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WORKSHOP ON NICOTINE ADDICTION AND

THE NICOTINE CONTENT OF TOBACCO

A COLLABORATIVE ACTIVITY OF THE:

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTE ON DRUG ABUSE
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
NATIONAL INSTITUTE ON CHILD HEALTH AND HUMAN DEVELOPMENT

DECEMBER 7, 1995

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C O N T E N T S

PROCEEDINGS

WELCOME

DR. GLYNN: I want to thank everyone for coming. Ed Sondik ended up having to get on a plane this morning and go to Atlanta. So I am representing Ed Sondik, who has been acting director of the NCI for some period until this summer, when our new director came in.

I also thank you for coming despite the threat of snow flurries in Washington, which would have paralyzed the city. But we avoided them.

I also know that a number of people have been in a previous meeting this week. So probably be driven to the edge if you hear nicotine for one more day. But if I can ask you to hold out, I think we have got some interesting work to do this morning and this afternoon.

I am speaking right now, because I raised my hand at an inopportune time this summer at a meeting, and now find actually the pleasure of participating here.

And I am representing several Institutes, NIH Institutes, who are collaborating to put this endeavor together, both the NCI; the National Heart, Lung, and Blood Institute; the National Institute on Drug Abuse; and National Institute on Child Health and Human Development. And we will hear from some of the representatives from those Institutes in a few minutes.

Now, at the risk of a social faux pas, I am going to reverse the order. It says introductions is next, but I would like to briefly review why we are here and what we hope to accomplish. And then let's do some introductions.

PURPOSE AND GOALS OF WORKSHOP

And, primarily, why we are here are the people on my right and left, Neal Benowitz and Jack Henningfield, who wrote an editorial in the *New England Journal* last year, which suggested a unique approach to tobacco use and control, and I am sure everyone is familiar with it.

They at least threw out the idea that we might be able to determine the nicotine threshold for addiction and then gradually reduce the nicotine content of tobacco and cigarettes to that threshold level, if it can be determined, and the predicted effect would be far fewer smokers and, in particular, far fewer youths starting to smoke. And I want to emphasize the interest here in prevention of youth beginning to smoke.

While Jack and Neal noted some substantial questions surrounding the concept, which they will address in a moment. They suggested that regulatory agencies in the U.S. at least consider their proposal.

And that suggestion was taken up by the FDA, and this summer, David Kessler, the commissioner, and several

NIH Institute directors and their representatives met to ask what the status of research is in this area. Not to endorse the concept or anything of that sort, but rather what are the research questions which surround the concept that Jack and Neal introduced?

And the answer was that research exists, and a lot more needs to be done. And at that point, the Institutes suggested that this meeting be held. The idea here is to develop a research agenda to properly address the concept from the *New England Journal* editorial.

What we really want to avoid is discussing the merits of the concept as much as what are the research issues that surround it? And I am going to be vicious during the day in trying to keep us to that agenda.

Because what we would like to do, and when I say "we," I am speaking for the other Institutes, is to consider the possibility of looking at a Program Announcement or Request for Applications -- we are not sure yet -- but surrounding what are the research questions to address in the idea of nicotine threshold and gradual reduction of nicotine in tobacco.

So what we came up with are the four questions listed in the agenda, and we are really at that point, is to address those questions and see what needs to be done in this field over the next few years, both in human and

in any additional animal research.

The other point I want to make is that we are not here to -- we need to remind ourselves at NIH all the time when we are talking -- particularly, in tobacco, that we are not trying to make policy. We are trying to inform policy in the future through research. And I think I will leave it at that point.

I also want to mention, took, that we are taping the meeting today, mostly because I can't write fast enough to take down all the ideas, I think, that we are going to hear over the next few hours, as well as -- I certainly can't spell most of what we will be talking about.

The meeting is being taped. When you do make a comment, if you could just very -- just quickly just state your name so it will be clear on the transcript. And at the end of the day, I want to spend a few minutes talking about what the possible follow-up to the meeting is. And we do have some ideas, and I would like to hear from you all as well.

So having said that, I just wanted to find out if any of the other Institute representatives have anything to say. I know Norm might from NICHD.

