 DR. SANTANA: Jerry?

1 DR. FINKELSTEIN: Well, I think what you're
2 doing is you are creating some publicity for the new
3 technology because if indeed it's age dependent -- and I am
4 one who feels that's a very crude prognostic sign -- the
5 new technology will give it some scientific basis. I think
6 that's what this afternoon is all about. The same thing
7 with acute lymphocytic leukemia. The new technology will
8 give it some scientific basis, and it's my prediction that
9 age will disappear and science will take over.
10 DR. SANTANA: Pat?
11 DR. REYNOLDS: Since you mentioned
12 neuroblastoma and also earlier small cell tumors, what
13 about small cell lung cancer and neuroblastoma? As a
14 medical student, one of my favorite tricks was to put a
15 small cell lung cancer slide on to my teacher and then say,
16 this came from an adrenal in a child. What is it?
17 Invariably they said it was a neuroblastoma.
18 I wonder if one couldn't make a case, since
19 small cell lung cancer does show amplification of the n-myc
20 oncogene in a number of the cases and does respond to a lot
21 of the same drugs, that one could tie those together even
22 though they are clearly biologically different.
23 DR. SANTANA: Before you answer that, it's
24 interesting. I always watch and read the adult lung cancer
25 literature to get clues about potentially what we could do

1 with neuroblastoma. So, we have the same thinking process.
2 David.
3 DR. PARHAM: Well, I think that's possible. I
4 can't speak to neuroblastoma because I haven't personally
5 tested that. That's a possibility. However, I know that
6 when you look at PNETs in adults -- and they do occur. As
7 a matter of fact, there is a paper again about PNETs in
8 adults -- I think that right now I'm not sure there's any
9 bottom line, histologic way to tell them apart, but you can
10 theoretically tell them apart by cytogenics with the
11 translocations in fusions. I don't have enough data
12 accumulated yet to say that that makes a difference in the
13 outcome.
14 DR. SANTANA: Todd?
15 DR. GOLUB: If I could just follow up on that,
16 I think one of the challenges is, for example, it may be
17 that neuroblastoma is more similar to small cell lung
18 cancer than anything else that you could imagine or
19 anything else that you could test, but how similar is
20 similar enough to have that information be sufficient to be
21 clinically useful? I think that has to remain an open
22 question, at least for now, and that's one of the
23 challenges, trying to understand the degrees of similarity
24 and how they relate to real biological and clinical
25 properties of the tumors.

1 DR. PARHAM: One can obtain the reverse, while
2 we're on the subject of neuroblastoma and PNET, with those
3 two entities because we recognize them as two markedly
4 different entities from a clinical standpoint. Yet, it has
5 been my experience that by pathology it's often difficult
6 to tell them apart. Now, we do have markers that we can
7 use without resorting to molecular genetics to make the
8 distinction, but certainly molecular genetics is another
9 way of telling the one tumor which has the n-myc
10 amplification and the other one has the EWS fusions. So,
11 there are two tumors which can look very similar, yet we
12 consider them totally different entities.
13 DR. SANTANA: Thanks, David.
14 Our next discussant is Dr. Burger who will tell
15 us his thoughts on the classification of brain tumors in
16 childhood and how it relates to adults.
17 DR. HIRSCHFELD: While there's a scene change,
18 I'll just give you some insight into the FDA thought and
19 analytic process. You may think we asked Dr. Burger
20 because he was such an internationally known pathologist
21 and author of an atlas that everyone refers to or because
22 everyone says he's one of the nicest guys you could deal
23 with. But the real reason we invited Dr. Burger is because
24 he lives an hour away.
25 DR. BURGER: It's cheap.

1 DR. SANTANA: But it probably takes him just as
2 long to get here with all the traffic.
3 (Laughter.)
4 DR. SANTANA: Dr. Burger?
5 DR. BURGER: Thank you all. It's always nice
6 to go to a meeting and hear one of the preceding speakers
7 refer to your publications. Having mine referred to as a
8 bird book, though --
9 (Laughter.)
10 DR. BURGER: But the fact is, I have used this
11 very analogy, not perhaps the same pictures, but I have
12 used the cover picture from Tory Peterson's book in my own
13 talks. It's a very good description of what anatomic
14 pathologists do. It has all the similarities to looking at
15 the habitat of a bird versus the location of a brain tumor,
16 the small glimpse that David mentioned, which we get
17 sometimes in small specimens. So, that's a very good
18 analogy.
19 But like the ornithologist, we're going a step
20 further and beginning to classify these lesions on other
21 bases, and I'll mention some of that.
22 But the talk that I think Dr. Hirschfeld and I
23 decided on was more the challenges presented by CNS tumors
24 in classification. I will go through some of these and
25 then will summarize this picture. This outline is present

1 in today's handout.
2 The first challenge is that unlike birds which
3 occur as distinct species, albeit sometimes difficult to
4 recognize if you don't get a good look, brain tumors
5 overlap a good bit in their histologic appearances, and it
6 is a very subjective endeavor. And it is an art. I think
7 David is quite right. You see medical students that come
8 to this instantaneously and are very good at diagnosis
9 within weeks, and other ones it's obvious that, no matter
10 how brilliant they are in other spheres, cannot tell a
11 sparrow from a cardinal.
12 (Laughter.)
13 DR. BURGER: So, this is not a claim this is
14 anything unique. It is a talent.
15 Looking at the brain tumors can be difficult
16 because they overlap. Where this can best be seen in the
17 current problem is this issue of astrocytoma and
18 oligodendroglioma. Now, this is not a burning issue in the
19 pediatric arena, but it is a burning issue for adult brain
20 tumors.
21 Now, to me this is an obvious astrocytoma.
22 We're not going to belabor it. I won't go through the
23 histology. It's not a histology course, but the shape and
24 distribution of the nuclei are those that I would expect of
25 an infiltrating form of astrocytoma, the kind of lesion

1 that in some patients becomes glioblastoma later on.

2 This is an oligodendroglioma. For the
3 physicians in the audience, you can remember the medical
4 lectures about the so-called fried egg cells perhaps.
5 These are typical of oligodendrogliomas.

6 These represent the two obvious extremes. The
7 fact is that in practice, these can look very, very
8 similar, and it is an entirely subjective decision on the
9 part of the pathologist, well, is this oligodendroglioma or
10 is this astrocytoma or is this hybrid entity a so-called
11 mixed glioma? There is no easy answer to this in many
12 cases on histology sections. In the last 10 years, I would
13 say we now have what I would classify as an epidemic of
14 oligodendrogliomas because the standards have become so
15 variable and so loose at many institutions that every brain
16 tumor practically is now called oligodendroglioma.

