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Tobacco: Nicotine [2]

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1 nicotine -- we selected them based on a report that they
2 had smoked at least 15 cigarettes per day for at least two
3 years.

4 At least for some people, that is not sufficient
5 to establish life-long dependence, and indeed, by the time
6 we see them out here somewhere, they look no different
7 than these chippers who never smoked heavily. So
8 exposure, even at a relatively high level, is not
9 sufficient to develop nicotine dependence.

10 (Slide.)

11 That is some of the things we think we know.
12 There are lots of things we don't know. I think these are
13 really basic questions.

14 One is -- and I gather this is the sort of
15 question that Dr. Kessler was asking of us -- how much
16 smoking, and I think we need to be careful with what the
17 units are -- time, unit doses, or total nicotine
18 absorption -- how much smoking is needed to produce
19 dependence? I think that is a key question.

20 How does escalation proceed? Again, we know
21 something about we proceed to daily smoking, very little
22 about what happens after that.

23 What is the nicotine delivery of cigarette smoke
24 by new initiates? I am sure you have all had the same
25 experience. That when you think about a field that is not

1 entirely your own, you think, oh, they must know all this
2 stuff.

3 I just assumed we knew the nicotine delivery of
4 cigarettes that kids smoked. I am prepared to be
5 corrected, but we were unable to find that. That is, we
6 know the brands they smoke.

7 They smoke the heavily promoted brands like
8 Marlboro, but Marlboros know come in so many varieties and
9 nicotine deliveries, that that doesn't tell us much about
10 the amount of nicotine they get.

11 So this is an easy question to answer, but we
12 need an answer to it, and how this changes over time. And
13 I guess Martin Jarvis was suggesting he has some data on
14 this.

15 And I think, critically, we need to ask what is
16 the role of nicotine *per se* in each stage of initiation,
17 and I am using initiation broadly to talk also about the
18 development of dependence.

19 (Slide.)

20 We tend to think of this in a stage model. So
21 that is how I have outlined it. I have tried to outline
22 what I think we know, often not very certainly, about the
23 contribution of psychosocial and pharmacological
24 processes.

25 Obviously, for first exposure, pharmacology

1 can't have any effect, because the organism has not been
2 exposed, although the effect of that first exposure, that
3 is, whether you like it or not, whether you get sick or
4 not, may well be a function, for example, of
5 constitutional differences in nicotine tolerance and
6 sensitivity.

7 We think we know that after first exposure,
8 there occurs a period of intermittent highly variable use.
9 In our retrospective data, and in Howie Leventhal's
10 prospective data, what you see is that lots of people, for
11 example, may go a year from the first cigarette to the
12 second. Others progress in the first day. So huge
13 variability, and there is just a period when smoking is
14 highly variable.

15 We know that psychosocial factors play a role.
16 I don't think we know much about pharmacological factors.
17 But I think there is something we can speculate on that, I
18 think, is very important.

19 And that is, there is some evidence that if the
20 first cigarette makes you feel awfully sick, you are less
21 likely to progress to the second cigarette. That is the
22 prospective data from Leventhal.

23 To the extent that nicotine toxicity itself is
24 responsible for some of that feeling sick, that is where
25 one of the potential harms from the policy could result.

12/94
1 That is -- Jack already raised this -- we could
2 develop a wonderful starter product that you can learn to
3 use without making yourself and thereby enhance the number
4 of kids who persist in smoking after that first one.
5 So reducing nicotine effects may not be an unalloyed good
6 thing.

7 There is a period of probably -- this, I think,
8 we don't know -- but I am fairly certain that smoking then
9 regularizes somewhat at less than daily. There is then a
10 period of daily smoking, during which I think we don't
11 know whether addiction set in, but there may well be a
12 period of daily but not addictive smoking.

13 And, again, theoretically -- there is no data on
14 this that I know of -- it has been proposed that these
15 stages where the person is not yet dependent, it may be
16 the non-dependent-related pharmacological effects of
17 nicotine that are important.

18 That is, the person may be starting to
19 experience negative affect management with nicotine. They
20 may be starting to experience performance enhancement
21 effects of nicotine, perhaps appetite control effects.

22 So we need to consider how effects of nicotine
23 other than dependence and withdrawal play into this part
24 of the process, and then there is a period probably of
25 acceleration from this, during which tolerance and

1 dependence are developing.

2 The point is -- [tape gap] -- about the role of
3 nicotine out here, and I think, very little at these
4 earlier stages. And particularly because we know that the
5 vast majority of people who enter this funnel out here
6 will not progress to this outcome, which is of greatest
7 concern to us, we need to understand what role nicotine
8 plays in that process.

9 (Slide.)

10 And I have already raised the issue of
11 unintended negative consequences, one of which being
12 reducing the adversiveness of an initial exposure.

13 The other is: Let's assume that even before
14 dependence -- back-track -- we usually think of nicotine
15 regulation and titration as a function of dependence; that
16 is, that in order to avoid withdrawal, people sort of
17 upregulate their intake from cigarettes in order to
18 maintain a certain nicotine level.

19 But it is also probably the case, as the
20 example, I guess, Jack raised of near beer -- well, he
21 didn't raise that one exactly -- but, you know, there are
22 policies in some states, I think, still today that if you
23 are below a certain age, you can buy beer, but it has a
24 lower, could we say, alcohol delivery, alcohol yield.

25 The effect of that policy from a brief survey of

1 my teen-age friends is to get them to drink a lot of beer,
2 probably with adverse consequences for kidney and bladder.

3 So the point is that even -- and it is not
4 because they are dependent -- it is because they are
5 seeking alcohol effects.

6 So it seems to me at least possible that
7 reducing the nicotine yield may produce increased smoking
8 even in non-dependent smokers and thereby increase the
9 harms that are due to carbon monoxide and tars. So that
10 is another possible adverse consequence.

11 (Slide.)

12 One point that Jack has already raised, and
13 Ovide really raised it already, is that we can't assume
14 that the population that we are addressing with a policy
15 or a study is homogeneous.

16 And we need to consider genetic variability,
17 psychosocial variability. Naomi Breslau established quite
18 nicely that depression is a huge risk factor for adoption
19 of smoking and development of smoking, of nicotine
20 dependence.

21 The question is whether changing the nicotine
22 delivery of cigarettes will have a different impact on
23 people who have this risk factor than people who don't.
24 and since we know that social factors like having peers
25 who smoke are important factors, we need to know how that

1 plays or interacts with a policy or experimental change.

2 (Slide.)

3 I think a critical research need is -- and this
4 goes in the category of tools, along with experimental
5 cigarettes -- is some good method for assessing the
6 dependence in adolescents.

7 Again, the literature has mostly not even tried
8 to do this. And I think there is some significant
9 barriers. For example, it may be at those stages, it is
10 less tied to smoking rate. So that some of our adult
11 measures that rely a lot on smoking rate may be apt.

12 But also that smoking may have a very different
13 ecology. And let me give you an example of what I mean by
14 that. All of you know that one of the best markers of
15 dependence in adult-dependent smokers is how soon after
16 waking you have your first cigarette.

17 Well, if you are a 15-year old, that is probably
18 controlled by whether your parents are home or not rather
19 than by your inherent nicotine need. So I don't think --
20 my point is I don't think we can take adult measures, dumb
21 down the language, draw cute little pictures, and have it
22 be a kiddie dependence measure.

23 I think we need to develop measures, and I think
24 that will help get us at early indicators and markers so
25 that we don't have to do the 15-year prospective study.

1 (Slide.)

2 So the -- let me change the order -- a word
3 about methods. I am very cognizant of the issue that Tom
4 has raised, which is, if this research is to be policy
5 relevant, it needs to be quick. And if this research is
6 to happen, it needs to be relatively cheap.

7 And so I think we need to ask ourselves not only
8 what is the absolute best way to answer this question, but
9 also what is a reasonable approximation that may be cheap
10 and quick. And there is a cost for cheap and quick, but
11 there are also some benefits.

12 So, for example, at the extreme end of validity,
13 the things we regard as most valid, are probably
14 experimental studies. We have touched on the fact that
15 experimental studies in humans about development of
16 dependence may have significant practical and ethical
17 problems.

18 In this case, actually, animal studies may be
19 extremely useful, because we can do things in those
20 contexts that we can't teen-agers.

21 I think something we need to consider is what
22 data we already have that address these questions. And
23 without being able to give you the specifics, I am quite
24 convinced that the data are -- or significant amounts of
25 data are already in the file cabinets and computer files

1 of people around this table and elsewhere.

2 That is, for example, while the data in papers
3 are often reported in terms of age, it wouldn't surprise
4 me if many of those investigators had data on age of onset
5 and could, therefore, translate this developmental
6 description in number of years smoking rather than age.

7 Another example is I don't know whether the
8 brand data were collected in more detail, but aggregated
9 into name brands like Marlboro. So there is a lot of data
10 we may already have, and that is by far the quickest and
11 cheapest way to get at this.

12 While I think longitudinal data have huge
13 advantages, I think we need to look at whether cross-
14 sectional data, especially if they are carefully designed,
15 have some utility.

16 And I think we need to look at quasi-
17 experimental designs. For example, it is my understanding
18 that the shift in nicotine delivery of cigarettes that has
19 occurred in the United States over the last 15 years
20 toward lower yield brands has not taken place in some
21 other countries.

22 And so we have, in essence, we have a quasi-
23 experimental design, where one could potentially study
24 what does the process of initiation and development of
25 dependence look like when the market is dominated by low-

1 yield cigarettes versus high-yield cigarettes.

2 Again, my point is that we need to consider a
3 variety of designs that may be imperfect, but fast and
4 cheap.

5 (Slide.)

6 To sum up some key questions then around this
7 central question, I think there is a tools question about
8 how to assess nicotine dependence in adolescents. I think
9 we need to look at not just the question of does nicotine
10 delivery influence dependence, but to ask that question by
11 stage, because the answer is likely to be different.

12 This is the question I kind of raised earlier.
13 Whether it is the total dose of nicotine that matters
14 versus the kind of dynamics of nicotine over the smoking
15 day.

16 We need to ask, I think, about unintended
17 negative consequences, both about whether a low nicotine
18 cigarette might be a starter product that gets more kids
19 to take up smoking.

20 And whether compensation occurs earlier in the
21 smoking career, not because of dependence and trough
22 maintenance, but because kids may, at some point, be
23 smoking for direct nicotine effect.

24 So those are, I think, are some of the overall
25 questions. And with that, let me stop and get the ball

1 rolling.

2 DR. GLYNN: Thank you. It is rolling well.

3 While all the questions that we are addressing today are
4 important, I think this is one more, and equal in
5 importance -- this is more equal than others, dealing with
6 the children's issue in the U.S. right now.

7 Also, just as an overlay, too, Norm Krasnegor
8 made the suggestion earlier about dealing with the ethics
9 of dealing with adolescents, and it is something we do
10 have to address in the questions that we are dealing with,
11 particularly as you have to go through IRBs.

12 Saul raised a lot o questions. I see a lot of
13 hands. Let's start -- I am left-handed -- we will start
14 going from left to Michael Russell.

15 DR. RUSSELL: Thank you. I think one of the
16 important things is you mentioned the pharmacological and
17 the psychosocial aspects.

18 One of the important things is how important
19 some of the pharmacologic facts in the very early stages.
20 I think that an even more important thing is how they
21 interact in a positive way with the psychosocial.

22 Because in animals, it has been shown how very
23 rapidly smoking doses of nicotine induce the enduring
24 adaptive changes of both tolerance and sensitization after
25 only ---

1 It starts after five, say, daily injections of
2 nicotine at smoking equivalent levels, and by the time of
3 10 days, you have got changes that are enduring as long as
4 the rat has had no nicotine for as long as 90 days. And
5 if you then give the shot of nicotine again, it is like
6 the newly adapted state.

7 Now, why children escalate, I think, is that we
8 have heard that if you start off and it is an unpleasant
9 experience, initially the effects of nicotine are not
10 rewarding.

11 If the psychosocial motives to have the next
12 cigarette are strong enough to make the person have
13 another one despite knowing that it is not very pleasant,
14 or even unpleasant, what chances have they got of not
15 going on, when they rapidly -- their system changes to
16 finding it tolerant to the unpleasant effect and perhaps
17 even starting to get sensitization to more pleasant
18 effects.