DR. KRASNEGOR: Well, it is a real pleasure to be here.

DR. GLYNN: Norm Krasnegor, NICHD.

DR. KRASNEGOR: Many of the people sitting around this table are long-time friends, and we all made it actually, which is kind of interesting, for me at least, being an old man like I am.

But I just was talking with Mike Russell about some things we did back in the last '70s, and those were certainly prescient vis-a-vis where we are now in terms of the science that we know, which has filled in some of the blanks that we thought needed.

And the kind of job that I have now, and have had for the past 15 years, working with child development and kids, really put together those two pieces.

And I would just like to say that I think that our Institute is extremely interested in working with the community of scientists who are looking at this particular issue. Because we see, as David Kessler does, that cigarette smoking and its ravages later in life, is a pediatric disease.

DR. GLYNN: Thank you. Don or Jeff, John Boren.

DR. BOREN: I am older than Norm. I want to get a couple of things said. One is that I have seen ---

REPORTER: Excuse me. Could you ---

DR. BOREN: Forget that old part. I have seen research in this area for a long time, maybe not as -- a

lot of people haven't seen it longer -- but we know a tremendous amount about smoking and nicotine.

And what really appalled me is that when Kessler took the bull by the horns with a tremendous amount of integrity and guts, and decided he was going to regulate it, he found out there wasn't enough information to know how to do it.

We have been -- you know, I was brought up with the concept that we contribute to the fund of knowledge through these many, many years and these many, many studies, and then when the times come to do something, which will affect the society and the public health, we ought to be able to dip into that fund of knowledge and come up the answers. And he dipped into that fund, and the answers were not there.

My hope for this meeting is that we will be able to really specify the research that needs to be done and try to figure out a way to do it. And my fear is that we will get some suggestions that we need more contributions to the fund of knowledge.

We need more basic research in order to fully understand it so that every person does just exactly what they want to do, write a grant proposal. We are doing that.

But my hope is that we get something really

specific and really helpful that will really seriously pertain to the issue which Kessler is facing.

DR. GLYNN: Thank you. Jeff Cutler, NHLBI.

DR. CUTLER: Our lead person, Peer Kaufmann, who is head of our Behavioral Medicine Group, seems to have been delayed and is the proper person to kind of state any orientation on behalf of our Institute.

I am head of the Clinical Applications and Prevention Program. Much of the smoking-related research in the Institute takes place in our division, the Division of Epidemiology. We also have a Division of Lung Diseases. So, obviously, we do have considerable interest in this area.

Besides Peter, joining our group today is Nancy Geller, behind me, who is head of our Office of Biostatistics Research, and perhaps Denise Simons-Morton, whose place is also empty at this point, who is another person in our Intervention Group.

DR. GLYNN: Thanks. And I also want to mention that my compatriot in this is Marc Manley from NCI, who has also been instrumental in putting the meeting together.

At this point, why don't we just -- I know most people know each other, but I know from just talking before the meeting that not everyone knows each other. So

let's do a brief set of introductions, and then we will get going, and I will go to my right.

INTRODUCTIONS

DR. GLYNN: I am, first of all, Tom Glynn for people who I have not met from the National Cancer Institute and have been in tobacco longer than I thought until I began -- seeing people again that I hadn't seen in a long time this morning. Neal.

DR. BENOWITZ: I am Neal Benowitz from UC-San Francisco. I am an internist and a clinical pharmacologist, who has been involved in studying the pharmacology of nicotine in people.

DR. HATSUKAMI: I am Dorothy Hatsukami. I am from the University of Minnesota, the Department of Psychiatry.

DR. ROSE: I am Jed Rose at Duke University. I have been doing nicotine research for only about 15 years or so. But it shows that nicotine research is addictive, too, and my current interest is developing improved smoking cessation treatments.

DR. MANLEY: I am Marc Manley from the National Cancer Institute. I guess my interest in tobacco tend more toward public policy and public health programs. So as we start to link up laboratory and public policy ideas, that is where I will have something to say to this.