17 Fortunately, in the last 5 or 6 years, it's
18 become recognized that there is a genetic abnormality which
19 seems to typify oligodendrogliomas. At least the classic
20 versions. This is a simultaneous loss of chromosome 1p and
21 19q. This patient also had some other chromosomal losses,
22 but this combined loss of these two chromosomal arms --
23 usually it's the entire arm of both chromosomes, but not
24 always -- seems to represent the molecular equivalent of at
25 least the large number of the oligodendrogliomas. This is,

1 of course, very good for us, because this is the potential
2 answer to what is now a burning issue as far as diagnosis
3 of adult brain tumors.
4 If one looks at the effect of this abnormality
5 on outcome, one finds very striking and satisfying results,
6 as well as an illustration of the problem of diagnosis by
7 conventional means. This was from the rather landmark
8 study from Cairncross and Lewis on the effect of treatment
9 on malignant oligodendrogliomas when compared to the
10 genetic abnormality. Those high grade lesions which had
11 the particular chromosomal abnormality had a relatively
12 favorable survival where those that did not had a very poor
13 survival. What it illustrates is that all of these were
14 called malignant oligodendrogliomas by the pathologists and
15 yet almost a third of them did not match on the basis of
16 the genetic testing.
17 We have a study from the group that we're
18 involved in where there was a panel of neuropathologists
19 looking at this same issue. There were three of us and the
20 diagnosis was reached if two of the three of us would agree
21 on the diagnosis. There were I think 40 or so that were
22 called oligodendrogliomas by at least two out of the three
23 of us. Well, fully a third of those turned out not to be
24 oligodendrogliomas if you assumed the genetic abnormality.
25 So, it showed that even with experienced people, you get

1 different diagnoses. When all three of us agreed and by
2 strict criteria, we were right almost every time. So, it
3 tells you that bird watching in terms of tumor analysis can
4 be very subjective. It depends on one's own sense for this
5 and criteria and, of course, the size of the specimens
6 we'll talk about later.
7 Another problem in CNS tumors, as it is in
8 other tumors, that's well known but perhaps belatedly known
9 in brain tumors, is that one diagnosis may have several
10 different, distinctive genetic subtypes. Glioblastoma now
11 is recognized, to a large extent, as occurring in at least
12 two and probably other subtypes, known as primary and
13 secondary. I'll show you a slide in a minute that the
14 medulloblastoma is now clearly multiple neoplasms that
15 could hide under the same name.
16 This is an illustration, which I believe was in
17 the blue book which you got earlier, summarizing two of
18 these pathways in the glioblastoma multiforme. This was a
19 diagnosis which 10 years ago was just glioblastoma
20 multiforme, recognized as having different histologic
21 appearances, but the assumption was it was basically the
22 same tumor.
23 Well, in the last few years, the work in a
24 number of laboratories has sorted this out in part that
25 some of these are known as primary. These are the classic

1 lesions of adults, particularly the older adults. It makes
2 up perhaps 80 percent of glioblastomas.
3 The idea is that there's no obvious precursor
4 lesion in these lesions. You don't have a biopsy at age 40
5 that is a lower grade astrocytoma that then evolves into a
6 glioblastoma. These patients present with a fully
7 malignant lesion. It's not to say they don't evolve, but
8 if they do, we don't notice it. They have a certain
9 genetic abnormality -- and we'll show you an example of
10 this -- such an amplification of the epidermal growth
11 factor receptor which is associated with a rapid
12 proliferative rate. There are p16 deletions, RB
13 alterations as well.
14 The so-called secondary lesion is one which can
15 be observed in many instances. The lesion begins as a
16 lower grade astrocytoma like a grade 2 lesion and then,
17 with time, progresses to be overtly a grade 4 or a
18 glioblastoma. This is the kind of lesion that appears
19 that's much more common in children, particularly in the
20 brainstem, and we'll come back to that.
21 These lesions very early on -- the first
22 genetic change that is noteworthy is the p53 mutation, and
23 there are occasional cases that do occur in the Li-Fraumeni
24 syndrome. So, this probably is an early if not a
25 gatekeeper event in this pathway, but it is not in this

1 one. It can occur here later, but it's not operative early
2 on.
3 These can get other alterations, and the two
4 can overlap in a number of ways. But this concept of two
5 pathways is a good example of heterogeneity of neoplasms
6 within one blanket diagnosis.
7 At present, there's no known prognostic
8 significance to this, although it may shortly be the case.
9 The so-called primary lesion has certain
10 molecular changes. It occurs without this precursor and
11 occurs generally speaking in the cerebral hemispheres of
12 older adults.
13 This would be a good example of the so-called
14 primary glioblastoma multiforme. This was a diagram, a
15 horizontal section of the basal ganglia. The ventricle is
16 here. These dots are just an attempt to represent small
17 tumor cells, and if one does any number of genetic studies,
18 in this case FISH, for EGFR these cells have multiple
19 signals consistent with a high degree of amplification, a
20 typical primary glioblastoma.
21 The so-called secondary lesion has certain
22 molecular changes. Notably the p53 mutation occurs early.
23 They can be shown in some cases to evolve from a lower
24 grade lesion. They occur on the cerebral hemispheres of
25 young adults -- and by young adults I mean 20s and early

1 30s -- and in the brainstem of children, which is a classic
2 spot for astrocytomas in children. They also occur in some
3 variant, which is known as the giant cell type, which is
4 perhaps a third pathway.
5 These lesions are rather heterogeneous
6 microscopically. One can find areas in some of them at
7 least of the precursor lesion which is presumed to have
8 been there for years, and if one does FISH, you get the
9 appropriate two signals for the gene itself and controls
10 rather than seeing this advanced degree of amplification.
11 Now, medulloblastoma is a similar but, in a
12 way, perhaps better defined. It's a lesion which is
13 intriguing a lot of people because of its subdivisions.
14 There are a number of molecular alterations which can be
15 summarized here. One is the loss of much, if not all, of
16 the short arm of chromosome 17p creating this
17 isochromosome, since there's a duplication of the long arm.
18 There is a group of genes that are abnormal in the so-
19 called hedgehog signaling pathway, the principal of which
20 is the PTCH1, but there are several others that occur with
21 lesser frequency. There are abnormalities in the WNT
22 signaling pathway, particularly the beta-catenin gene, and
23 occasionally an APC gene. Then there are some lesions
24 which are amplified for either c-myc or n-myc, generally
25 c-myc. You can easily suspect that these represent, at

1 least this group and this group, entirely separate
2 neoplasms, although they've been given the same name.
3 It's of interest that this PTCH group has been
4 thought by some observers to be the very nodular lesions,
5 and it's the nodular lesions which have the PTCH receptors.
6 This is part of the paradigm which you heard of earlier
7 from Scott Pomeroy for lesions which do better. So, there
8 may be a correlate in that chart earlier that these
9 represent the track receptors in the nodular lesions and
10 they have this gene and belong to this pathway and are
11 quite different biologically than this group.
12 Amplification in medulloblastoma is not a
13 common event, and it's not clear where it occurs in here.
14 But it would appear to be a very highly unfavorable
15 prognostic feature.
16 Now, another abnormality of the brain tumors
17 that makes it difficult, as I said earlier, is this
18 heterogeneity. We have some lesions which are in the
19 brainstem that have one type of pathway, whereas the
20 glioblastomas in the cerebral hemisphere of the adult are
21 in another different pathway. So, if you compare adults
22 and children with glioblastomas, most of the lesions in
23 adults, at least by the current concepts, would not have a
24 strict equivalent in children. They would be the primary
25 type, where it's the subset of the adult lesions which

1 correspond to the pediatric lesions.