19 That means that it is very important the stage
20 at which they get the unit dose that is going to give the
21 pharmacological effect. So you need to -- in trying to
22 study, see when they are getting a unit dose of nicotine
23 that is going to give a pharmacological effect.

24 Now, cotinine, you have got to work it out in a
25 certain way. I suggest you also incorporate into your

1 design expired carbon monoxide and take it before -- the
2 trouble is you have got to get them to smoke a cigarette.

3 But if you can pass that ethically, if you could
4 get a nicotine boost from -- a CO boost from before to
5 after, 6 parts per million CO, expired CO boost, will tell
6 you that that child is getting a pharmacological effect of
7 nicotine sufficient to sensitize the (?) dopamine system
8 and develop tolerance to other aspects.

9 DR. GLYNN: Thanks. Steve.

10 DR. GOLDBERG: Well, it was mentioned a few
11 times that the possibility of using preclinical studies,
12 and that actually my focus.

13 What we are doing -- what we have been doing
14 recently, and there is very little work that has been done
15 with things such as acquisition or initiation of drug-
16 taking behavior, even with more commonly drugs such as
17 cocaine.

18 You can use groups of naive subjects if you are
19 using animals to study initiation of nicotine self-
20 administration and dependence. If you are using rodents,
21 for example, you can do it over relatively short periods
22 of time. We are using baselines of 14 to 28 days now.

23 Baselines in which we have completely naive
24 subjects, put them into an experimental once a day, do no
25 manipulation so that everything remains constant.

1 And with those studies, you can look at a number
2 of the things you mentioned. For example, there are
3 individual differences.

4 If you go through different rat strains, you
5 find strains such as Fisher that acquire nicotine self-
6 administration very slowly. Lewis also do surprisingly,
7 although they are fast with cocaine. And strains such as
8 the hooded and Sprague-Dawley appear to acquire it, in our
9 hands, quite rapidly.

10 It is also interesting in regard to what was
11 just mentioned that -- so far, our results are preliminary
12 -- but it doesn't appear to be a monotonic function. We
13 started out a dose that worked well on a maintenance
14 basis, and since we have been starting different groups of
15 rats at different doses of nicotine.

16 What we have found is that the optimal dose for
17 acquisition right now is an intermediate dose. So, in
18 fact, by dropping dose, we have speeded up acquisition,
19 and I, unfortunately, can't tell you what the final
20 baseline is. We are still trying to decide whether or not
21 we should stop at 14, 28, or 36 days, what is optimal.

22 Another thing that has come up is that you can
23 very easily look at such things as caffeine exposure or
24 alcohol exposure or other drugs that might have fairly
25 dramatic effects on the tendency to stop using nicotine.

1 And we find very striking effects of caffeine in both
2 squirrel monkeys and rats.

3 For example, we get about a 100 percent increase
4 in acquisition rates with Sprague-Dawley rats that have
5 caffeine in their drinking water over the period of time
6 the experiment is conducted.

7 And in monkeys, we find that in situations where
8 they will not self-administer nicotine, if they are
9 exposed to caffeine, we then get dramatic facilitation and
10 nicotine becomes an effective reinforcer.

11 One of the problems has been that nicotine,
12 although we have demonstrated can function as a reinforcer
13 by itself, usually, the set of conditions is very limited.
14 And you appear to be able to broaden that out in caffeine-
15 tolerant subjects. That is a clear question for human
16 studies.

17 I think Jack did some preliminary things that
18 did not bear that out, but it is clearly something that is
19 supported by correlational studies.

20 It is also possible with these types of
21 procedures to look at things such as tolerance or
22 sensitization that develops in concert with the
23 acquisition of self-administration by studying the animals
24 and other procedures at different times. You can look at
25 cotinine levels.

1 So there is a lot that can be done with animal
2 studies that you just can't probably do with human
3 studies.

4 I have been involved in some human studies with
5 Jack using intravenous models, and you can get very nice
6 self-administration in humans with nicotine. You could
7 probably study acquisition over a period of several months
8 rather than decades.

9 I guess I am just curious to what extent you
10 would be limited in the use of naive subjects on paradigms
11 such as that that might not translate over to
12 susceptibility in tobacco smoking.

13 DR. HENNINGFIELD: I think Norm's idea is a good
14 one there.

15 DR. GLYNN: Yes. Dietrich.

16 DR. HOFFMAN: Saul Shiffman showed a graph when
17 a chipper becomes a habitual dependent smoker, he --
18 (inaudible) -- more cotinine than expected. So
19 biochemical -- (inaudible) -- induced.

20 Now I ask to the experts here. Has it ever been
21 measured? (Inaudible) -- and the activity of -- activity,
22 which could be -- dependent on nicotine before, any time
23 you use, you were a chipper. This is biochemical -- that
24 could be measured very well in animals.

25 DR. GLYNN: Neal.

1 DR. BENOWITZ: Well, I would like to respond.
2 There are two lines of evidence in humans that that is not
3 the case.

4 One is that if you give intravenous nicotine to
5 non-smokers and smokers, the clearance is the same. In
6 fact, if anything, the clearance is faster in the non-
7 smokers than the smokers. So there is no evidence of
8 induction. There may be something in smoking that
9 inhibits nicotine metabolism.

10 The second are from Saul's data, where we look
11 at half-life, which is -- you know, admittedly, a function
12 of clearance as well as distribution volume -- but
13 assuming that the distribution volume is the same, the
14 half-lives were identical in chippers and regular smokers.

15 So I don't think there is any evidence that
16 metabolism induction is playing a role.

17 DR. HOFFMAN: Why does he see then more when
18 they become dependent on nicotine -- higher cotinine --
19 the -- went up.

20 DR. BENOWITZ: Well, I think what he is showing
21 that people become more efficient smokers. They take in
22 more nicotine per cigarette as they learn to smoke. I
23 think that is what he is showing.

24 DR. HOFFMAN: (Inaudible) -- assume it has never
25 been measured. Has it been ever measured was my question.

1 You base -- by logical reasoning, you would not assume it.
2 My question is: Has it been ever done -- (inaudible).

3 DR. BENOWITZ: Well, the ultimate pudding is
4 human clearance, and that has been measured. The actual
5 p450, I think, has been looked at in animals. I don't
6 know the data.

7 DR. HOFFMAN: I don't know. I don't know.

8 DR GLYNN: Martin.

9 MR. JARVIS: I think Saul showed that in sort of
10 magic explosion, leading to dependence, happening after
11 daily cigarette smoking had been reached.

12 But I think one of the really critical questions
13 is whether it has happened before that. That daily
14 cigarette smoking is actually the endpoint, and the major
15 features have happened by then.

16 That really does reinforce this need to get the
17 very fine grain look at the psychosocial and the
18 pharmacological processes going on over that quite short
19 period often between their first experimentation and
20 getting to the daily smoking point.

21 DR. GLYNN: Jed Rose.

22 DR. ROSE: You have further challenged one of
23 Saul's assumptions, which, in a way, was the most obvious
24 assumption. I am not sure that it is documented and may
25 be a hole that needs to be filled; that is, that the first

1 cigarette ever smoked is not smoked for pharmacologic
2 reasons.

3 If we allow for interactions between
4 psychosocial factors and pharmacology, in line with what
5 Mike Russell was saying, how do we know that some teen-
6 agers don't start to smoke because they heard that smoking
7 calms you down, because of a pharmacologic effect.

8 So, in other words, if there are cigarettes in
9 the market that have pharmacologic effects, that can
10 influence the person's decision to light up that very,
11 very first cigarette.

12 So we need to find out if people -- is there any
13 way of getting a handle on how many teen-agers smokes
14 because of anticipated pharmacologic effects.

15 But, if so, then there could be not only an
16 unintended adverse effect, but actually an unintended
17 positive effect, which is that not only is the progression
18 from experimentation to addiction retarded by removing
19 most of the nicotine, but maybe even experimentation is
20 reduced, because the nicotine has been taken out.

21 DR. GLYNN: Let's go across the back here:
22 Harry, Norman, and Elaine.

23 DR. LANDO: The population that we may want to
24 look at, and I am thinking about some of the ethical
25 issues in adolescents -- we are doing intervention now in

1 a very large population of Air Force recruits in basic
2 training. I think the average age is about 18.7. They
3 cannot smoke during basic, and that is under six weeks.

4 One of the concerns is that there is huge
5 initiation approximately -- the last group I had -- of 13
6 percent non-smokers initiate smoking the year after they
7 enter the Air Force.

8 This may be an interesting population to look
9 at. It may be a bit telescoped in terms of rapidity of
10 acquisition, but we may be able to address some of the
11 questions using that type of a population.

12 DR. GLYNN: Norm.

13 DR. KRASNEGOR: Norm Krasnegor. The most
14 extraordinary part of smoking in youth is something that
15 most of us around this table know about, but I think it
16 bears repeating in every context that we are at.

17 The ethnic differences are extraordinary, so
18 extraordinary that it bears a study of some sort. Is it
19 because black kids don't start, or they start and they
20 remain chippers, or that somehow there are protective
21 effects, or the psychosocial effects are going on?

22 There is such a myriad of questions there, and I
23 believe that some keys to what we are asking about in this
24 part of our meeting lie there, and I would put bucks on
25 that.

1 DR. GLYNN: Thanks. Elaine. I don't mean not
2 to be following up on a lot of these, but we want to get
3 them clearly in the record.

4 MS. STONE: I wanted to follow up on a point
5 that Saul made, and that is, I think there are a number of
6 studies that all of us have underway that we could
7 certainly look at to see if we are answering some of these
8 questions and pull them out so that we have them and share
9 them, or add in some of some excellent questions that we
10 have in the next wave of collections or things of that
11 sort. I think we need to pay attention to that.

12 And then perhaps we could use existing
13 mechanisms, such as the small grants or supplements or
14 some of our training awards to add money into existing
15 studies to go back and reanalyze, as you say, a number of
16 the data sets that are sitting there.

17 We maybe have a lot of the information, but it
18 has just not been pulled out or analyzed in a certain way.
19 I know we have done a lot of that with our data sets with
20 a lot of the gender differences, especially with women and
21 have found we have just a wealth of data that are very
22 valuable to the field.

23 And I would suggest another practical way is
24 perhaps is Tom Glynn has been very, very successful in
25 past years, and I think Norm did it also when he had a lot

1 of smoking grants, and that is, bringing together a number
2 of grantees that are doing the research to kind of
3 standardize some of the questions that are added in, even
4 though they are different kinds of studies going on under
5 either collaborative trials or R01s. But that you can
6 still collect some similar kind of information that is
7 very cost effective to advance the field.

8 DR. GLYNN: Thank you. I mean, both of those
9 are good suggestions in the sense of turning things around
10 reasonably quickly and being low cost and getting some of
11 the information that we are talking about. John.

12 DR. HUGHES: Yes, I just want to talk a little
13 bit about Norm's question about ethics. NIAAA has put out
14 a pamphlet about administering alcohol to recovering
15 alcoholics. CPDD has put a manuscript about administering
16 cocaine to humans.

17 Perhaps either SRNT or some inter-agency should
18 get together -- not being prospective about what you can
19 and can't do, but raise the issues.

20 For example, we have done studies where we have
21 given nicotine to never smokers and then followed them for
22 three months to see if any of them initiated smoking and
23 had a control group and showed that in these younger
24 people, that the rates of taking up smoking weren't any
25 greater than the subjects in our study that we exposed to

1 nicotine than the others.

2 So there are ways around this, I think. I don't
3 know. But that would be a very helpful thing.

4 DR. GLYNN: Okay. Well, that is something that
5 clearly needs to get into this then is that suggestion for
6 that research -- it is not research, but it certainly is a
7 need in order to facilitate the research.

8 DR. HUGHES: The main reason is each -- IRBs are
9 -- I call them "boy scientists," a bunch of "boy
10 scientists." Some of them will say, the only thing you
11 can do this is people already smoking. Some people say,
12 no, no, they already dependent. You are making it worse.
13 You can only do this in people that sort of chipping.

14 Somebody says, no, no, because they will make
15 them progress to dependent, and other people say, you can
16 do this in naive people. And other people will say, no,
17 no, because then you will make them go from naive to that.