DR. SHIFFMAN: I am Saul Shiffman. I am a psychologist at the University of Pittsburgh. I am doing this for 20 years, or 22 years, and always remember that I think I may have done my first talk on smoking at a meeting that Norm Krasnegor organized many years ago. So it is your fault.

MR. JARVIS: I am Martin Jarvis from London, from the Imperial Cancer Research Fund. I am a clinical psychologist, been working on smoking with Mike Russell for nearly 20 years, and I would like to thank you very much for inviting me here today.

DR. HOFFMAN: My name is Dietrich Hoffman. I am a biochemist. My interest is tobacco carcinogenesis for many moons, and I am with the American Health Foundation.

DR. HUGHES: I am John Hughes at the University of Vermont, and I am so unfocused, I can't tell you that I have one area of research.

DR. PECHACEK: I am Terry Pechacek. I am now with the Office on Smoking Health, but I couldn't keep my hand out of the Washington policy side of things, and OSH has offered me a great opportunity to come in and work with them. I thank them for that.

And one small correction My lousy writing, and not Marilyn Massey's problem, but my E-mail address is: txp2, not z. I seem to be totally dependent on E-mail

nowadays. It is getting to be almost 50 percent of my inter-communication with people.

DR. LANDO: I am Harry Lando, and actually Terry's successor at the University of Minnesota. Psychologist by training, (?) School of Public Health, which may be indicative of where I am going. And I was a lot younger when I started in this field.

DR. PERKINS: I am Ken Perkins at the University of Pittsburgh. I am a psychologist. I do basic lab research with human volunteers on the behavioral, subjective, and physiological effects of nicotine. I have been doing this for only about 10 years. And I also have an E-mail correction. I am at vms.cis, not e, on the bottom of page 4. That is cis.

DR. SHIFFMAN: If we are doing corrections ---

DR. GLYNN: Let me suggest this. If you can make the correction and then give it to Pat Davenport, we will get a new set out to you.

Because I was really adamant about wanting to get the E-mails, because, as Terry -- I am becoming very dependent on it, and this is a way I could probably create a whole group and get all of you at one keystroke.

So if you can correct it, and just give it to Pat, we get a new set done, and everything will be all put together.

DR. KRASNEGOR: I am Norm Krasnegor. I currently am at the Child Health Institute. I am chief of the Human Learning and Behavior Branch.

In part, I guess I am one of the relics of history, and I am here to be a part of what I think is a very exciting and, I hope, really fruitful investigation that will lead to something, as John said, very specific.

What is very gratifying for me is that the work that we did at NIDA on smoking has really borne fruit. I am just very excited to be here. Thank you.

DR. GIOVINO: My name is Gary Giovino. I am chief o the Epidemiology Branch at the Office on Smoking and Health. I am very much a relative newcomer to the field, and I am delighted to be here.

We do surveillance and analysis of tobacco use and dependence in the United States and estimate tobacco-attributable mortality and do policy and intervention evaluations.

DR. POMERLEAU: I am Ovide Pomerleau. I am a psychologist by training. I am at the University of Michigan. I started in smoking field somewhere in the middle '70s, thinking that it might be a good place to do a little research a couple of years and then move on to some more difficult problems. I am still here, which I guess says something about the difficulty of the problem.

And I just want to make an additional note. That it is refreshing to find that public policy is asking to be guided by scientific research. As a matter of fact, it is such a rare exception, I can't think of any other occasion where it has occurred.

DR. RUSSELL: I am Michael Russell. I am a psychiatrist from ---

REPORTER: Use your mic please.

DR. RUSSELL: What? Michael Russell, a psychiatrist from the Institute of Psychiatry at Maudsley Hospital in London. I think Dietrich Hoffman was the only one here in smoking research before I started in August 1969.

But so I have been able to watch a lot happening, and I welcome the opportunity now in joining you in what looks to be a very -- potentially very important exercise.

DR. HALL: I am Sharon Hall. I am from the University of California at San Francisco. I am a clinical psychologist. Most of my work in smoking has been in treatment trials and outcomes research.