2 There's not been a great deal of work on

3 classifying pediatric high grade gliomas.

4 Another possibility is that some pediatric

5 gliomas arise from genetic or microsatellite instability,

6 defects in DNA repair, which are very, very uncommon in the

7 adult scene. So, that's perhaps another or additional

8 difference between these two.

9 Another challenge or special challenge of the

10 CNS tumor is what we refer to as regional heterogeneity.

11 This obviously occurs in other tumors, but it seems

12 especially prominent in brain tumors. If you look at a

13 diagram of a glioblastoma, you'll note various sizes and

14 shapes of symbols. It's just an attempt to illustrate the

15 complexity of glioblastomas in terms of the differences in

16 histologic appearance, region by region.

17 There's been very little work on arrays or

18 cytogenetics of these various regions. So, I'm not sure

19 what this means, but it is a fact that many of the brain

20 tumors are different from one region to another. So,

21 studying one part may not provide results that are

22 applicable to others.

23 So, there is variation in profile by age. I

24 illustrated the pontine glioblastoma, and that appears to

25 be similar to the secondary GBM of adults. The pediatric

1 glioblastomas seem to be different in this respect. There
2 is certainly regional heterogeneity.
3 Then finally we come to specimen size. This is
4 one of our constant comments at meetings, particularly when
5 we get a chance to collar neurosurgeons, that the size of
6 the specimen is very determining sometimes about our
7 ability to come to a specific diagnosis. It's like
8 identifying the sparrow by one feather. It's possible
9 sometimes, but it's not always possible. So, the needle
10 biopsy enters this lesion, for example, which is a
11 glioblastoma, and if it happens to pass within a millimeter
12 in this case, one gets a diagnosis of an astrocytoma of
13 perhaps grade 2 or grade 3, vastly underestimating the
14 malignancy of the lesion. So, the sampling problem in
15 dealing with CNS specimens is quite real.
16 Here is a needle biopsy. The surgeon is
17 extracting the tissue from the canula. Actually this is
18 not a bad size piece. If we went to the OR and got this,
19 we wouldn't be complaining. Well, we'd be complaining but
20 not too much.
21 This is a specimen. This is not a bad
22 specimen. Last week I photographed with these in place,
23 and these are grains of table salt. So, it gives you an
24 idea of the size of specimen that we get. Again, this is
25 not, by any means, a small specimen. We deal with this all

1 the time. We certainly deal with specimens that could
2 easily be covered by one grain of salt. Now, sometimes you
3 can make a diagnosis. Other times it's totally
4 noncontributory. Other times you can say, well, there's a
5 tumor here but we can't be sure what it is.
6 This, of course, is the appeal of the genetic
7 approach to this. We can imagine that the grain of table
8 salt will call for hundreds of nuclei, which with today's
9 amplification techniques, we could get a perfectly adequate
10 view of the genetics of these lesions even in this
11 specimen, which is very small. There's a lot of work going
12 on into pathology doing exactly that, developing the micro-
13 dissection techniques by which we can pick out an area of a
14 tumor and then have it assayed for its genetic or gene
15 expression qualities.
16 Then this effect of size might be illustrated
17 here. We'll look at two different birds. This is the
18 classic brainstem glioma, which makes up 85 percent of the
19 so-called brainstem gliomas. It's an astrocytoma. It has
20 the p53 mutation. It progresses quite commonly to
21 glioblastoma, and despite any treatments, most of the
22 patients are dead within a year. It's a miserable disease.
23 It fattens the brainstem for reasons which are not clear,
24 almost always occurs right in the base of the pons, not
25 usually in the midbrain or the medulla, and no effective

1 treatment.

2 This is another brainstem astrocytoma. This is
3 the pilocytic astrocytoma, which David illustrated earlier.
4 In this case it's an enhancing mass which, as is not
5 uncommon, occurs here on the medulla. Unlike the previous
6 lesion which diffuses throughout the brainstem and is not a
7 candidate for surgical removal, this lesion is fairly well
8 circumscribed and lends itself to excision, at least
9 partial excision. Even if it's partially excised, it may
10 persist for years or decades without doing much harm
11 because it is generally slowly growing.

12 But they're both astrocytomas. In a small
13 specimen, they can look very similar, and many pilocytic
14 lesions have been diagnosed as just astrocytoma, which is
15 true. It is an astrocytoma, but it's not a specific
16 diagnosis and it is really not as helpful as it might be.

17 These are survival curves. We went through a
18 series at Hopkins of brainstem astrocytomas, and we looked
19 at them by the pathologic features. The curve at the top,
20 the magenta curve, is the pilocytic lesions. As you can
21 see, they do extremely well, albeit not always without
22 symptoms. This group, which I illustrated in the MR scan,
23 is the so-called fibrillary lesions. As I said, most of
24 these patients are dead in one year. So, here you have two
25 astrocytomas, different types which behave in entirely

1 different ways.

2 Hopefully, we can distinguish these in part by
3 their clinical features and their neuro-imaging, as David
4 Parham indicated, but it does call for the need for better
5 techniques than histology because we get very small pieces,
6 as you might imagine, from brainstem glioma. So, molecular
7 approaches or expression approaches to brain tumors are
8 highly welcome by those of us who have to deal with trying
9 to identify birds at midnight when we really can only see
10 back end of them.

11 Now, the last thing is the idea of entities.
12 The question comes up quickly, well, what is an entity?
13 Birds are pretty obvious. They do fall in the very strict
14 category. At least I assume they do. I guess they can
15 interbreed, but I don't think that happens very often. I
16 presume that genetically they can be segregated as well.

17 Well, these are the entities of brain tumors,
18 and this is from our bird book that David illustrated. You
19 can see there are lots of them. The problem is that this
20 is not an exclusive list. I'm quite sure that many of
21 these entities here are really multiple entities of one.
22 You've heard about medulloblastomas. It's a well-defined
23 entity right here, but it's clearly three or four diseases
24 in one and probably in different degrees of malignancy,
25 even within a given disease.