18 DR. GLYNN: Mike Fiore.

19 DR. FIORE: Saul raised two possible harms to
20 this nicotine reduction idea, and one is that if you
21 reduce the adverse effects, then maybe more kids will
22 start. And the second was that maybe kids will smoke more
23 in order to get the delivered dose.

24 I don't know how to get at the first very well,
25 but one possible way to get at the second, and might be

1 addressed in relation to Jacks discussions of developing
2 cigarettes that we would test, is why not have one with
3 zero nicotine and compare that to one with whatever this
4 minimal level is that you are doing?

5 I guess I -- as I was thinking about this, it
6 raises the issue, why go for a minimal level? Why not
7 just have the goal zero nicotine, because that is going to
8 particularly relate as well to adults who are already
9 current smokers. I know this whole issue of how long it
10 takes to get to that level.

11 What are your thoughts, Neal and Jack, on your
12 proposal to go to a minimal level as opposed to having as
13 your goal zero nicotine?

14 DR. HENNINGFIELD: On the range of cigarettes
15 that we need, I think placebo has to be as absolutely
16 close to zero as possible. But there is almost no such
17 thing as zero. There is always some threshold.

18 When you do a contract for the placebo
19 cigarettes that are non-nicotine cigarettes, they won't
20 really be non-nicotine. We have got to set it as low as
21 we possible can, and I think, for research purposes, you
22 need as close to zero as you can possibly get.

23 Then the research is going to determine whether
24 or not you would ever even want to consider some policy -
25 - which I think is a long way from today -- the research

1 would also tell you whether or not, say, down the road,
2 one of the warning labels becomes, "Cigarettes are
3 addictive."

4 And a manufacturer says, I don't think I should
5 have that label. I want to be like non-alcoholic beer. I
6 want to call myself -- I don't warrant it.

7 What is the level that is the cut-off? Again,
8 it is not zero. In the real world, it is not zero. It is
9 some teeny-tiny amount that everybody debates. But I
10 think you are right, for research, it has got to be as
11 close to zero as we can get it.

12 But whether or not you would want to introduce
13 something and do the policy, that is different ---

14 DR. GLYNN: Let's start moving then, left to
15 right. Nancy.

16 DR. GELLER: I have been sitting here, trying to
17 figure out how one could possibly study adolescents
18 prospectively, and then Dr. Lando mentioned the military
19 study. It has certain aspects to it that are just
20 perfect.

21 The first thing is that you know where those
22 people are going to be for a while. The second is that
23 since they are a little older, and by being in the
24 military, are functioning as adults, their tendency to
25 mislead you and lie is much less than in adolescence.

1 The third is that it is a quite an interesting
2 cross-section of the U.S. populating, having a good
3 representation of minorities.

4 I guess the only qualm I have is how much
5 coercion would be involved in making everybody enroll.
6 These are people who are able to sign an informed consent.
7 I really like the idea of studying a military population.

8 Certainly, there are some women. Although one
9 could argue about, I guess, how representative either the
10 men or the women are of the general population.

11 But, nonetheless, it has some very attractive
12 features that going off into the schoolyard to get the
13 smokers doesn't have.

14 DR. GLYNN: Thank you.

15 DR. SHIFFMAN: I think she acknowledged it has a
16 huge down side, which is we know there is some initiation
17 after age 18. We also know that that is atypical and that
18 early initiates are almost completely different than late
19 initiates. The probability of dependence is much higher.

20 So I am not saying we shouldn't do it, but we
21 shouldn't take it as representative of the typical case of
22 initiation -- late initiates have a very low probability
23 of progressing into stable dependence.

24 DR. GLYNN: Okay. Martin and then Terry.

25 MR. JARVIS: Just a comment on the truthfulness

1 of school children. I think my experience of that has
2 been that there is very little problem indeed. That you
3 get very highly accurate self reports.

4 There is very little deception, and it may be a
5 function partly of the fact that if kids are responding in
6 school, their friends all know full well what the truth
7 is, and they perhaps don't let each other get away with
8 telling you not the truth. But really we found very
9 little problem with indeed with that.

10 DR. GLYNN: Terry.

11 DR. GELLER: Just to respond to that, I think we
12 may be dealing with differences across the ocean here. I
13 think -- I don't know what it would take to get informed
14 consent for adolescents to participate in a study here,
15 but I suggest it might be quite different in the two
16 countries.

17 I mean, if the kid comes home -- the kid
18 probably is not going to come home with a consent form,
19 and there are some problems there.

20 DR. GLYNN: Terry and then Gary.

21 DR. PECHACEK: One of the issues that I think I
22 would encourage this group to be very much more open about
23 is non-cigarette delivery systems.

24 I think that we need to stop being behind the
25 industry and behind the curve on these things, and all the

1 companies have their patents in the waiting for both other
2 forms of nicotine delivery devices, RJR being the only one
3 that is venturing out into the open marketplace with
4 theirs. But everybody has them. Everybody is prepared
5 for it.

6 So this whole issue -- it should be discussed as
7 nicotine delivery devices, which may be a broader language
8 to be determined. We know that there are aspects of
9 tobacco, burned tobacco, that have a lot of sensory and
10 even pharmacological or other types of effects.

11 But in this whole issue, we need to be thinking
12 in terms of optimally realizing that there probably will
13 be for several generations more some forms of self-
14 administered nicotine in populations.

15 In terms of harm reduction, the optimal
16 situation is the least harmful modes of self-
17 administration, and those modes that are potentially lead
18 to the least forms of addiction. So it is nicotine
19 delivery in its multiple forms that I think we need to be
20 considering.

21 DR. GLYNN: Thank you. Gary.

22 DR. GIOVINO: [Not at microphone.] Gary
23 Giovino. Just a minor clarification. I think the school
24 surveys in America -- my view of literature -- (inaudible)
25 -- household surveys. Any survey that is being proposed

1 like this would need informed consent, and the process of
2 getting informed consent -- (inaudible) -- would influence
3 the sample ---

4 DR. GLYNN: Saul, then Marc.

5 DR. SHIFFMAN: Following up on Elaine Stone, who
6 was following up on something I said, that is, on the
7 issue of how to make use of data we already have in the
8 can, or are in the midst of collecting, I think a critical
9 issue is crossing -- I don't know what to call it --
10 subdisciplinary boundaries.

11 If you read the literature on adolescent
12 initiation, and you had just landed here from Mars, you
13 would have no idea that we were talking about a drug.
14 There is no -- there is zero -- awareness of
15 pharmacological factors.

16 So I think one of the critical things we need to
17 do that could be implemented, I think, fairly quickly is
18 to, we'll say, encourage, because we don't want to force,
19 collaborations between the people who typically are social
20 psychologists or epidemiologists who are doing these
21 studies of adolescents and more behaviorally and
22 pharmacologically oriented scientists. I think the
23 converse is also probably true.

24 A slightly different issue is that
25 epidemiologists have a problem, a challenge, that we don't

1 usually face, which is that they have to be very sparing
2 in subjects' time. They can't afford to administer a two-
3 hour assessment battery.

4 And, again, unfortunately, until recently, that
5 has led to a singular lack of attention to these issues.
6 That is, we don't to know how much you smoke, when you
7 smoke, just do you or don't you? Quick.

8 So, again, we need to put into place -- I think
9 it would be relatively inexpensive -- mechanisms that
10 would allow for more of this in-depth inquiry that is
11 needed for these questions in large, representative
12 projectable samples.

13 DR. GLYNN: Thank you. Marc.

14 DR. MANLEY: I want to ask what is known to see
15 if this is an area for future research.

16 Given what has come out recently about what the
17 tobacco industry knew and when they knew it, it seems
18 pretty clear to me that they are making decisions about
19 how to construct cigarettes for new smokers, new, young
20 smokers, and that they are basing their decisions, in
21 part, on laboratory studies and, in part, on marketing
22 data. So they probably do have the best information about
23 some of these questions.

24 We have seen in smokeless tobacco the idea of
25 progressing from a starter product to a more mature user's

1 product. And I wonder, do we know, number one, what new
2 smokers smoke, and do we know how those cigarettes differ
3 from -- how they are constructed and what they deliver
4 that is different from other cigarettes?

5 DR. GLYNN: Martin.

6 MR. JARVIS: I think we know a bit about that,
7 and paradoxically, it seems that children actually at the
8 moment tend to start on the high-yielding brands and move
9 down later.

10 They also start off, it is quite well
11 demonstrated, I think, on both sides of the Atlantic, on
12 the most heavily promoted brands. They start smoking the
13 brand leaders, which are the more expensive ones in the
14 U.K. and also high-yielding rather than lower-yielding.

15 DR. GLYNN: Mirjana.

16 DR. DJORDJEVIC: I would like to present some of
17 my data to show like what is going on among current
18 smokers across different populations. You can see what is
19 really happening, especially taking into account our
20 knowledge of how the cigarettes have changed in the last
21 two decades.

22 It started with non-filter cigarettes with very
23 high deliveries of nicotine and tar, and now we can have
24 a sales-weighted average tar of 10 milligrams per
25 cigarette or nicotine, .7, .8 milligrams per cigarette.

1 We just got some interesting data I would like
2 to share with you, and maybe that would give us some ideas
3 whether reduction of nicotine in cigarettes will
4 accomplish what you are trying to accomplish here.

5 DR. GLYNN: Over here please.

6 (Slide.)

7 DR. DJORDJEVIC: [Not at microphone.] (Inaudible)
8 -- related to smoking. The delivery of tar and nicotine
9 in cigarettes reduced from a sales-weighted average in the
10 '50s from 57 milligrams -- in these days, tar levels
11 around 12 milligrams per cigarette, and the nicotine
12 reduced from 2.7 milligrams in the '50s, and today it is
13 around .8, .9 milligrams per cigarette.

14 Of course, you can see that there is a lot of
15 reduction for nicotine was a little bit (?), because
16 people smoked because of nicotine, and if you have a
17 cigarette on the market with low nicotine levels, they
18 really don't sell well.

19 (Slide.)

20 So we designed our preliminary study to look at
21 the smoking behavior of different populations groups
22 smoking low nicotine/tar cigarettes and those of medium
23 nicotine/tar cigarettes.

24 We defined those low in nicotine, all the
25 cigarette brands which contain nicotine lower than .8

1 milligram per cigarette, and the medium nicotine
2 cigarettes those which contain from .9 to 1.2 milligrams
3 per cigarette.

4 You can see that from a population in Mount
5 Vernon, which consists of 50 percent of African-American
6 residents and 50 percent of white American residents, we
7 had accrual of 141 smokers. We recruited for this study 8
8 (?) smokers of low nicotine cigarettes and 4 (?) of medium
9 nicotine cigarettes.

10 Why did we concentrate on these two groups of
11 cigarettes is that they actually represented about 70
12 percent of the market. The cigarettes with ultra-low
13 nicotine yields are not very well accepted by smokers, and
14 they don't sell well.

15 (Slide.)

16 This is just a picture to show how we evaluate
17 smoking parameters.

18 (Slide.)

19 And on the basis of this evaluation, we get
20 information on smoking parameters, including like total
21 smoke to which smoker are exposed and also the puff
22 volumes and puff frequency and duration of puffs.

23 We also get lots of information on smokers'
24 backgrounds in terms of ethnic background, gender
25 information, when they started smoking, how many

1 cigarettes they smoke a day, et cetera.

2 (Slide.)

3 We always test whether our evaluation --
4 (inaudible) -- are correct by also measuring expired CO
5 levels in smoke after extinguishing cigarettes at 10
6 minutes after that.

7 (Slide.)

8 Also by measuring nicotine levels in butts.
9 This is ensure that smoking throughout the day is
10 reproducible. So when we have assessment of smoking
11 profiles, it doesn't really matter at which time of the
12 day we do that.

13 And, also, this is to show when people smoke
14 freely, and also by our computer system, the amount of
15 nicotine in the butt is the same. So we are pretty
16 confident that our laboratory studies reflect accurately
17 free smoking.

18 (Slide.)

19 On the basis of our determination of smoking
20 parameters, what we can see, that all smokers of low
21 nicotine cigarettes, whether they are men or women, or
22 whether they are white Americans or African-Americans,
23 they all take a puff volume which are much larger than
24 would be suggested by FTC methods.

25 They take almost like an average 52 milliliters

1 of puffs, and they puff much more frequently than it would
2 be suggested with FTC methods. Exposure to total smoke is
3 rather high.