DR. GOLDBERG: Steven Goldberg. I am chief of the Preclinical Pharmacology Branch at the National Institute of Drug Abuse. I was actually recruited to NIDA from Harvard in 1979 because of the absence of an animal

model of nicotine reinforcement, and my first few years were focused on that.

It is now about 20 percent of our research effort, and my main focus right now is trying to develop animal models of acquisition, extinction reacquisition, particularly for the purpose of looking at potential medications.

DR. FIORE: Good morning. I am Michael Fiore from the University of Wisconsin Medical School. I am an internist and a preventive medicine specialist and direct the Center for Tobacco Research and Intervention at UW.

And I am also currently serving as chair of the ACPR panel on developing clinical practice guidelines for smoking cessation and look forward to the day as they relate to those guidelines.

DR. DJORDJEVIC: I am Mirjana Djordjevic. I work with Dr. Hoffman at the American Health Foundation. I am an analytical chemist. Presently, we are working on assessment of actual dose of exposure of smokers to tar and nicotine and non-specific carcinogens.

We try to generate a data base to answer some questions which are raised by epidemiology. Why there are discrepancies between cancer risk -- in cancer risk between women and men, and why African-American people are (?) than white American people. Also, why there is such a

high increase of incidence of lung adenocarcinoma as compared to -- years (?).

DR. CUTLER: Jeff Cutler again. I will only add that our program supports research both in smoking cessation and smoking prevention within the context of cardiovascular disease prevention. And the only person around the table who I recognize is Terry from way back to the Multiple Risk Factor and Prevention Trial days.

DR. BOREN: I am John Boren from the National Institute on Drug Abuse. I am in the Treatment and Research Branch, and I am just looking forward to what we do today.

DR. BRESLAU: I am Naomi Breslau from Henry Ford Health System. I am a sociologist by training, and I do epidemiologic research in psychiatric disorders, among them nicotine dependence.

DR. HENNINGFIELD: I am Jack Henningfield. I am at the National Institute on Drug Abuse, Clinical Pharmacology Branch, and I have been studying a variety of drugs, but I guess, attesting to nicotine's addictiveness, keep coming back to nicotine.

MS. LEE: I am Brenda Lee from the Food and Drug Administration, Office of the Commissioner. I am basically here observing today. You all know what our interest is in this, and I am happy to be here to observe

the workings of the various Institutes.

DR. GERLACH: I am Karen Gerlach. I am a cancer prevention fellow at the National Cancer Institute.

DR. GELLER: I am Nancy Geller. I am director of the Office of Biostatistics Research at the Heart Institute, Heart, Lung, and Blood Institute. And I have an interest in design of clinical trials for treatment and prevention.

MS. MASSEY: I am Marilyn Massey with Massey Max Resources, responsible for making sure that you all have a, hopefully, (?)-free meeting today.

DR. GLYNN: Marilyn is also being modest. She has been involved in tobacco as long as any of us.

DR. WEINMANN: My name is Gail Weinmann. I am from the Division of Lung Diseases at NHLBI, and I will be -- (inaudible).

MS. LYNCH: I am Barbara Lynch. I am here today as an observer with Massey Max Resources, and I was the study director for the -- (inaudible).

MS. DAVENPORT: I am Pat Davenport.

DR. GLYNN: Pat is responsible for everything that goes on here. So -- I do apologize for people that are on the outside. We went through so many iterations on what the table would look like and what would fit with the microphones and so on. So grab seats at the table ---

DR. KRASNEGOR: You mean this is not the budget negotiations.

(Laughter.)

DR. GLYNN: We are being far too civil for that. I also want to point out it was John Boren who began this age thing that began as a theme throughout. Thank you very much for the very nice introductions.

Obviously, we have a stellar group to guide us for the day, including Elaine Stone at the NHLBI, who has just introduced herself.

And I think I would like to begin, as you see on the agenda here, with Jack and Neal spending a few minutes laying out what the background was to the concept.

And, again, as I say, I will be vicious about this during the day, but although it is tempting, I don't want to get into a debate on the merits of the concept as much as the research questions that it raises and the development of a research agenda around that.

So having said that, I am going to turn it over to Jack and Neal, if they can spend a few minutes introducing what led us to being here.