1 There are many new entities waiting to be
2 discovered. The problem is trying to recognize them and
3 define them. The question is, well, how do you define a
4 new entity? That's not always straightforward.
5 This is a kind of lesion that we have seen
6 every so often in the Pediatric Oncology Group and in our
7 consultation practice. It's a child with a very large,
8 hypothalamic, suprasellar lesion which has already spread
9 to the subarachnoid space. There's a separate nodule here
10 in the pre-pontine system in the subarachnoid space and in
11 the fourth ventricle.
12 This is a lesion which we call the pilomyxoid
13 astrocytoma, for use of a better word. It's piloid. The
14 cells are long like hair, and it's myxoid because it has
15 myxoid features. Our experience with these is that these
16 are 2 years of age or less. They're usually large and
17 suprasellar, as you see here. They have some features of
18 the pilocytic astrocytoma, which we illustrated a minute
19 ago, but not all of them. They're more prone to rapid
20 recurrence and CNS spread than the classic lesion.
21 The question is, is this separate from
22 pilocytic astrocytoma, and the answer is, I don't know that
23 yet. I think it's a separate entity, but our initial
24 genetic tests with comparative genomic hybridization have
25 not revealed anything specific about them. Ideally we'll

1 find at some point some genetic abnormality in the
2 pilocytics, which is not yet known, or in this group, and
3 we can compare them and establish is this indeed a new bird
4 species. It certainly behaves like one, but it overlaps a
5 bit with the pilocytic astrocytoma.
6 I'm quite sure there are many other entities
7 waiting to be described. We see a good bit of pediatric
8 material and you see things other people have trouble with,
9 and there's a high incidence of odd things in there. The
10 question comes up, well, is this something new? Is this a
11 new kind of bird or is this just a variation of an old kind
12 of bird that we recognize? I think that the genetic
13 techniques are just ideally suited, if we can make these
14 distinctions and create a molecular or gene expression
15 pedigree of various entities, which will help in
16 classification and treatment.
17 So, to summarize, there is a lot of overlap in
18 brain tumors, particularly astrocytoma and
19 oligodendroglioma, but also between astrocytomas. That
20 problem is complicated, of course, by the specimen size.
21 It can be very difficult in little pieces to determine what
22 this is. There are molecular subtypes of the glioblastoma
23 or the medulloblastoma. Ependymomas probably have
24 different types. The classic ependymoma of the spinal cord
25 in adults has frequent NF-2 gene mutations, whereas the

1 intracranial lesion, which is a childhood tumor, does not.
2 So, even though we have the same term, we're probably
3 dealing with different lesions.
4 There are variations by age. This will come
5 up, I'm sure, later when we look for treatments that might
6 be applicable both to adults and children. You can argue
7 that in the case of glioblastoma, there are those but they
8 are a minority of adult patients, but they are the majority
9 of pediatric tumors which fall into this so-called
10 secondary pathway.
11 There's extensive regional heterogeneity in
12 tumors.
13 I think importantly there are a host of
14 undescribed entities or subcategorization of entities that
15 exist already.
16 So, I really appreciate your attention. I'm
17 delighted that David brought up the subject of birds
18 because it really does fit in perfectly with my own
19 approach to the classification of tumors. Thank you.
20 DR. SANTANA: Thank you, Dr. Burger.
21 I think we do have time for some questions.
22 David?
23 DR. PARHAM: I think Peter brought up a point,
24 which is very key to what Dr. Golub was talking about, and
25 that is the availability of material for genetic and

1 molecular analyses because, in fact, over the past 20
2 years, the trend has been to obtain less and less tissue.
3 Now many pathologists and many practice groups are
4 advocating fine needle aspiration even for diagnosis of
5 small cell tumors. I think this is going to have a
6 profound effect on what he was proposing. So, if we do
7 develop a protocol, you have to take this into
8 consideration that there's actually a strong group that's
9 very vociferous about getting less tissue not more.
10 DR. SANTANA: Dr. Boyett?
11 DR. BOYETT: It seems to me, though, that you
12 could still have the same sampling problem because, as you
13 showed, with that needle biopsy, if you missed the primary
14 tumor location, it really doesn't matter whether you're
15 using your eyes or you're using gene microarray chips.
16 You're likely to get a different answer.
17 DR. BURGER: Well, we would hope that the
18 genetics would be more consistent from area to area, at
19 least a baseline level. There may be additions in some
20 spots, but the principal early lesions would be there. It
21 would be obvious what was going on.
22 DR. HIRSCHFELD: Dr. Burger, you've persuaded
23 us that it's much better to be a splitter than a lumper in
24 terms of classifying brain tumors. But are there classes
25 of tumors, similar to what Dr. Parham described for the

1 non-rhabdosarcomas, where the distribution between adults
2 and children is different but the classes are approximately
3 the same?

4 DR. BURGER: You mean classes in terms of
5 histologic -- well, the glioblastoma would be one with the
6 qualifications that they're not genetically always the
7 same. There's a subset of glioblastomas in young adults
8 that is similar to those in children.

9 Having said that, if you look at the lesions
10 that are called glioblastoma in children, you realize
11 pretty quickly that some of them look sort of odd, and you
12 really would wonder whether those are glioblastomas that
13 have anything to do with the same lesion in adults. It's a
14 largely unexplored area. Some of these terms like
15 glioblastoma are pretty vague. It's a pretty broad
16 description that will encompass many lesions. So, I think
17 again it's going to be the genetic or expression testing
18 that's going to say, well, this is a different category
19 even though it fulfills some criteria.

20 Medulloblastomas occur both in children and
21 adults, although it tails off pretty quickly after the 20s.
22 It has been claimed they're good news and bad news,
23 relatively in that group. Histologically they can look
24 quite similar to the pediatric ones, but even then,
25 pediatric ones have different histologic subsets.

1 Ependymomas look similar but the distribution
2 is different. They usually are spinal in adults and
3 probably different genetically. In pediatrics, they're
4 usually intracranial, often infratentorial. So, they
5 overlap in some sense but perhaps not genetically.
6 The oligodendrogliomas are just uncommon in
7 children.
8 That's the main groups.
9 DR. DAGHER: Just to follow up on that with
10 regard to the oligodendrogliomas, you mentioned the 1p and
11 9q deletions, and I think you were focusing there your
12 comments on the adult situation.
13 DR. BURGER: Right.
14 DR. DAGHER: So, again, trying to relate those
15 in children, knowing that they're less frequent in
16 children, in terms of the frequency of these two deletions
17 in children, is there much known about that versus the
18 frequency in adults and how they might relate to each
19 other?
20 DR. BURGER: I'm not aware of a study that has
21 a child in it. There probably is. Most of the ones come
22 from adult cooperative groups. It's a very good question.
23 That is probably the best example of a thing where the
24 genetics thing really means to mean something. It
25 correlates and has a biologic significance and probably is

1 useful in classification. But as you say, they're not too
2 common in children.
3 DR. SANTANA: No further comments or questions?
4 (No response.)
5 DR. SANTANA: Thank you, Dr. Burger.
6 I'm going to take the chairman's prerogative
7 and skip the break just temporarily and ask Dr. Balis to
8 give his presentation. After that, we'll take some
9 questions and then we'll take a break and then reconvene
10 for the final discussion. Dr. Balis?
11 DR. HIRSCHFELD: While we transition, Dr. Balis
12 mentioned that among his interests was training pediatric
13 oncologists. I had the privilege to receive training from
14 Dr. Balis. I was impressed with, among other things, the
15 breadth of his knowledge, his interest in leukemias and
16 brain tumors and pharmacology, but also that he tended to
17 do things somewhat differently than other people. As an
18 example, most people took the elevator to the 13th floor
19 clinic, and Dr. Balis would walk all the time. I asked him
20 once why he did that, and he said it's a better way to do
21 it. And I think that's why we wanted him on the panel too
22 because he's always looking for a better way.
23 DR. BALIS: At the NIH, it turns out to be a
24 faster way to do it too, unfortunately.
25 (Laughter.)