4 Also, what you can also see here is that onset
5 of smoking is at very early age. Average is 16, but some
6 people start even as early as 12.

7 (Slide.)

8 We also can see that people of medium nicotine
9 cigarettes also -- compensate for smoking or smoke more
10 intensely to get the nicotine level which is timed by
11 their physiological needs. They also take larger puffs
12 and more frequently than would be suggested by FTC
13 methods, and total volumes are also high.

14 We can see that also these people who smoke
15 medium nicotine cigarettes start smoking at early age.

16 (Slide.)

17 This is just a summary to show that compared to
18 FTC methods, both groups of smokers actually inhale much
19 larger volumes and more frequently, and therefore, they
20 are exposed to much larger amounts of smoke. The same is
21 with -- in a group of medium nicotine smokers.

22 (Slide.)

23 So this is just to show that when the smoke is
24 generated by machine smoking according to FTC conditions,
25 these are the levels of tar which were delivered and the

1 levels of nicotine.

2 We also looked at tobacco-specific nitrosamines,
3 especially this one, which is lung specific, regardless of
4 route of administration, laboratory animals, or regardless
5 of species.

6 This compound always induced lung
7 adenocarcinoma. B(a)P is a surrogate of pHs (?). It
8 induces in laboratory animals squamous cell carcinoma. So
9 we are following these compounds also in our study.

10 But what happens when smoke is generated under
11 human smoking conditions? What was originally known as a
12 low tar cigarette, and what probably -- who smokes --
13 actually knows about that -- and this is the basis of
14 their choice when they go and buy cigarettes.

15 We now all know that smoking is not so good for
16 you -- (inaudible) -- low tar, then you are better off.
17 The way they smoke, they get final exposure to tar levels
18 which are almost the same as it was in the '50s. And also
19 the nicotine levels are very high. We are seeing very
20 frequently -- 2 milligrams per cigarettes, and also the
21 levels of carcinogens and a very parallel increase of tar
22 and nicotine. NNK increase is also three-fold. B(a)P
23 increase is like two-fold.

24 (Slide.)

25 Just to put a little bit of our data in

1 perspective, because we are interested in lung cancer
2 epidemiology, if a smoker smokes a low nicotine cigarette
3 for 30 years, and if a smoker smokes 30 cigarettes a day,
4 then the total cumulative of NNK, which causes lung
5 carcinoma, is 1.6 milligrams per kilogram body weight.

6 And, in this case, for 40 years, it is 2.1
7 milligram. This is when people smoke menthol low nicotine
8 cigarettes. This is for regular.

9 If you look at Belinsky's animal data, we, of
10 course, cannot do a direct extrapolation here, but you can
11 see that minimal dose of NNK to cause adenocarcinoma is
12 1.8 milligrams per kilogram.

13 And that is exactly the order of magnitude of
14 our assessment of human exposure to NNK. If we would have
15 only FTC data, we would never reach this threshold of
16 induction of adenocarcinoma.

17 (Slide.)

18 Just to show you briefly here what happens with
19 the medium nicotine cigarettes when they are smoked under
20 human smoking conditions, again, the levels of tar are in
21 the 30s, 30 milligrams per cigarette, and again, nicotine
22 reaches 2 milligrams per cigarette.

23 (Slide.)

24 Just like to -- one slide more ---

25 DR. GLYNN: -- shorten it down.

1 DR. DJORDJEVIC: Oh, it is done. It is done.
2 Just really to show this. Like here we have the smokers
3 of low nicotine/tar cigarettes, and this is per cigarette
4 -- exposed to 30 milligrams per cigarette and 2 milligrams
5 of nicotine. I am not going to dwell on here.

6 If you take into account then number of
7 cigarettes they smoke per day, then the exposure to tar
8 and nicotine is the following. It seems here that people
9 are daily exposed up to 30 milligrams of nicotine. The
10 average is 27.

11 Almost the same type of numbers you get for
12 exposure to medium nicotine cigarettes. So by
13 compensating (?), they all reach this kind of magic
14 numbers.

15 If you then generalize for overall smokers
16 population, you are talking about 70 percent smokers in
17 the United States which get exposed to this type of
18 deliveries. I don't know whether this will help you in
19 discussion.

20 DR. GLYNN: (Inaudible.) It is relevant that
21 kids starting -- (inaudible). We have five minutes left.
22 Are there still any major questions as far as -- again, I
23 know there is overlap among them, but as far as focusing
24 on the issue of kids and introducing low nicotine and no
25 nicotine content -- there are some major questions we

1 still need to raise. Let's go to John and then Jed.

2 DR. HUGHES: Yes. Just another adverse
3 consequence, unintended effect, is will kids see low
4 nicotine cigarettes as safe cigarettes and, therefore,
5 acceptable cigarettes?

6 DR. GLYNN: Yes, and that goes into some of the
7 psychosocial questions that need to be asked in all of
8 this. Jed.

9 DR. ROSE: There is a basic question which --
10 before I was arguing that based on nicotine patch data
11 that a low sustained level of nicotine is probably going
12 to engender a lot of dependence.

13 However, that should be put more to the
14 experimental test, and one type of finding that has come
15 out of *in vitro* laboratory studies, which could be
16 incredibly relevant, is that, for example, Al Collins'
17 group and Mike Marks and Sharon Grady at the University of
18 Colorado have shown that nicotine receptors on dopamine
19 terminals release dopamine and are thought to be important
20 for the rewarding actions of nicotine can be sensitized by
21 levels of nicotine that correspond to less than 2
22 nanograms per milliliter of concentration.

23 So what may happen if people smoke what are
24 essentially denicotinized cigarettes, but still have a
25 tiny bit of nicotine, is they will, nonetheless, be

1 desensitizing receptors, maybe not activating. But we
2 have no idea what the consequences of persistent receptor
3 desensitization are, and that should be subject to more
4 tests.

5 DR. PECHACEK: In the adolescents, we need to be
6 aware of multiple methods of self-administration and be
7 looking at smokeless mixed with cigarettes.

8 And as smoking bans are now becoming more
9 prevalent in the schools, just coming from the Chronic
10 Disease Conference, some of the tobacco control people in
11 the states are already noting -- now, this is totally
12 anecdotal ---

13 But the fast adaptation of children to the
14 smokeless bans of using Bandit smokeless packets between
15 their toes, in their shoes, in order to self-administer in
16 school. They are incredibly adaptive to this self-
17 administration.

18 DR. SHIFFMAN: Could we do a contract to develop
19 a suppository?

20 DR. PECHACEK: So I think this issue of looking
21 at the initiation, as Jed is saying -- is the steady state
22 use a way of maintaining -- using smokeless as a form of
23 maintaining some degree of steady state and how that
24 interplays with peak pharmacological effects of occasional
25 cigarettes. That needs to be studies in the adolescents,

1 or the early initiator.

2 DR. GLYNN: Dorothy.

3 DR. HATSUKAMI: No, I -- yes, that was what I
4 wanted to do is reinforce the notion that we do have to
5 attend to smokeless tobacco. And just the whole issue of
6 looking at does different pharmacokinetics of the drug
7 affect the escalation of dependence, or obviously, it
8 would have to be used but -- and the ease in terms of
9 quitting.

10 DR. GLYNN: Neal, did you have something?

11 DR. BENOWITZ: I just wanted to reinforce
12 something which came up before. We have tried to set up
13 some studies looking at smoking behavior and kinetics and
14 responses in adolescents and have had enormous difficulty
15 trying to get clearance to do that.

16 I think that is something we touched on a little
17 bit, but that has really got to be dealt with. How do we
18 get IRBs, how do we get ethical consensus, for studying
19 adolescents?

20 That is really the most important question that
21 underlies all of Saul's topic. We have no way right now
22 of studying adolescents to look at smoking.

23 DR. GLYNN: Thank you. Let's kind of segue into
24 the next session. Harry will be beginning the next
25 session except for the cigarette question. Let's end with

1 Harry.

2 DR. LANDO: I think this really is a segue in a
3 sense, because I am thinking about, you know, the issues
4 raised about alternative products or other products -- we
5 think mostly about cigarettes, and smokeless is clearly
6 important -- but other delivery systems that now may be
7 used for treating people.

8 The question is how that affects initiation in
9 adolescents. What options might be available for
10 adolescents. And also in the treatment context with
11 adults, and I will talk a little bit when I get to my
12 section, what impact may be as far promoting cessation f
13 continued use of nicotine.

14 DR. GLYNN: Thanks. I know there are other
15 questions and other issues. Save them please. Let's get
16 back to them after, because I do have an obligation to get
17 people on airplanes, at least to the West Coast tonight,
18 by 5:00.

19 We are going to eat in the Versailles dining
20 room here. We have a half-hour set out. I was joking
21 before about eight or nine minutes. Let's take the half-
22 hour.

23 But I think I really would like to get us
24 started again at 12:15, spend the first 20 minutes as Jack
25 makes -- gets us started on the issue of experimental

1 cigarettes, which, as Neal pointed out, is key to all of
2 this; and then we will get to Harry's section; steal a
3 little bit of time from him and maybe a little bit of time
4 from the last section ---

5 (Whereupon, a luncheon recess was taken.)

6

1 A F T E R N O O N S E S S I O N

2 DR. GLYNN: There is no break scheduled in the
3 afternoon, which means that if you need to get up and walk
4 around or get something to drink, just go back and do it.
5 And also I am sorry that people you want to talk to, they
6 are not going to get to talk to before you leave.

7 So with that, if you don't get the sign-up sheet
8 for the shuttle, and you do need it, make sure you get to
9 Pat Davenport before two o'clock, when we will be making
10 the calls.

11 (Inaudible) -- going to go back to Jack, and we
12 are going to talk about the experimental cigarettes and
13 what we can do to facilitate that.

14 DR. HENNINGFIELD: [Not at microphone.] The
15 idea isn't to work out all the details, but to just ---

16 REPORTER: Will you use the lavalier
17 microphone?

18 DR. HENNINGFIELD: Okay. What we would like to
19 do, and our drill sergeant will keep us to task, I am
20 sure, is spend just about 15 minutes going over a couple
21 of kinds of parameters of cigarettes that would be useful
22 for researchers.

23 Is there anybody that is taking notes or can
24 take -- because rather than put it on the board -- it will
25 take me more time to write out the things.

1 What I just passed out -- those folks can walk
2 on water, because I just gave her the fax about 10 minutes
3 ago -- this is embarrassing, but I thought it might be
4 useful to see what we did.

5 In the contract process, what we have to do is
6 come up with some specs, and then you order it. So this
7 is a little spec sheet that we did last summer. We should
8 get delivery on these things in a couple of months.

9 There were several constraints. One is it is
10 \$10,000 for the whole thing. I did it on my own budget.
11 I didn't have much money to work with. So we just wrote
12 something that we felt would give us something that we
13 could at least start working with, if they are a decent
14 tasting cigarette.

15 The contractor is somebody who comes from the
16 tobacco industry that is really into things like flavor
17 and draw and pressure drop and all those kinds of things.
18 We had a bunch of general things at the end of it for
19 future research. Plans may call for menthol cigarettes,
20 longer cigarettes, non-filtered, filtered.

21 I think it would be a huge mistake, plus there
22 isn't enough money, to try to replicate what National
23 Cancer Institute was doing -- what was that -- 15 years
24 ago or so, with the huge development of cigarettes.

25 But, on the other hand, I don't think we can

1 just find on the marketplace everything that we need. And
2 even if we find a store where they are selling that Philip
3 Morris Next cigarette, that is not a perfect placebo
4 either. And our specs call for something that has half
5 the nicotine of that even, roughly.

6 So what are a couple of kinds of parameters that
7 we should considering, and maybe what we will be able to
8 do is draft something up. And I don't know why we
9 couldn't circulate it back to everybody here, because we
10 don't even know who is going to pay for it yet.
11 Presumably, it is going to be much bigger than this.

12 But within a couple of months, we should have
13 something in your hands that we can see if we are on the
14 right track or not.

15 DR. HOFFMAN: [Not at microphone.] You cannot
16 get any tobacco -- (inaudible) -- with no nicotine;
17 therefore, you will have to -- (inaudible).