THE CONCEPT OF ESTABLISHING A NICOTINE THRESHOLD FOR ADDICTION

DR. HENNINGFIELD: We are just going to spend a few minutes discussing how we -- some of the things that

led to this.

And as John Boren mentioned, NIDA and other Institutes have been doing research for a number of years, and Dr. Kessler came along, and he must have one of the quickest and most inquisitive minds, and he started asking all these questions.

Like what is the dose that this occurs? What is the dose that you get a therapeutic effect of nicotine? Are kids more sensitive? How would you affect population prevalence? There are lots of different issues.

And thanks to, you know, people like Norm Krasnegor at NIDA that helped launch programs, people like -- in the earlier ages, Michael Russell, who helped provide the basis to even launch such a program, there was a lot of information.

But there were lots of holes and surprising holes. Surprising holes in some of the most basic issues. You know, like what level of nicotine in a cigarette is necessary to enable a person to become addicted?

And in drug abuse, often we don't even think about that issue in terms of the formulation, because we assume that anybody can get any amount, to a degree, if it is out there.

But here you have a formulation that is marketed. And that means, in principle, it is possible to

determine what levels product what kinds of effects. And we just had surprisingly little data.

There was a lot of data generated and attempted at this in the last couple of decades. And that produced a lot of knowledge, but also holes in the knowledge. And those studies led us -- you know, they brought us so far, and they led us to what we didn't know.

And, in part, our efforts were limited by things like not having adequate research cigarettes and adequate placebo cigarettes. So over the last year, we are working on a contract to provide some -- pilot such cigarettes.

We could have them within a couple of months. The day we get them, anybody that wants to try them out, we will give them to you, because I think that is going to be one of the many things that we need to have if we are going to pursue research.

There, too, you know, you look at what other field of drug abuse proceeds without even having good placebos. This area has been hampered by not having good placebos in a good range. So we have used things like the Tobacco Institute or the University of Kentucky cigarettes and so forth.

Some of the many issues beyond those issues have to do with population variability. What is the variability in the population? Are different ethnic

groups differentially sensitive? Does the dosing issue relate to this?

This led Neal Benowitz and I, who were -- among other people in this room and many other people involved in a lot of these discussions -- to start thinking more actively about how far does our knowledge go, and to propose a hypothesis.

And what we found in proposing the hypothesis is that, as Neal will show you in the next few minutes, there is a basis to come up with some doses. But as soon as you do that, you see how limited our knowledge really is.

And we thought it might be useful to start out this morning by just providing a little bit of an overview of how we got here. And it is not policy *per se*. It doesn't have anything to do with policy at the present time.

And, in fact, in the FDA's tobacco proposal, there is nothing about any of this. And it is not even on the near future radar screen, in part, because, as John said, there isn't the knowledge to do it, if you wanted to. You don't even have thin ice. You are walking on water in some of these areas.

So what came out of the meeting last summer was the notion that it might be fruitful for a variety of NIH Institutes to get involved in a program of research, and

that you would need many different Institutes involved.

Because you have got issues like youth sensitivity and what factors affect youth uptake of smoking. If you can't eliminate sampling, what can you do to decrease the development of addiction?

So you get into some broad issues. And I think Neal is going to make some comments more specific about where the hypothesis came from.

DR. BENOWITZ: What I would like to do is go over some of the elements of the thought process, and what the proposal was that was discussed as an idea for nicotine regulation, and then point out where -- what the research questions are based on that.

I would also say that some people question the value of exercise, but it was exercise that was really the catalyst for this. Jack and I had a meeting in Glasgow about a year-and-a-half ago or so. And just running out in the winds for an hour or so, and it was basically was during that job that this whole concept came together. Exercise -- (inaudible).

DR. HENNINGFIELD: We got lost.

(Laughter.)

DR. BENOWITZ: So I wanted to just show a few slides to guide you through this.

(Slide.)

The first slide is the conception of cigarette smoking from the point of view of a clinical pharmacologist, who thinks about kinetics.