1 DR. BALIS: The development of new drugs and
2 new therapeutic approaches in children I think to a large
3 extent, at least the way we currently do it, parallels that
4 in adults. When I use the word "parallel" in terms of
5 development, I'm really referring there to the approach.
6 In chronological terms, that obviously occurs in a serial
7 fashion, not so much in a parallel fashion.
8 We heard this morning a very excellent review
9 by Malcolm Smith that focused this primarily on efficacy
10 testing of new treatment approaches. So, I had planned to
11 focus my attention primarily on earlier stages of drug
12 development speaking specifically about investigational
13 drugs. There are two specific topics that I want to
14 address that I think are having a major impact on our
15 ability to do these trials.
16 One is the changing characteristics of the
17 patient population that is being treated on these studies,
18 and secondly the potential change that we're, I think, on
19 the verge of seeing in the characteristics of the drugs
20 that we will be studying in these patients.
21 Now, the other thing we heard this morning was
22 that we're doing much better in treating childhood cancers
23 overall. Approximately 75 percent of children diagnosed in
24 the early 1990s to 1995 will survive at least 5 years. The
25 converse of that is that, as Malcolm mentioned, there's

1 still 25 percent -- in fact, it's at least 25 percent -- of
2 children who will not survive these 5 years. There may be
3 many more that aren't cured because we may be able to get
4 patients through 5 years, but they may not be cured of
5 their disease.
6 Secondly -- and this I think is an under-
7 appreciated fact because we begin to take these things for
8 granted -- is that the acute toxicity of the current
9 therapy, which has become more dose intensive and involves
10 many more agents, can be life-threatening to patients. I
11 think we've gradually gotten to the point of accepting this
12 because it's happened over a number of years. I'll show
13 you an example, in just a minute, of how impressive it
14 really is.
15 Thirdly -- and this is a particularly important
16 point for pediatrics -- is that the long-term effects of
17 cancer therapy can be debilitating or life-threatening.
18 I've heard statistics that in this millennium somewhere in
19 the range of 1 in 1,000 adults walking on the street will
20 be a childhood cancer survivor. If even half of those
21 patients have some long-term effect of their therapy,
22 that's really a major epidemic. And there are all sorts of
23 effects, some of which we heard about this morning: growth
24 delays, cognitive effects, hormonal and reproductive
25 problems, permanent tissue or organ damage to pretty

1 significant organs like the heart and lungs, and secondary
2 cancers which may become more and more significant as we go
3 along.
4 Now, this is data that was published as a small
5 table in the report of the Intergroup Rhabdomyosarcoma
6 Study III. What that table had in there, which I've
7 plotted out as a graph here, is the worst degree of any
8 toxicity that occurred in each patient treated on that
9 study. There were 1,062 patients. They were treated on
10 one of seven chemotherapy arms which we would consider
11 standard therapy for cancer. It's really, obviously,
12 disease specific, but the drugs that we use are not that
13 different from one solid tumor to the next.
14 80 percent of those patients had at least one
15 toxicity that was considered severe, life-threatening, or
16 was fatal to the patient. Now, in any other type of
17 disease or with any other drug, that would be totally
18 unacceptable in terms of the degree of toxicity that it's
19 producing. In fact, it would probably be scandalous if
20 that was reported for another disease. But we've come to
21 accept that as part of what we have to do to treat these
22 patients and to cure them. But I think we should, as
23 people who are looking for new therapies, still consider
24 that unacceptable as the most optimal way to treat our
25 patients.

1 I want to go through this very quickly. I
2 think most people in here are familiar with this, but just
3 to make sure that we are all coming from the same place.
4 The way that we do these studies currently is in phases.
5 The initial phase of clinical testing. The
6 primary objective of that is to define the optimal dose of
7 a drug. The way we currently define the optimal dose is
8 the maximum tolerated dose. What that means is that the
9 drug effect that we are primarily measuring is a toxic
10 effect, not a therapeutic effect of the agents.
11 In addition, we're looking at the spectrum of
12 toxicity of the drugs and at their pharmacokinetics.
13 That's an important point also because that may be one of
14 the differences that we're looking at between adults and
15 children.
16 Phase I studies are not disease specific. So,
17 patients with all diagnoses are eligible.
18 They're obviously done in a dose escalation
19 fashion, and we'll talk a little bit later about how that
20 is selected.
21 The endpoint, obviously, is one of toxicity not
22 therapeutic effect. That is another way that cancer drug
23 development differs in an important way from the way we
24 develop other agents for different diseases.
25 So, once we've defined this so-called optimal

1 dose, then we move to look at the activity spectrum. These
2 studies are done, obviously, in specific diseases at the
3 dose that we've defined in phase I. The primary endpoint
4 of these studies is response, looking at the size of the
5 tumor beforehand and see if it shrinks, which is a
6 relatively crude way of looking at activity.
7 Then phase III, I think as I mentioned, was
8 largely covered this morning. These are efficacy studies.
9 Again, they're disease specific, generally at the same
10 optimal dose unless we have been able to redefine that in
11 phase II. Then the ultimate endpoint of these trials,
12 which I think probably won't change, is survival.
13 Now, the other issue that is obviously
14 tantamount to what we're discussing today is the need for
15 doing separate pediatric clinical trials. There are really
16 two primary reasons for that. One is that we assume that
17 developmental changes that occur during childhood can
18 impact on drug disposition -- I'm referring there
19 specifically to the pharmacokinetics of the drug -- or on
20 the tissue and organ sensitivity, or pharmacodynamics.
21 Now, we are learning more and more about
22 pharmacokinetics, specifically developmental
23 pharmacokinetics, in children. Most of the changes that
24 occur that have the greatest impact on drug disposition
25 occur very early in life. For example, renal function

1 after birth increases dramatically within the first few
2 days of life as renal blood flow increases, and generally
3 by 6 months to a year of age, children have a glomerular
4 filtration rate that is equivalent to what occurs in
5 adults, and tubular function follows pretty closely behind
6 that.
7 Now, if you consider the other primary route of
8 drug elimination, which is probably the most important
9 factor in determining drug levels -- and that's hepatic
10 drug clearance -- it's a lot more unpredictable. It
11 obviously is dependent on the specific enzymes that are
12 involved which are pretty highly complex and not something
13 I'm going to get into today. But in general, most of those
14 changes also occur relatively early in life, at least the
15 most dramatic changes.
16 The other issue here, the issue of tissue/organ
17 sensitivity, is something that we have much less
18 understanding of, but I think one of the things that should
19 forewarn us about what we're doing with current treatment
20 are the data that have been published in the last few years
21 regarding the long-term effects of adriamycin
22 cardiotoxicity in children. With long-term follow-up, we
23 obviously see a lot more problems, which is suggestive, at
24 least for that drug, that a pediatric heart is particularly
25 more sensitive to the toxic effects than is an adult heart.