18 The disadvantage of -- (inaudible) -- is that
19 you lose some flavor -- you have to insist that they
20 separate in the distillate (?) the nicotine from the
21 flavor component and to give the flavor component back.
22 Otherwise, it would really be the people who smoke --
23 would immediately know the difference.

24 DR. HENNINGFIELD: So independently of what
25 cigarettes we decide, there are manufacturing specs that

1 you could help us with?

2 DR. HOFFMAN: [Not at microphone.] This is
3 -- (inaudible) -- Next. That cigarette is not free of
4 nicotine, because you never get 100 percent.

5 DR. HENNINGFIELD: Yes.

6 DR HOFFMAN: I am only 98. You never make 100
7 percent. But the disadvantage is they lose flavor with
8 the distillate. You put the tobacco under pressure --
9 comes a fluid, extracts it. You open up -- with the --
10 goes the flavor to nicotine over, condensing.

11 Now, you have to separate nicotine from flavor.
12 Flavor has to go back. When you don't do this, you will
13 immediately taste this is a nicotine-free cigarette,
14 because it lacks taste. So that is very important.

15 DR. HENNINGFIELD: One of the principles ---

16 DR. DJORDJEVIC: -- tobacco this way -- you also
17 extract tobacco-specific nitrosamines. So after removal
18 of nicotine and then you return that flavor fraction back,
19 you return also nitrosamines.

20 We analyzed that Next cigarette in the '90s, and
21 it contained a pretty high level of nitrosamines. So that
22 should be considered if you are doing experiments with
23 humans. That will be high delivery cigarettes for
24 nitrosamines.

25 DR. HENNINGFIELD: One of the concepts that is

1 hitting me from this is that we probably have -- it would
2 make sense to specify a couple of different kinds of
3 placebos, in the absence of being able to determine what
4 is the perfect placebo.

5 It may very well be that we need three or four
6 different kinds of placebo cigarettes that involve
7 different processes maybe. And maybe -- again, the Philip
8 Morris Next, as Dr. Hoffman has mentioned, has nicotine,
9 but what we specified was something even lower than that

10 But maybe we need several different types, and
11 that is what we need to know. What are the research
12 needs?

13 DR. BENOWITZ: Jack, you are not looking at
14 placebos -- (inaudible) -- full change -- be tested.

15 DR. HENNINGFIELD: Yes, and how far we go in
16 that direction determines how long it will take, the cost,
17 and what the priorities would be. So we have done that in
18 our first contract.

19 DR. SHIFFMAN: Let me just comment on that.
20 Your proposal, that *New England Journal* editorial, took a
21 first stab at sort of what the level of content or
22 delivery might be based on chippers work. That is a good
23 place to start.

24 But the reality is that we don't know, and
25 therefore, we certainly don't want to build the specs of

1 these cigarettes around this guess that we don't know.

2 That suggests that (a) one needs a range, that
3 we need to have some cigarettes that are lower than we
4 think the threshold is, higher than what we think the
5 threshold is.

6 Since we are thinking pie in the sky, we are
7 thinking of discrete cigarettes, and I am wondering if it
8 might be possible in some way to create a product that
9 was, in some way, manipulable so it was continuously
10 variable.

11 That is, I realize that you are focused on
12 content, because of the issue of compensation, but if
13 certain mechanisms like those -- filter ventilation lends
14 itself more to compensation than others -- if one could
15 imagine a filtration mechanism that doesn't easily lend
16 itself to compensation by the behavior of puffing, et
17 cetera, then perhaps it would be possible ---

18 My mind just goes to some sort of filter where,
19 depending on how it set it, you get a different ---

20 DR. HENNINGFIELD: Well, Jed has done something
21 like this, and we have done it with him, by using
22 hypodermic to add some nicotine.

23 Again, part of the reason that we started with
24 just -- mainly, because we didn't have much money -- just
25 a placebo, which, by the way, is half of the level -- half

1 of the content that Neal and I set. So we are starting
2 lower. The reason it wasn't lower still, because our
3 contractor said he couldn't do it any lower and still give
4 something that tastes like ---

5 DR. SHIFFMAN: No, but since Tom is going to put
6 a lot of money into this, we can ---

7 DR. HENNINGFIELD: We can ask for the sky.

8 DR. SHIFFMAN: Yes.

9 DR. HENNINGFIELD: The possibility that there is
10 a way to have, say, three different series of placebos --
11 see, if you had three or four different placebo types,
12 say, you have got menthol, non-menthol, a couple of
13 different things, and then a whole range of nicotine
14 series, real quick, you are talking about 30 or 40
15 cigarette types, and a boondoggle.

16 DR. RUSSELL: Are you talking about cigarettes
17 that are the type you want that are impossible to
18 compensate, if that is all you can get out of them? Or
19 are you talking about an earlier phase than that, to
20 decide on what levels?

21 DR. HENNINGFIELD: What I am really talking
22 about is what you and others needs. That is, if we get
23 together across a couple of Institutes and put something
24 together and then make it available to the field, what
25 does the field want?

1 I mean, all I have done in this thing, and I
2 just handed it out to give you an example, how we just
3 wrote up a little thing, what you have got to put in to
4 order something.

5 DR. ROSE: Yes, I mean, I agree with you. It is
6 important to have cigarettes with the nicotine extracted
7 from the tobacco. But following up on Saul's point, it is
8 possible to discourage compensation with even ventilated
9 filters.

10 For instance, we published a study a year or so
11 ago, where we took highly ventilated low tar and low
12 nicotine cigarettes and measured smoking in the lab and
13 found that, of course, people compensated on those
14 cigarettes unless we treated those cigarettes with, in
15 this case, capsaicin, which being an extract of pepper,
16 gave a little tingle, you know, throat impact sensation
17 that completely prevented compensatory smoking.

18 So they really got the low nicotine delivery
19 that was programmed by those, even though, in theory, they
20 could have defeated the purpose.

21 But that raises the general issue, which you
22 have also raised of keeping sensory qualities as similar
23 as possible, and having tried to do that with kitchen
24 shelf technology for a number of years, it is not that
25 easy to do. But it is not impossible either.

1 And one of the more promising things, Jack, that
2 you mentioned before the break was whether possibly a
3 nicotine agonist that doesn't cross the blood/brain
4 barrier, which has actually been developed at UCLA, a
5 methylated derivative, which doesn't cross the blood/brain
6 barrier, might have peripheral sensory qualities that
7 match it.

8 If it could be shown that it doesn't get
9 pyrolyzed into nicotine and so forth in the cigarette --
10 although we have shown that you can put these things into
11 the filter of the cigarette, which does not get very hot,
12 and still get some conveyance from the mainstream smoke
13 passing through the filter, picking up the substance,
14 going into the mouth. So there may be a way around that
15 problem.

16 The other possibility you mentioned, which I
17 don't think is very promising, is the DL stereo isomers in
18 nicotine, because it turns out they have radically
19 different taste potency, in addition to CNS potency,
20 because there are nicotine receptors in the mouth and in
21 the respiratory tract, which mediates some of these
22 sensations.

23 It makes it very challenging, because there is
24 some -- in other words, there is a kernel of truth in what
25 the tobacco industry says, which is that nicotine does

1 have marked sensory qualities, and it is going to be a
2 challenge to match those.

3 But I think it would be worth a stab at some
4 sort of non-sensorially active mimic that could make these
5 a placebo.

6 DR. HENNINGFIELD: On the ventilated issue,
7 these are wonderful, and again, what we can do is put
8 together some things and send it back out around. Because
9 it doesn't make any sense to develop something that
10 everybody says is not what we wanted.

11 But on the ventilated issues, you know, from one
12 perspective, you don't want ventilated cigarettes, because
13 you don't want any possibility people defeating the dose.

14 Maybe you need at least two different series of
15 cigarettes: one where the entire series is ventilated,
16 since what -- about 70 percent of the American market in
17 cigarettes is ventilated?

18 If that is an important feature of the
19 sensations, maybe you have to have a series like that, at
20 least core research, even though it would have
21 limitations. The question is: How many series can we pay
22 for? How many priorities?

23 DR. HUGHES: Jack, I think one of the things
24 that I would suggest is that you have high nicotine
25 cigarettes in this series as well, because many of the

1 dose response functions are inverted U functions. You
2 need to know where you are on that curve. So we need the
3 high ones as well as the low ones.

4 DR. HENNINGFIELD: Absolutely. I think, without
5 any question, we need a full range -- real high, in the
6 high end.

7 DR. : [Not at microphone.] NCI had
8 -- standard reference cigarettes -- in the '70s. They are
9 still available now -- (inaudible) -- for what that is
10 worth. I don't know where they stand ---

11 DR. HENNINGFIELD: They, unfortunately, don't
12 have a good placebo. I think, in fact, the best ---

13 DR. : [Not at microphone.] No, no
14 placebo, but you were talking about high end.

15 DR. HENNINGFIELD: Yes.

16 DR. SHIFFMAN: They are awful cigarettes in
17 terms of palatability. We are using them.

18 DR. HENNINGFIELD: My subjects -- of Camels.
19 And they said, a real camel.

20 DR. : Or what is behind the camel.

21 DR. : Like I say, I never tried one,
22 but I know they are available -- (inaudible).

23 MR. SHOPLAND: Weren't those really to look at
24 animal models? They were not used, I don't believe, for
25 human adaptation.

1 DR. HENNINGFIELD: We had to sign a form that
2 said we wouldn't give them to people or something.

3 NCI had a better series. They didn't have a
4 placebo, but they had a more palatable series.

5 DR. GLYNN: Jack, is the way of proceeding then
6 with this is you -- it sounds like you might be able to
7 put something together -- research -- actually come out
8 with a different set of specs that everyone can ---

9 DR. HENNINGFIELD: Well, I think I have got
10 enough material to start drafting something, and over the
11 next week, if you folks take a look at this three-page
12 thing, and just use it as a model, and just pencil in your
13 own wish list. That would be real helpful. Then you will
14 see some of the kinds of things that have to be
15 considered.

16 DR. SHIFFMAN: Jack, we have heard some, I
17 think, creative ideas about how to do this in a way that
18 would be very slick, but wouldn't probably take a while to
19 accomplish. Maybe it makes sense to think of short-term
20 and long-term agendas.

21 A short-term agenda is to get something out to
22 this research community quickly, using current technology,
23 which is, I think, where you have been headed, and I think
24 we need that. And then maybe there needs to be a longer-
25 term development track to think about, you know, the

1 methylated nicotine or some of these more novel strategies
2 for the long run.

3 DR. HENNINGFIELD: When you give us feedback,
4 prioritize. Say what would you like as quick as possible.

5 DR. HOFFMAN: [Not at microphone.] Additives
6 you cannot do. You cannot have anything -- (inaudible)
7 -- U.S. government agency -- additive -- irritation of the
8 throat, you are a dead dog -- you cannot do that.

9 DR. HENNINGFIELD: Yes, this has been a tricky
10 process.

11 DR. BENOWITZ: You know, I also add to what
12 Dietrich said. That these cigarettes need to be as close
13 to what we think might be a marketable type of cigarette,
14 or a palatable cigarette, especially if we are going look
15 at things like compensation experimentally.

16 Because we don't know what are people really
17 going to do with these cigarettes, as if these cigarettes
18 were the ones that were available. They have to be
19 acceptable cigarettes that taste and have to meet ---

20 DR. HOFFMAN: Right. Obviously -- (inaudible)
21 -- very low dose -- then two, three -- you can't do that.

22 DR. HENNINGFIELD: As soon as we get whatever we
23 get, anybody that -- and somehow we will let people know
24 -- I forget how many. It is a lot more than we need, but
25 not enough to do a lot with. As far as I know, we can

1 just send them out to investigators.

2 DR. HOFFMAN: May I -- the major effort --
3 before I use this cigarette -- (inaudible) -- that they
4 meet your requirements -- (inaudible) -- studies done.
5 Therefore, I would be very sure before you give this
6 cigarette out that they have met your requirements.

7 DR. HENNINGFIELD: That is why I would like to
8 send them to you. I have already talked to a number of
9 people, which is why we would like to, as soon as we get
10 them, send them to investigators, not people, especially
11 those animal investigators.

12 Because we have to find out -- we might find out
13 in five minutes that I spent \$10,000 for shoe leather --
14 we wanted to get the process -- so we came up with this
15 last summer as we were waiting ---

16 DR. HOFFMAN: -- crazy ways of spending ---

17 DR. HENNINGFIELD: The shut-down slowed up a
18 little bit in phase 2, but I was told last that in January
19 we should have them.