1 I think this may be true for other tissues and it's
2 something that we need to observe and study better than we
3 have in the past.
4 The other topic, obviously, is the one that
5 we're discussing here today, and that's that childhood
6 differ from adult cancers. In tissue of origin, pediatric
7 tumors being embryonal or mesenchymal primarily; adult
8 cancers being epithelial. The pathogenesis of these
9 diseases -- and we're now down to a molecular/genetic level
10 in defining that at this point. The disease manifestations
11 differ, and the other thing that maybe hasn't been
12 discussed so much is that drug sensitivity is quite
13 different. We know that pediatric cancers respond much
14 better to current therapy than do adult tumors.
15 Now, to get into the topic that I want to
16 discuss primarily, and that first revolves around the
17 characteristics of the population of patients that we are
18 studying, particularly in phase I trials. Phase I studies,
19 as I mentioned, are the dose finding studies which are done
20 relatively rapidly in a small number of patients but are
21 obviously critical to the success or failure of that drug
22 in subsequent phases of clinical development.
23 This was a study that was done by investigators
24 at CTEP in the early 1980s and was published, I think, in
25 1982 or around that time looking at a comparison of doses

1 that were defined -- the MTD there stands for maximum
2 tolerated dose -- from phase I trials that were performed
3 in the 1970s. The overall impression from that was that --
4 and you can see it from the graph there. What's plotted
5 here is the percent difference between adult and pediatric
6 MTDs. So, let's just take for ICRF-187, the pediatric dose
7 was almost 200 percent higher than the adult dose on the
8 same schedule.
9 So, overall what you can see from this graph is
10 that pediatric patients tolerated these drugs, because
11 that's how we define the optimal dose -- it's the maximum
12 tolerated dose -- better than adults. On average, I think
13 there was about a 30 percent higher MTD in children than in
14 adults. There were only three drugs where the MTD was
15 lower in children than adults, and for the most part, they
16 were at least 80 percent of the adult MTD.
17 So, the recommendation, which we still use
18 today, is that pediatric phase I studies use a starting
19 dose that's 80 percent of the adult MTD on the same
20 schedule. For the most part, adult phase I studies will
21 have been completed before the pediatric trials start.
22 Now, I did a similar analysis, although I'm
23 sure not as comprehensive. I tried to look up results from
24 trials that were done in the 1990s. What's in this list,
25 which is I'm sure less than complete, are studies that were

1 published in both adults and pediatrics on the same
2 schedule or studies that I knew the results of personally
3 that may not have been published. But as I mentioned, it's
4 not completely comprehensive.
5 I plotted the same thing, that is, the percent
6 difference in the pediatric and adult MTDs in a percentage.
7 So, what you can see here, just in looking at this graph,
8 is that now most of the bars fall on the negative side, so
9 that in most of these trials, with the exception of these
10 two down here at the bottom, the pediatric MTD was actually
11 less than the adult MTD.
12 Now, I don't think that we're making children
13 differently or there has been a sudden shift in the gene
14 pool that makes them less tolerant of therapy. I think
15 what we're seeing an impact of is the effect of their prior
16 therapy which has changed dramatically from the 1970s to
17 the 1990s and is the reason that we're curing more patients
18 now than we used to.
19 So, this slide is meant to illustrate that, and
20 what it shows is the pathway that patients take and that
21 drugs take through the clinical drug development process.
22 Patients, obviously, start down here at the bottom in phase
23 III trials as their first treatment. These are
24 conventional therapies, and they obviously, if cured, never
25 go past that. As we mentioned, fortunately more and more

1 of the patients are taking this pathway and out after their
2 primary therapy, and fewer are going in this direction,
3 fortunately.
4 But those that relapse -- and sometimes they
5 may have relapsed multiple times -- will eventually
6 potentially get to the point where they are involved in
7 investigational drug studies, and generally they are
8 treated on phase II trials looking at drug activity where
9 hopefully we're treating patients that are less heavily
10 pretreated before they get to phase I studies, which is
11 what we looked at on the last two slides. So, at this
12 point these patients may have relapsed and received a lot
13 of therapy, particularly much more dose-intensive therapy
14 than they did back in the 1970s.
15 Now, the agents obviously pass through the
16 other direction, phase I first where they're used, as I
17 mentioned, in patients that are heavily pretreated, and if
18 they're too toxic, that's the end of it, although generally
19 we can usually define a dose that is tolerable in patients,
20 and then go to phase II where they're inactive, they stop.
21 Down to phase III, if they're not efficacious, that's the
22 end of it, until they get to this point which is obviously
23 a pretty arduous road to take and very few get to this
24 point, even in childhood cancers.
25 Now, as evidence of what I think is a change in

1 the population, this is a phase I study that we did, in
2 collaboration with the Children's Cancer Group, of
3 docetaxel, which is a drug is myelosuppressive.
4 I didn't mention when I had those other two
5 slides up that the drugs that were looked at in the 1970s,
6 those 13 drugs, all 13 of those had myelosuppression as the
7 dose-limiting toxicity in adults, and in 11 of the 13
8 pediatric trials, that was also the dose-limiting toxicity.
9 So, the difference wasn't a pharmacodynamic difference,
10 that is, a difference in sensitivity of specific organs
11 that made those doses different, and the same I think is
12 true for the studies that were done in the 1990s. There
13 was pretty good concordance in terms of what the dose-
14 limiting toxicity was between adult and pediatric trials.
15 It's the dose that was different.
16 So, in this study, we treated initially a
17 fairly standard population of patients that had reached the
18 point of being eligible for phase I trials, and that means
19 that they were pretty heavily pretreated with either
20 standard and sometimes other investigational drugs before
21 they entered onto the study. We escalated up from a
22 relatively high dose in terms of what was being done in
23 adults at that time and rapidly identified a dose-limiting
24 toxicity, being neutropenia, which is the same dose-
25 limiting toxicity that occurred in adults. Our maximum

1 tolerated dose was 65 milligrams per meter squared, which
2 at the time was substantially less than the 100 milligrams
3 per meter squared that was being recommended as an adult
4 dose.
5 So, rather than stop at that point and move
6 this dose into phase I testing, we redefined our
7 eligibility criteria to try to enter a less heavily
8 pretreated population of patients. We limited the amount
9 of radiation they could have had beforehand. We limited
10 the number of prior chemotherapy regimens they could have
11 had. Just by doing that, we were to essentially double the
12 dose. Now, the dose-limiting toxicity which was still the
13 same, primarily myelosuppression, but the maximum tolerated
14 dose was 125 milligrams per meter squared, two times higher
15 than the original MTD.
16 Now, this was a phase I study, but in children
17 especially we do look for responses, and there were a few
18 responses that occurred, all of them above the dose of 65
19 milligrams per meter squared. So, all of them occurred at
20 75 milligrams or above. That's not very much to base on,
21 but it's possible that we could have identified a dose that
22 wasn't optimal in terms of a therapeutic effect based on
23 the fact that these patients were heavily pretreated coming
24 into the study.
25 Now, the other thing that Steven had originally