20 DR. GLYNN: Assuming that December 15 is not
21 another shut-down.

22 DR. HENNINGFIELD: Well, that wouldn't affect
23 this -- second phase of money.

24 DR. GLYNN: That is true.

25 DR. BRESLAU: (Inaudible.)

1 DR. GLYNN: Obviously, this is an overriding
2 factor. No experimental cigarettes, no experiments. So
3 it is something we need to address, and it sounds like we
4 have got a good start on.

5 The next topic actually mirrors the last topic
6 of the morning, where we talked about whether reducing
7 nicotine content in cigarettes would -- how that would
8 affect youth uptake?

9 Clearly, what came out there was that we don't
10 know a lot to start with. So there is a whole different
11 set of questions or many different questions from what
12 we might anticipate with adults, where we do know a little
13 -- a decent amount more.

14 Harry Lando has agreed -- and I can't remember
15 what I -- I know I used patriotism with Saul. I can't
16 remember whether it was ---

17 DR. LANDO: It wasn't Bosnia.

18 DR. GLYNN: It wasn't Bosnia, and it certainly
19 wasn't (?). Harry out of the goodness of his heart agreed
20 to lead this discussion and get us started.

21 WILL REDUCING THE NICOTINE CONTENT OF TOBACCO OVER
22 TIME FACILITATE SMOKING CESSATION IN ADULTS?

23 DR. LANDO: Thank you. Okay. I speak in the
24 mic here? Okay.

25 I have to admit I had some trepidation in terms

1 of agreeing to do this, because there is a very serious
2 question in my own mind as to how relevant some of the
3 work that we have done with adult smokers, volunteers who
4 are interested in quitting, who we have done nicotine
5 fading with over a period of three weeks, would translate
6 to the kind of national experiment that we are talking
7 about with people who often have little or no interest in
8 quitting. Let me get the first slide here.

9 (Slide.)

10 But what I want to do -- I am just going to try
11 to prime the pump a bit -- present a minimal amount of
12 data that we have got and then try to raise a few
13 questions.

14 What we had done several years ago on a study
15 that Paul McGovern and I published was to compare nicotine
16 reduction filters against brand switch, and assuming that
17 these filters would be more resistant to compensation than
18 simply switching brands of cigarettes.

19 (Slide.)

20 It was something that people could readily do.
21 We were using the context of treatment. We wanted to give
22 people a concrete success experience.

23 (Slide.)

24 This particular study, 110 subjects evenly
25 divided between men and women, fairly heavy smokers.

1 Baseline reported consumption 32.6 cigarettes per day.
2 The nicotine-rated content at .83.

3 (Slide.)

4 These people actually went through a smoking
5 cessation clinic, and a reason for that was to try to
6 maximize compliance in terms that we were taking cotinine
7 measures and taking carbon monoxide measures. People were
8 trying to quit, and we wanted to make sure that we were
9 getting those measures.

10 (Slide.)

11 Out of the 110 subjects, 10 actually quit
12 prematurely. So we lost some data from them.

13 What we found as far as CO reductions in this
14 volunteer population -- remember that the rated levels of
15 the cigarettes and the rated levels of the filters were 30
16 percent, 50 percent, 80 percent reduction, one week at
17 each level.

18 By the end of week three, the nominal reduction
19 should have been 80 percent. It was actually 35 percent
20 with no overall significant difference the nicotine fading
21 filters or the brand switching.

22 (Slide.)

23 Now, I don't want to get into this too much.
24 There is kind of old history, but, you know, our cotinine
25 data is somewhat limited by problems in terms of unusable

1 samples, samples actually being lost by the laboratory.
2 So there is complete measurement for only about half of
3 the sample.

4 (Slide.)

5 And what we found was a non-significant
6 difference, but in the direction of the filters, leading
7 to a greater nicotine, as far as cotinine. Approximately
8 half the cotinine being eliminated.

9 (Slide.)

10 And this just puts it in table form. You can
11 see, I think, the biggest reduction occurs after they
12 have been on the rated 80 percent reduction filters or the
13 brand of cigarettes rates 80 percent less. So at that
14 time, you are seeing approximately a 50 percent reduction
15 in cotinine levels.

16 (Slide.)

17 We found -- this is more -- relevant to the
18 treatment context -- that rated self-efficacy increased
19 rather dramatically between baseline and quit. It is a
20 relatively small sample.

21 We had limited power for detecting differences,
22 but you know, reasonable point prevalence abstinence in
23 the context of a smoking cessation clinic, using this kind
24 of method.

25 We use nicotine fading a lot as a preparation

1 method for quitting. Again, in motivated adults, and
2 again, in a very circumscribed time frame.

3 (Slide.)

4 Now, very preliminary data -- just saw this in
5 the last few days -- where we were looking at using
6 nicotine fading as preparation for nicotine replacement,
7 basically three conditions.

8 Assigning to active nicotine reduction filters
9 or to placebo filters and then following with nicotine
10 replacement, either active filters which we thought would
11 reduce the cotinine, but 50 percent, based on the prior
12 research, followed by an 11 milligram patch or placebo
13 followed by either an 11 milligram patch or 22 milligrams.

14 But we found in this particular case, that the
15 actual cotinine reduction was only about 28 percent rather
16 than the 50 percent we had gotten before.

17 (Slide.)

18 This is a bit busy. I guess the key point --
19 the zero is the baseline level. There were three weeks
20 then when they were doing the preparation in terms of
21 reducing by rated 30, 50, 80 percent.

22 You are seeing the drops really occurring at the
23 point where they are doing the rated 80 percent reduction.
24 And then weeks four and five, they have actually been on
25 nicotine replacement, the 11 milligram or the 22

1 milligram. So these are the cotinine levels you are
2 getting with nicotine replacement.

3 Part of what we are trying to do is to smooth
4 the transition from the preparation to the use of nicotine
5 replacement and possibly look at putting people on lower
6 doses and shorter doses of nicotine replacement.

7 (Slide.)

8 We looked at withdrawal symptoms, using the
9 Hughes and Hatsukami scale. Again, it is kind of busy,
10 but a thing that I think stands out, recognizing there is
11 only a 28 percent reduction on cotinine in the active
12 filter condition, and there was no reduction in the other
13 conditions, as you would have expected ---

14 But you are not seeing, as you look particularly
15 at week three, where there as the reduction in week three,
16 we are not seeing any kind of significant withdrawal
17 effects or increasing withdrawal, which we might have
18 expected.

19 And that is probably not surprising, given some
20 of the past literature, 28 percent reduction, we really
21 are not seeing anything. We are seeing an increase in
22 withdrawal when people are quitting and are now on
23 nicotine replacement, al though they are not dramatically
24 high figures.

25 (Slide.)

1 So that is one piece. We have done a fair
2 amount of work with nicotine fading. Another thing is
3 kind of stimulated by Saul's work with chippers in a
4 slightly different context.

5 A large-scale work site intervention, and we
6 looked kind of *post hoc* at occasional smokers in this
7 population.

8 (Slide.)

9 So it had the advantage of being a longitudinal
10 evaluation. It had the advantage of being rather large
11 with 32 different work sites. Random (?) workers were in
12 each site These were not just smokers.

13 (Slide.)

14 The intervention was for weight and smoking, but
15 we had a pretty sizable sample. We had 5,600 employees,
16 almost 700 employees interviewed at baseline. We had a
17 cohort that was then followed up two years later, so we
18 could see some trends in a longitudinal study.

19 (Slide.)

20 Of our smokers, 18 percent were occasional
21 smokers at baseline, which was defined in this case as
22 less than daily smoking, and only 13 percent of those
23 smokers were what we call uptake smokers. In other words,
24 only 13 percent of these less than daily smokers had
25 started smoking within the previous five years.

1 Of these smokers, one thing that I thought
2 interesting is that more than half, almost 60 percent, had
3 at one time smoked more than 10 cigarettes a day, and 28
4 percent, at one time, had smoked more than 20 cigarettes a
5 day. So a number of these occasional smokers were at one
6 time moderate or heavy smokers who had converted.

7 (Slide.)

8 We also found in this -- and this was primarily
9 non-intervention -- the occasional smokers, within a two-
10 year period, 31 percent of them had quit at follow-up.
11 That compared to 15 percent for the overall smoking
12 population.

13 You can see that most of them then remained
14 either occasional or light smokers. Only 11 percent over
15 the two years had moved to smoking either at a moderate or
16 heavy level.

17 Okay. So that is just a bit of a teaser for
18 some data we have. What I would also like to do is just
19 raise a few questions, and I need my overheads here.

20 (Overhead.)

21 That helps. So you can probably read it a
22 little better this way anyhow. Some of these, I think --
23 there were some questions that clearly, I think, were
24 anticipated this morning.

25 There is some overlap. Some of them are fairly

1 obvious; some of them may be less obvious. Some of them
2 may be figments of my own imagination. And I should also
3 say and thank -- Dorothy Hatsukami really helped me go
4 over some of this stuff and think about some issues.

5 Clearly, one question is the impact in terms of
6 people who already smoke low nicotine cigarettes. How
7 much that does translate into increased quitting.
8 Obviously, there has been a lot of self-selection there.

9 A key issue, clearly -- thinking about policy
10 issues, practical issues, and issues from the standpoint
11 of implementation.

12 From the standpoint of implementation, how
13 rapidly should we do this? One of the things that is
14 going to be addressed later this afternoon is the issue,
15 clearly, of compensation.

16 There is a down side to having a 10-year or
17 anywhere in that neighborhood implementation period. It
18 may be possible to do it a lot faster. We don't really
19 know.

20 I think we need to really assess more how
21 quickly, in terms of withdrawal discomfort and other kind
22 of issues, we might be able introduce these reductions.
23 To what extent does natural history inform our inquiry?

24 One concern that we have has to do with special
25 populations or vulnerable populations, and I think that

1 was raised in a different context this morning.

2 So for people who are clinically depressed, how
3 do we handle that? People who really use nicotine for
4 mood regulation, which relates to the last point as well.

5 (Slide.)

6 An interesting issue from a treatment standpoint
7 is, obviously we use nicotine replacement a great deal.
8 What is the implication of this for nicotine replacement,
9 and how it is going to be used in the future?

10 Obviously, there are still acceptability issues
11 we need to look at. One thing I would find interesting,
12 and I think it was alluded to this morning, is if we are
13 reducing nicotine content, and we are reducing the
14 satisfaction, to what extent, as we are reducing the
15 effect of nicotine intake, might consumers be more
16 responsive to policy changes, including price increases?

17 All this is not going to be happening in a
18 vacuum. There are other kind of things that are going to
19 be going on, including, presumably, excise tax increases,
20 that may have an enhanced effect.

21 Of course, my more radical idea is to eliminate
22 the tobacco industry altogether, but that is not on
23 today's agenda.

24 So policy issues -- I think Saul has done
25 excellent work in terms of chipers and the implications

1 from what they can tell us as far as quitting.

2 We are concerned about individual difference in
3 responsiveness. Obviously, we don't have a magic
4 threshold that works for everybody.

5 And then, again, the impact of gradual reduction
6 on smokers who are accustomed particularly using
7 cigarettes or other tobacco products for mood regulation.

8 (Overhead.)

9 We propose one outline of experiment here. The
10 concern I have got -- and maybe some of the work that has
11 been done before on people who are not necessarily
12 interested in quitting, is more relevant. Our work has
13 been done virtually exclusively with people who are trying
14 to quit smoking.

15 In this natural experiment involving the whole
16 country, we need to look at the impact of people who are
17 not necessarily interested in quitting. We potentially
18 pay people for participation.

19 Some of this relates, I think, to some points
20 you made this morning, Jed, as far as -- I am thinking
21 about different schedules that we can introduce. I
22 realize -- we don't have 15 years to do a longitudinal
23 study.

24 We could, very feasible, assess time lines maybe
25 as long as two years within the context of an R01 type

1 grant. We could maybe provide financial incentives for
2 maintaining target cotinine levels.

3 We are going to be interested, clearly, in
4 parameters beyond just, you know, the pharmacology. We
5 are going to be interested in some of the psychological
6 issues like progression from stage to stage as people are
7 getting less nicotine. How much does that potentially
8 accelerate the process in people who start out not being
9 interested?