1 asked me to talk about, and I'm not sure exactly how you
2 would ever address it, is how the drugs that we currently
3 use for treating childhood cancers were selected or how did
4 we come to using what we now call standard therapy. I
5 still don't know how I can answer that question because I
6 think there were many paths that drugs got there, and a lot
7 of it was empirical, particularly back in the 1970s.
8 But one of the points I did want to make
9 regarding that issue is how we currently select front line
10 treatment regimens because this is, again, something that
11 we sort of take for granted because this is the way we've
12 always done it. But I think we have to relook at this
13 again because it really is related to what we're talking
14 about today.
15 For all types of cancer -- and this is a
16 generalization, and this really includes pediatric and
17 adult cancers -- if we have a patient that's standing
18 before us, the way we select their therapy is based on
19 their tumor histology, the stage of their cancer, meaning
20 whether they were localized or widely disseminated, and in
21 some instances based on other prognostic characteristics.
22 I know age has gotten a lot of bad press today, but age is
23 an important one for a lot of tumors. The advantage of it
24 is it's easy to measure, it can be rapidly measured, and
25 it's very reliable, down probably to the day.

1 (Laughter.)

2 DR. BALIS: And it's inexpensive. In fact, I'd

3 be willing to do it for $10 a patient if you want to just

4 send me the birth date and the current date.

5 (Laughter.)

6 DR. BALIS: So, what we are doing here

7 implicitly is basing the selection of therapy for this

8 patient on our experience with previous patients. We pick

9 a drug or a group of drugs because we know they worked in a

10 reasonable percentage of patients that had the same disease

11 stage and prognostic characteristics. We don't base it on

12 this patient's tumor. That's one of the big differences

13 between treating cancer and, for example, infectious

14 diseases where there are a lot of correlates. We can take

15 a bacteria from a patient, test it in vitro, and

16 individualize the therapy for that patient. We haven't got

17 to that stage with treating cancer, and I think if we were

18 at that stage, we probably wouldn't be having this

19 discussion today.

20 So, this approach to treating cancer

21 essentially also drives the way we study new drugs. So,

22 when we stratify patients for studying activity or response

23 of new agents, they're also stratified by tumor histology,

24 not by any other factors.

25 Well, we heard this morning that we were on the

1 verge I think of a revolution in cancer drug discovery, and
2 that's going to, obviously, have a huge impact on the way
3 we develop drugs clinically. That is, now that we're to
4 the point of using what we've learned about the molecular
5 pathogenesis of cancer in developing new treatments and
6 that is developing molecularly targeted drugs.
7 So, these agents are going to be specific for
8 the molecular target or lesion. And I've used the example
9 here of a mutant ras oncogene rather than necessarily on
10 histology. Ras is a gene that's mutated in approximately
11 30 percent of all human cancers, but it's not disease
12 specific and there are diseases where ras mutations occur
13 in a very high percentage, but others where it occurs in
14 maybe less than half.
15 So, we may be basing patient treatment
16 decisions on whether or not this molecular lesion that
17 we're targeting is present rather than on what their tumor
18 histology is. If that's the case, then maybe when we do
19 our drug development trials, phase II studies specifically,
20 that we will also not be stratifying by histology, we'll be
21 stratifying by whether this particular lesion is present
22 before we put patients on study. So, this may change the
23 whole paradigm of the way that we not only develop drugs
24 but by the way we treat patients and select therapy for
25 them at the beginning.

1 Secondly -- and this I think is true for most
2 tumors -- the molecular pathogenesis of adult and childhood
3 cancers are different. Now, this has the potential, I
4 think, to have a huge impact on pediatric cancers
5 especially. Up until now, the way that we've developed new
6 therapies for childhood cancers is to take drugs that are
7 being developed in adults that have been primarily screened
8 in adult tumors. We talked about the 60 cell line this
9 morning, which is being used as a way to randomly screen
10 for drugs. There are no pediatric cell lines in that
11 screen. So, we take drugs that have been screened for
12 because they're active in adult cancers and apply them to
13 pediatric tumors, and because they've been relatively
14 nonspecific up to this point, it worked.
15 But if we now are looking at drugs that are
16 being screened in adult cancers that have a different
17 pathogenesis and are very targeted to that pathogenesis,
18 they may not be applicable to childhood cancers. It's
19 going to be difficult, I think, to convince, drug companies
20 especially to look specifically at the pathogenic lesions
21 in pediatric cancers that occur in 200 patients a year
22 compared to adult tumors like colorectal cancer which occur
23 in 100,000 patients a year. So, we have to be very careful
24 as to how this is going to impact on our approach to
25 developing drugs overall.

1 We then get down to the point of endpoints of
2 the trials when we develop these, starting at phase I. I
3 mentioned earlier on that our primary endpoint in phase I
4 studies is evaluating a dose-effect relationship with
5 toxicity. If we now are able to identify a specific
6 target, we may be able to look at blocking that target as
7 an endpoint of phase I studies, a pharmacodynamic endpoint,
8 a therapeutic endpoint, rather than a toxicity endpoint for
9 the studies. So, that's another paradigm shift in the way
10 that we develop agents, or at least in the dose-finding
11 studies.
12 Then the other thing that is likely to be very
13 different and hopefully will be improved over what we have
14 now is that the toxicity profile and dose-limiting
15 toxicities may be different than for cytotoxic agents, and
16 I think not only does this has the potential advantage of
17 having less toxic therapy for children, which I think is
18 still an important goal to strive for, but it's going to
19 also impact on how we do phase I studies and how we select
20 a starting dose because we may not be able to base it on
21 the same data that we've used for selecting a starting dose
22 based on adult trials with cytotoxic drugs.
23 I think the one example that we have to show
24 for that from that previous graph that I showed you are
25 retinoids. Retinoic acid was developed because of its

1 activity in acute promyelocytic leukemia, but there's a lot
2 of data that Pat I'm sure could tell us about that
3 retinoids may also be important for differentiation of
4 pediatric tumors. But this is a drug that doesn't have
5 myelosuppression as a dose-limiting toxicity. Look at the
6 difference between the pediatric sensitivity to that. A
7 dose is almost 80 percent less than adult doses. So, we
8 can't assume, I think, with new agents that come along that
9 aren't cytotoxic that we can use 80 percent of the adult
10 dose as a starting dose for pediatrics. We have to start
11 over in looking at how we're going to do even dose-finding
12 studies with these agents.
13 I think that's all I have to say. Thank you.
14 DR. SANTANA: Thanks, Frank.
15 Questions? We have a couple minutes for
16 questions. Jim.
17 DR. BOYETT: I think you made a good point
18 about phase II trials when you're using an agent that has a
19 specific target, but I think I'm reminded of an example --
20 and I may not have this quite biologically correct, but
21 McDonald's virus that kills cells has a particular mutation
22 in the p53 gene. When that was used, they were surprised
23 to see responses in patients who didn't have that mutation.
24 What happened was all they had to have is a nonfunctioning
25 p53 pathway. So, I think we have to be careful that, at