10 For example, in our work site study, 9 percent
11 of our pre-contemplators over the two years became
12 maintained abstainers. So there is movement. To what
13 extent, does this enhance that?

14 And these are just some of the factors I would
15 like to look at. I think adherence is a key issue, and I
16 think there were issues raised before about compliance,
17 issues raised about other types of products.

18 A concern I have, which may not be shared by
19 many others, is as we eliminate nicotine, or go down to
20 this very low threshold level, what is going to be the
21 market for other kind of products, potentially licit and
22 illicit?

23 If we get to this threshold level, how much of a
24 problem will be areas like black market, frankly, of
25 higher nicotine products? I have no answer for that.

1 So, with that, I hope I have been able to prime
2 the pump a little bit.

3 DR. GLYNN: Thanks you, Harry. I think,
4 obviously -- somewhat different questions, and let's get
5 started on them. Ovide.

6 DR. POMERLEAU: Yes. I think that the program
7 of research that has been outlined throughout the day, I
8 think, has much scientific merit and is of great interest.
9 I have been asking myself as I have been listening to this
10 afternoon's presentations what is the policy impact? What
11 are we trying to accomplish that has public health
12 implications?

13 And I just wanted to get back to something that
14 I am starting to lose sight of. If we agree that nicotine
15 is the reinforcing agent, and further, if we agree that
16 cigarette smoke is the major source of the harmful effects
17 of smoking, then the rest of the question, why not focus
18 on alternative source of nicotine delivery that do not
19 require smoke as a vehicle?

20 It sort of comes back to something Harry said
21 toward the end; that is, he was concerned that if we
22 actually got to this threshold, this cigarette diet, that
23 we would actually create -- assuming the demand -- the
24 organism hasn't changed -- people still want nicotine as a
25 reinforcer -- would that not create a market for a variety

1 of products, some of which would come from other countries
2 that have Eastern European style cigarettes, let's say.

3 Or other -- let's consider, for example, the
4 ease of organized crime learning to use hypodermic
5 syringes to dose the legal cigarettes in such a way that
6 they contain mega-Camel type levels.

7 There is a lot of -- even if you do it very
8 gradually -- my point is, again, you still have to pay
9 attention to individual differences. Harry has said,
10 quite accurately, is part of the data that he is showing
11 are in people motivated to quit.

12 We are talking about, presumably, something that
13 would be useful to the entire population, which is going
14 to include people who are, presumably, not motivated to
15 quit, for whom nicotine is highly reinforcing.

16 I guess the suggestion I am having is should not
17 there be a two-pronged approach? Even if there were a
18 diet -- if we are serious about having a successful diet
19 with respect to weaning people from smoke, which is really
20 the main harmful constituent in cigarettes, should we not
21 provide some alternative form of nicotine that is presumed
22 to be somewhat safer.

23 In other words, should we not be doing two
24 things at once? I hate to complicate the discourse. But
25 if there is real intent to have a public health impact, it

1 seems to me that we are going to have to address that
2 sooner or later.

3 DR. BENOWITZ: Well, I respond that that is an
4 important issue, but it really is an entirely separate
5 issue from this question, which would say, sort of in
6 legalistic terms:

7 If nicotine has a liability because -- if
8 cigarettes are a liability because they have enough
9 nicotine to be addicting, and if regulation would say that
10 is not allowable, it can't be addicting.

11 It could be available. People want to have a
12 casual cigarette from time to time, but it can't be
13 something results in loss of control over use. Then that
14 really requires research on the cigarette and nicotine
15 content.

16 What you are saying, I think, is part -- if you
17 are developing a comprehensive program, which would be the
18 big picture, but I think the other question still has to
19 be answered.

20 You know, I would also say in terms of the black
21 market thing, that is another area of research which is
22 probably relevant, but we can't address -- that is sort of
23 the policy implications of it, which I -- sure, that is
24 going to happen.

25 My own perspective is if you look at all the

1 smokers around -- even if 10 percent, black market
2 cigarettes -- so what? The health benefits are
3 phenomenal.

4 People won't be smoking cigarettes any worse
5 than they are smoking before. Even if people black market
6 it, it is not really a health issue. It is more a
7 political issue, and it is more of a policy issue, I would
8 think.

9 DR. ROSE: I think Ovide has a good point,
10 because, I mean, I think that black market issues could be
11 researched in a model sort of situation.

12 In other words, imagine you do the following
13 kind of experiment, you have a group of smokers who are
14 told that they are supposed ---

15 One group told they are supposed to smoke a high
16 tar, very low nicotine cigarette as the policy we are
17 considering advocates. Another group is told to smoke
18 something like Premiere or some very high nicotine, low
19 tar cigarette that might, in fact, be less toxic.

20 One could try to simulate the incentives that
21 would be prevalent in society. For example, they get a
22 certain amount of money, which they sacrifice certain
23 penalties like a fine every time they smoke a commercial
24 cigarette, which could be detected by the compliance
25 measures and see which regimen, a high tar, low nicotine

1 cigarette or a high nicotine, low tar cigarette keeps
2 people away from the forbidden black market cigarettes
3 more effectively.

4 One could actually design a study that would
5 start to get at some of the issues of how hard somebody is
6 going to work, or what rules they are willing to violate,
7 in order to go off the cigarettes we provided them with to
8 alternatives.

9 My bet would be that a Premiere type cigarette,
10 or a sensory acceptable Premiere-type cigarette, which
11 gives a lot of nicotine, but no tar, there would be a lot
12 more compliance with people using those and less incentive
13 to violate the rules.

14 But the point is not whatever I predict, but
15 that it is a researchable issue, and that as you pointed
16 out in your *New England Journal* article, there are two
17 diametrically opposite policies to take.

18 But given that they can be researched, and given
19 that, as a matter of law, you could mandate either -- in
20 other words, a tobacco company, if they were told that
21 legally they had to make cigarettes below a certain tar
22 level, but a lot of nicotine, they could do that just as
23 easily as they could do the reverse.

24 So it is not like one is a practical feasible
25 technologic solution, and the other isn't. They are both

1 technologically feasible.

2 DR. GLYNN: Jack.

3 DR. HENNINGFIELD: There are a lot of issues.
4 Some of them are, I think -- could be major research
5 issues. Others are minor. Some are -- I think NIH
6 research has to focus as much as possible on the public
7 health, the biomedical knowledge that we gain.

8 For example, on the issue of how long does it
9 take to do something, biomedically, the answer might be in
10 a year. In reality, because of other factors that affect
11 policy, like jobs, it might be 10 or 20 years. The same
12 thing with auto pollution reductions. We know what the
13 answer from a public health perspective.

14 But it seems to me that a real core, major
15 question here is that, to date, most of our research
16 relevant is on people trying to quit smoking. And we
17 don't know what happens when you impose on people that are
18 not actively trying to quit smoking these cigarettes.

19 And we have a little bit of data back from
20 Finnegan, Larson, and Haig. They did something like this,
21 very crudely. But I think that is a core research
22 question that we really have to address. Do things
23 fundamentally different happen in those populations?

24 DR. GLYNN: Martin.

25 MR. JARVIS: Currently, in the U.K., there is a

1 very strong relationship between socioeconomic factors and
2 smoking low yield cigarettes. It is essentially a middle
3 class phenomenon.

4 If one looks at cessation rates at the sort of
5 affluent end, it is over 50 percent. But at the really
6 deprived end, quit rates in the population are less than 5
7 percent.

8 So I think that one of the issues that is going
9 to come into play when one looks at the potential
10 implications of these kinds of cigarettes for quitting in
11 the population is that we are going to need to think very
12 hard about the more deprived members of society who
13 currently do not smoke lower-yielding cigarettes even when
14 they could and who are not quitting.

15 Maybe that is going to reinforce some of the
16 concerns, you know, perhaps encouraging illicit markets,
17 which are going to prey particularly on the more deprived
18 people in society.

19 DR. GLYNN: I don't think any of this can be
20 done -- I mean, I think Gary has used the phrase "in a
21 vacuum." It is not going to take place in a vacuum, and
22 the question that Ovide raises has to be considered.

23 In fact, as we are talking, I am thinking what
24 an announcement for research in this area might look like
25 and, clearly, has to include some -- we don't have to call

1 them policy relevant areas as much as social concerns that
2 clearly are going to come up, such as black markets and
3 things of that sort.

4 We can't avoid it and don't want to. Because we
5 can do all the pharmacological research we want, If it
6 turns out that it works great, but on the other hand, it
7 results in a black market that just takes up the slack, it
8 is not going to have made a difference. Terry.

9 DR. PECHACEK: One of the strongest policy
10 implication issues is actually this discussion. The
11 industry loves to say nothing more than the fact that our
12 ultimate purpose is to prohibit nicotine and/or tobacco,
13 and that is our ultimate goal.

14 Therefore, through the history of the failures
15 of all other forms of prohibition an drug control, that
16 all such steps in that direction should be stopped as
17 quickly as possible.

18 Therefore, I think we fall into a great policy
19 trap of even implicating in any degree that this research
20 is leading toward any form of prohibition. I think that
21 from -- that is kind of fractious statement.

22 Now from a more of an opinion type of statement
23 is that the history of drug control in societies is that
24 we have never really eliminated anything very
25 successfully, and people love to self-administer the drugs

1 of their choice. So that I think that kind of perspective
2 probably is wiser.

3 That we probably need to recognize, as Ovide was
4 saying, that some portion of all free living populations
5 are going to self-administer the drugs, i.e., nicotine and
6 others, of their choice. And can't we make them safer in
7 the packaging, in the delivery systems?

8 DR. GLYNN: Saul.

9 DR. SHIFFMAN: I have a question that, I think,
10 links this topic back to some of the topics in the
11 morning, which had to do with where the threshold is for
12 maintaining addiction. And I am addressing this in part
13 to Harry, because he may have observed this phenomenon in
14 the research he has reported to us.

15 But, anecdotally, in research in the '60s on an
16 attempt to use nicotine fading, or gradual reduction, to
17 help people quit, if you looked at the data carefully,
18 what really happened is people would reduce very nicely.
19 They were very compliant, nice folks until 10 or 12
20 cigarettes a day.

21 And at that point, people either quit smoking or
22 they quit the study. That, in fact, I take as significant
23 evidence for the idea that there is a threshold below
24 which people don't easily drop.

25 And what I am wondering -- actually, one very

1 important point is that sometimes the data about drop-outs
2 and non-compliance is not a defect in the data. That can
3 be the most interesting data. So I think that is very
4 important.

5 I am just wondering, Harry, whether you observed
6 anything like that when you are fading people down using
7 these filter strategies.

8 DR. LANDO: I think it is an excellent question,
9 and actually not very much, because I think our story is
10 different. One reason why we use the nicotine fading is
11 people can maintain their number of cigarettes and,
12 particularly with filters, a lot of the same kind of taste
13 characteristics.

14 So I don't think we are getting to that kind of
15 threshold the way earlier studies that tried to reduce
16 people gradually all the way to zero did.

17 DR. SHIFFMAN: But it is -- then it is -- now,
18 you showed us that the actual nicotine intake was reduced
19 perhaps by half.

20 DR. LANDO: As much as half.

21 DR. SHIFFMAN: But then the research question
22 that might be asked: Is that if we had a filter which was
23 resistant to defeating by compensation, and which reduced
24 people below that, would we, in fact, see a discontinuity,
25 where people won't drop below that, which would be another

1 way to get at this threshold level.

2 DR. GLYNN: John.

3 DR. HUGHES: Just to respond to your question,
4 another way to -- are there doses of drug that prime
5 further use than pacify. What is the dose response
6 function for that?

7 I am sort of thinking of the Ben and Jerry's ice
8 cream phenomenon. I would rather have no Ben and Jerry's
9 than have to eat one tablespoon a day. Okay. Because all
10 it does is prime the pump.

11 I think that -- Maxine Stitzer (?) has some data
12 on that, and that is another way to look at that.

13 I want to also want to mention about unintended
14 effects. I think the other issue is the issue of as we
15 decrease the nicotine yield for smokers, do they see this
16 as a safe haven, and do we undermine cessation attempts?

17 That is, that -- like you said, we can't do this
18 out of a context. We have a context of trying to get
19 people to, and are we undermining that effort by saying
20 that these cigarettes are safer?

21 DR. GLYNN: Nancy and then Sharon.

22 DR. GELLER: I agree that getting the data on
23 non-compliance is one of the most interesting aspects of
24 cessation or tapering studies. I am only worried getting
25 good at it.

1 People are not likely to confess. You don't
2 start the study by telling them -- you tell them they are
3 not supposed to deviate from this plan you have put them
4 on. Because otherwise, they will deviate right away.

5 So it is very hard to believe it is okay to tell
6 you that they deviated. So they won't. In fact, getting
7 the data on non-compliance is really the hardest part, and
8 I suggest that it is even worse -- that there will be
9 worst non-compliance, whether you can get the data or not,
10 in a population that doesn't really want to stop smoking.

11 We are going to do this in the real world. In
12 the real world, you can go out and buy a pack of
13 cigarettes or a carton.

14 DR. GLYNN: Sharon and Norm.

15 DR. HALL: I was looking at the issue of special
16 populations, and it is true you can't generalize from
17 these to the general population. But, in some ways, they
18 do provide us with an interesting laboratory.

19 You could take substance abusers in inpatient
20 units, who can be given, for no cost, the reduced nicotine
21 cigarette, and see what their behavior is.

22 At what point they go out and buy cigarettes?
23 At what point do they go the drug store and buy nicotine
24 gum, which I think is going to be -- is it possible
25 now -- is going to be possible fairly soon.

1 So institutional populations are kind of a neat
2 laboratory, at least for substance abuse. I think the
3 depressed population is a little different, because I
4 don't think they know why they smoke. I mean, I don't
5 think we know they smoke to regulate mood. We just know
6 they tend to more likely to smoke.

7 So how this is going to affect them, I don't
8 know, but substance abuse seems to me an interesting area
9 to study, any institutionalized population.

10 DR. GLYNN: Thank you. Norm.

11 DR. KRASNEGOR: I would like to just -- Norm
12 Krasnegor -- say that any clinical trial that is going to
13 be conducted cannot just make assumptions about compliance
14 or non-compliance.

15 We have done some work on compliance, and I did
16 a book on this on medical compliance in kids, and it has
17 to be a separate study that goes along with the study that
18 you are doing, or separate study totally, to try and
19 understand how to work on this issue of compliance.

20 It is a research question. You cannot make
21 assumptions about it. You have to study the point, and
22 unless you do that, I feel you just sort of whistling
23 *Dixie* about this.

24 Some people, early on when they were starting to
25 study smoking, had the bogus pipeline issue that they

1 worked up, and people worked on other ways, getting serum
2 cotinine and so forth, with patches and saliva. So some
3 things were working.

4 But that does not in and of itself what
5 compliance is about. It is a way of getting some issues
6 about it. You have to study the question about how do you
7 best estimate compliance.

8 Another point, about 20 years ago or so, I put
9 together a study for the National Academy of Sciences,
10 which had as its focus smoking, drinking, overeating, and
11 drug abuse, all the biggies.

12 We were trying to understand whether there might
13 be a system or systems, and I will say what I mean by
14 that, that kind of underpin those kinds of behaviors. We
15 didn't simply mean physiological or CNS. We meant
16 economic systems and a whole lot of things.

17 There is a book that came out of that study, and
18 Tom Shelley, who is now at the University of Maryland, I
19 believe, did some very good economic analyses.

20 I think you ought to go either to talk to him or
21 to look at the book, and you will get some interesting
22 ideas, if nothing else, about how to look at the issue of
23 changing the content as it relates to what Ovide said
24 about black marketeering.

25 Because economists do make assumptions and

1 models, and that was a long time ago. I think they may
2 have better models.

3 DR. GLYNN: Harry.

4 DR. LANDO: I also want to raise the issue of
5 black market. I mean to say that that, in any way,
6 invalidates this whole proposal. I think it is testable
7 question.

8 I guess, maybe what I didn't make as clear as I
9 would have liked to in kind of our sample study is that we
10 like to design in a way that we really do look at
11 compliance issues. I think there are ways where you can
12 measure, and cotinine will give us some indication. There
13 may be other markers we can build in terms of experimental
14 cigarettes.

15 But I think it would be of interest to see how
16 well, as we manipulate incentives in the context where
17 other cigarettes are available, people do comply to that,
18 and people do move on.

19 But I think another thing, as we keep saying, it
20 has to be considered in a broader context. If this type
21 of proposal were implemented, it might open the door to
22 other alternatives, which would be safer kinds of nicotine
23 delivery systems that did not have the tar and might be --
24 more attractive in this kind of environment.

25 DR. GLYNN: Gary.

1 DR. GIOVINO: Gary Giovino. I have been trying
2 to think if lower nicotine -- (inaudible) -- and trying to
3 relate that to some natural studies that exist, and I can
4 come up with none.

5 But I have come up with two situations that
6 might be a little relevant.

7 One is in Canada, it is my understanding that
8 when the tax was lowered that sales of Nicorette pummeled
9 and sales of cigarettes went up, especially almost
10 directly proportional to -- the sales of Nicorette went
11 down in the provinces where the tax was lowered the most
12 and didn't change much when the tax wasn't changed.

13 It is not exactly relevant, but it is sort of a
14 natural experiment. I don't -- (a) -- I don't have that
15 documented. I have only heard that verbally. I don't
16 know if that is documented. But it might be useful to be
17 able to document that if that is something -- (inaudible).

18 The second point is just recapitulate some data
19 I presented at the President's Cancer Panel with Don for
20 the (?) of the Federal Trade Commission. We looked at the
21 adult tobacco survey data and looked at that as a -- we
22 looked at the quit ratio, the quit index, the prevalence
23 of cessation, whatever. It is a cross-sectional measure
24 with all those limitations.

25 But we found that people who used low tar

1 cigarettes were less likely to have quit than people who
2 used the higher tar cigarettes. It suggested to us that
3 -- the data also suggested that the low tar were more
4 likely to have tried to quit in the previous year. That
5 is a cross-sectional survey.

6 I was thinking of this Air Force model. There
7 are lots of models, but one of the ideas here is to come
8 up with research designs. Perhaps the people enter the
9 Air Force could be studied, the cohort that smoked the
10 high tar cigarette and the low tar cigarettes, and then
11 who are forced to abstain for six months. Perhaps they
12 could be studied to see who goes back.

13 The problem with all this stuff is that it is so
14 heavily influenced by marketing and by perceptions of --
15 there are some cigarettes that are relatively safe and
16 others aren't. So I live in the world of sort of natural
17 experiments and trying to make sense out of them, and
18 there is nothing I can see that is totally applicable
19 here.

20 DR. GLYNN: Still, we need to look for those
21 opportunities, though.

22 DR. HUGHES: Gary, it seems to me a very easy
23 one is a prospective study of taking, you know, a hundred
24 people and tracking prospectively the ones that switch to
25 low nicotine cigarettes and then just following them, and

1 then an age and sex match cohort of people who didn't
2 switch. Now somebody has got to have that data set
3 somewhere.

4 DR. PECHACEK: -- COMMIT data set, 20,000
5 smokers, and we have got their brand -- switching data ---

6 DR. PECHACEK: If that supports Gary's finding
7 in ---

8 DR. PECHACEK: All that detail hasn't been
9 analyzed out.

10 DR. GLYNN: But it is analyzable, right?

11 DR. PECHACEK: It is analyzable, and Mike
12 Cummings, if you give him a call, will start the rest
13 tomorrow.

14 DR. GLYNN: Okay. When we are talking about
15 quick turn-around, we can take John's comment there and
16 turn that around fairly quickly. Dietrich.

17 DR. HOFFMAN: Responding to Mike Jarvis's
18 observation in the U.S., in the United States --
19 (inaudible) -- prospective case control study going on.
20 So more educated men -- men, I repeat -- the less likely
21 is he a smoker.

22 What has changed is the high tar cigarettes, the
23 smokers of the high tar cigarettes, have increased,
24 percentile, not the total number, but as a shift to high
25 tar cigarettes -- at least in this case -- large case

1 control study -- and you decrease in the percentage of
2 smokers who smoke low -- cigarettes.

3 But also the smoking-related diseases that
4 somebody has said has become social diseases -- more
5 educated, it is more likely not to be a smoker than the
6 less educated. It is an observation we have made.

7 But I have a question to Dr. Lando -- two
8 questions, in fact. We have observed in our studies that
9 males are quitters after 40. Before, you hardly get ex-
10 smokers. Do you make the same observation?

11 DR. LANDO: I am sorry. That males ---

12 DR. HOFFMAN: When you are 40 plus, you are more
13 likely to become an ex-smoker than when you are -- did you
14 make the same observation?

15 DR. LANDO: Not as consistently. But, again, we
16 are dealing with a different population. Remember, we are
17 dealing with self-referred volunteers who are coming to
18 treatment.

19 DR. HOFFMAN: But you had the interesting group,
20 the second study.

21 DR. LANDO: These are still -- you know, these
22 are still -- they are volunteers.

23 DR. HOFFMAN: And my next question was: What
24 was your highest amount of nicotine according to FTC --
25 cigarette, from which you went down?

1 DR. LANDO: I guess at the average -- we don't
2 have that analyzed for the second study -- the first
3 study, it started at .86.

4 DR. HOFFMAN: .86 -- FTC -- (inaudible).

5 DR. LANDO: Was the average.

6 DR. HOFFMAN: So then these people compensate
7 already. So you go down -- so you can't much more
8 compensate. You understand my point?

9 DR. LANDO: I understand your point.

10 DR. HOFFMAN: When you have .86 milligram, there
11 is a very strong compensation in the majority of the
12 smokers. You go now down to .5. There is not much left
13 for further compensation.

14 DR. LANDO: But they did it.

15 DR. HOFFMAN: Yes, but you have expected a
16 bigger cessation. Because they already compensate. When
17 you see -- the very low nicotine cigarettes don't sell,
18 because you cannot get enough nicotine kick by
19 compensating.

20 DR. LANDO: It is interesting that like in our
21 in our studies generally, we don't find sort of the same
22 kind of relationships that have often been observed -- in
23 even some things like the amount of consumption and so
24 forth related to outcome.

25 I think -- part of this -- we deal with a very

1 heavy smoking self-selected population. So it really is
2 different. People who -- like in our major study, half
3 the people in the study had gone to formal programs before
4 in an effort to quit. That is very uncharacteristic --
5 population.

6 DR. GLYNN: Let's go to Neal and then to Don
7 Shopland.

8 DR. BENOWITZ: There is one issue that, I think,
9 needs to be incorporated in adult studies. That is, if
10 you look at surveys about the adult population, even those
11 who are not currently trying to quit, most of them say
12 they would like to quit, I think, 70 or 80 percent.

13 When our proposal first hit the press, there
14 were a bunch of interviews with smokers about what they
15 like, and actually most smokers welcomed the idea that
16 this might be something that would help them quit, even
17 though they weren't immediately ready to stop smoking.

18 So it is an interesting issue in terms of
19 selecting subjects. Clearly, you have to select subjects
20 who are not about to quit right now. But I think there is
21 also an issue of taking people who would like eventually
22 to quit versus those people who say I have no interest
23 ever in quitting.

24 I think the larger population will be the
25 former, but all studies should probably assess this sort

1 of behavior. Because the response to any sort of program
2 may be quite different.

3 DR. GLYNN: Don.

4 MR. SHOPLAND: I wonder, as we talk about
5 different populations, as we talk about a natural
6 experiment, if there is not some way that we could look at
7 a prison population.

8 I know it is kind of laughable at the onset, but
9 if you could enlist the support of the administration of
10 prisons, where you actually control the sort of flow of
11 cigarettes.

12 We were talking about the types of cigarettes
13 that we are trying to manufacture. If you gave them free
14 cigarettes and then looked at -- had a chance in the
15 nicotine content without their knowledge, would there be
16 any change in consumption?

17 I see people smiling. It might be ludicrous on
18 the face. I have no idea.

19 DR. GELLER: I think there are real ethical
20 difficulties with that. Prisoners have lost their
21 freedom, but yet they maintain certain right, and I think
22 we would not be able to do such a thing.

23 But, I again go back to the military population.
24 That is confined in a sense, but it is free living in
25 another sense.