1 least in the beginning, to think we know exactly the
2 mechanism of action that some of these things that we think
3 are targeted.
4 DR. BALIS: Well, I think that's absolutely
5 true. One of the disadvantages of molecularly targeted
6 drug development is that we focus in drug screening down to
7 a sub-cellular level. I think the approaches at treating
8 ras mutations is a good example of that. The primary
9 approach we talked about this morning was the development
10 of farnesyl transferase inhibitors. Ras is a farnesylated
11 protein and farnesylation is required for membrane binding
12 and activity. So, these drugs were screened looking at how
13 well they inhibit that enzyme specifically. In actual
14 fact, if you expose cells that don't have mutant ras to
15 these drugs in vitro, it works just as well as in cell
16 lines that have mutated ras.
17 So, the biological effect, when you move from
18 an enzyme to a cell to an organism, may not be predictable
19 from what happens in the initial screening process. I
20 guess it's like not seeing the forests for the trees. We
21 have to evaluate that at every step along the way.
22 DR. SANTANA: I want to comment a little bit on
23 this problem that I think we're going to be facing. I
24 think it would be fair to say that for traditional
25 cytotoxics, the types of toxicities that we see in children

1 versus adults are very similar. The degree and the
2 incidence may be different, but the spectrum as a whole is
3 the same.
4 I think the problem and the challenge is going
5 to be with newer agents, whose mechanism of action is not
6 the traditional cytotoxic, whether there will be unique
7 toxicities that can only be ascertained in a pediatric
8 population. I'm trying to think of, for example, the
9 angiogenesis inhibitors and whether those have anything to
10 do with retinal development and things like that that you
11 could not identify in an adult population, but will become
12 uniquely identified in a pediatric population. How do we
13 do those studies but at the same time not hinder the
14 development of those agents in pediatrics? Because they
15 may be active in certain scenarios. Can you comment on
16 that quandary, Frank?
17 DR. BALIS: Well, I think what it means, just
18 like it has for many years, is that separate studies will
19 have to be done starting with phase I trials in children.
20 We have to be vigilant and anticipate that there may be
21 side effects that can occur that weren't described in
22 adults. Certainly that was the case with retinoids. I
23 suppose there are adults with pseudotumor cerebri that have
24 taken retinoids, but I don't think it's very common,
25 although we did pick it up when we did the phase I trial as

1 a dose-limiting toxicity.

2 DR. SANTANA: Dr. Finkelstein?

3 DR. FINKELSTEIN: I wonder if you'd comment on
4 the following. Based on the very interesting curves you
5 showed of the 1970s and 1990s, up to now pediatrics has
6 waited for the phase I study in the adult before we've been
7 almost "permitted" to use it in the child. Based on your
8 data, would it not be reasonable to conclude that the basic
9 scientists in pediatric oncology should pick the drug and
10 there's no reason to wait for the adult study, and they can
11 go on in parallel?

12 DR. BALIS: I think that there are arguments on
13 both sides of that. On one extreme when we wait, there are
14 instances where drugs get approved for adult indications,
15 and that makes it much more difficult to do pediatric
16 trials because you can prescribe the drug. So, for agents
17 like taxol, there was a period of time after it was
18 initially approved that people were just giving it because
19 they knew it was an active agent, and it was very difficult
20 to study it in a pediatric population.

21 On the other hand, if a drug has a catastrophic
22 toxicity that's not picked up in animal toxicology studies,
23 I don't think you'd want to learn that in a pediatric
24 population.

25 But there is a compromise in between, and we've

1 in fact proposed doing combined trials that start with
2 adult patients and on the same study but a step behind,
3 start entering pediatric patients. We can finish those
4 studies within one dose escalation within a couple of weeks
5 to months in adults and children at the same time, but
6 still provide a safety margin of being able to observe a
7 dose or a drug in adults before they're treated in
8 children.
9 DR. SANTANA: Malcolm?
10 DR. SMITH: It is a difficult situation, and in
11 large measure it always comes back to the problem of the
12 limited numbers of children that, thankfully, are available
13 for phase I trials and, therefore, the limited number of
14 agents that can be developed. So, to a large extent, we
15 depend on the adult studies and those initial phase I
16 studies and, in some cases, the early phase II studies to
17 identify which agents are too toxic, which agents have some
18 unrecognized, unanticipated toxicity that precludes their
19 further development, and which agents look like they're
20 going to be real drugs that not only have cured mice or
21 delayed tumor growth in mice, but actually can achieve a
22 therapeutic window in humans.
23 So, if we started a phase I study with every
24 adult phase I study, it's impossible. There just aren't
25 enough patients to do that. So, how do we prioritize, and

1 how do we learn what we can from the adult studies and I
2 think what we discussed this morning, how can we be smarter
3 about using preclinical data in a uniform and systematic
4 way to pick which of the new drugs we're going to
5 prioritize for evaluation in the pediatric population?
6 DR. REYNOLDS: Frank, I've been a big fan of
7 the concept of one-step-behind combined studies until I
8 really started to think about it and realized that the
9 adults are starting so far down on the scale at 10 percent
10 of the toxic dose in animals. So, I wonder if there's some
11 modification of that concept needs to --
12 DR. BALIS: Yes, exactly right. I think
13 obviously there need to be some criteria as to when the
14 pediatric patients start. It wouldn't be at the same dose
15 level.
16 The advantages, though, as you probably know,
17 are first of all we'd be looking at the same dose levels.
18 What happens now when we start at 80 percent of the adult
19 MTD is that we end up not looking at the same dose levels
20 that adults did, just by the fact that we're starting at 80
21 percent of what they picked as their dose and we're
22 escalating by somewhere between 20 and 30 percent upward,
23 sometimes de-escalating as we saw on those slides. But
24 that makes it difficult to compare. We don't do the
25 pharmacokinetics in the same way. It's a different group

1 that's measuring it. They may be using different sampling
2 times. We're obviously looking at different doses.
3 One of the things that we should be learning
4 from phase I studies is how children compare to adults.
5 That's the whole point of doing them separately, but I
6 don't think they're optimally designed to do that because
7 there are lots of things about them that aren't comparable.
8 The other thing, obviously, is how you define
9 an MTD, what you'd call dose-limiting toxicity? They may
10 be different, and that's one of the difficulties in doing
11 that analysis that I showed you. It varies obviously
12 amongst different adults. It's gotten a lot more
13 standardized now than it has been, but it still isn't
14 standardized to the point where it may be the same on every
15 study that's done. I think if we can't compare children to
16 adults, then we're losing a lot of information from doing
17 these trials separately.
18 DR. BOYETT: Perhaps we should also rethink the
19 design for phase I trials. The MTD is empirically defined
20 as a function of patients who present themselves and has
21 really no statistical basis whatsoever. It's only been
22 statistical apologists in later years who have tried to
23 give some justification for the 3 and 6 design we use. And
24 we've gotten comfortable I think with the 2 and 6 and sort
25 of what that empirically might say about the underlying