It analyzes the clearance of cigarette smokers -- how many of are you getting rid of in a certain amount of time. It is about a 3 percent annual quit rate, about 1.2 million per year quitting, plus about 420,000 a year dying -- (inaudible) ---

And then if one looks at an input rate, there is about 3,000 new smokers per day, or 1.1 million a year. The net change, which is the balance of the clearance rate with the input rate, is a zero decrease/increase in smoking prevalence, at least between 1990 and 1993.

Well, clearly, we have been doing a lot and continuing to do a lot to try to increase the clearance rate of smokers. The question that came up on the basis of this proposal is what can we do about the input rate?

(Slide.)

Now, if we look at the input in terms of new cigarette smokers, it is clear that these com among adolescents. These are cumulative percentage smoking rates at different ages, and it shows the first cigarette of the day, which is the solid line, and then began daily smoking, which is the dashed line.

Clearly, 90 percent of people smoke their fist

cigarettes before the age of 20, and almost 80 percent of people who become daily smokers become so before the age of 20.

The other thing you can see is there us about a three-year shift in these curves. And if one takes daily cigarette smoking as a point of addiction or dependence, or at least a predictor of later addiction as adults, it gives about a three-year period of time during which kids are experimenting with tobacco, but are not yet addicted.

And so the question came up: Is it possible to intervene in this three-year period of time, assuming kids will continue to experiment with cigarettes, to intervene in this period of time to prevent the transition from experimental use to addicted use.

It is also relevant here that many surveys have asked kids what they think they are going to be doing with regard smoking later on in life. And most kids, when they start smoking, really have a concept that there is a long-term risk, but short-term, it is not a big risk to me, and if I smoke for a few years for social reasons or whatever, I can quit before it is going to harm me.

They don't quit, obviously, because they become addicted, but the idea of being able to smoke a cigarette and not be addicted, I think, is one which is not adverse even to kids who insist on trying to smoke cigarettes.

(Slide.)

So the question came up: Is it possible somehow to address this pharmacologically? Is there a nicotine factor or a threshold for addiction that might be applied so as if kids start experimenting, they don't become addicted?

And the concept was approached in a way shown here The non-addicted smoking group, which Saul Shiffman has studied quite a bit, is characterized by people who smoked five or fewer cigarettes per day, who don't smoke every day, who can go without cigarettes without having withdrawal symptoms, who smoke mostly in the context of positive affect rather than negative affect, and have quitting rates that are higher than more dependent smokers.

And so if one wants to say, okay, maybe this is some pharmacologic threshold for addiction, although that is obviously a question, we could say: Well, how much nicotine do these people take in? And from data from Saul's subjects, the average serum cotinine was about 54 nanograms per mil with an average cigarette consumption of 3.9 cigarettes per day.

And based on pharmacokinetic studies we have done in the past, we could estimate that about 4 to 6 milligrams over nicotine intake per day seemed to be this

level of consumption that was the upper limit for these non-dependent smokers.

So it was assumed that perhaps this might be a threshold for addiction and might be a basis for regulating nicotine products.

The next question is: If you are going to say let's try to limit intake of nicotine to, say, 5 milligrams a day, how can one do that with respect to the product?

(Slide.)

And the two bits of data that are important -- this is a study we published many years ago. Actually Michael Russell published one in the U.K. even longer than that ago, which just shows the nominal machine yields of nicotine versus the blood cotinine concentrations, which is an indicator of nicotine exposure or intake, and showed a relatively flat curve.

So even though there was a 10-fold or more range in nicotine yields by machine testing, there was only a 25 percent or so change in average intake of cotinine in a population.

So, clearly, the existing range of cigarettes were not very effective in terms of restricting nicotine intake. And this is because of nicotine regulation, of course.

(Slide.)

Now, the other thing about this, and we looked at this in early studies, if one looks at the amount of nicotine in cigarettes, again looking at the different machine yield cigarettes, or machine-measured yield cigarettes, on the top, it shows a concentration of nicotine per gram of tobacco.

And you see that there is not only no positive relationship between machine yield and nicotine content, but there is a slight inverse relationship.

And on the bottom shows the total nicotine per cigarette, which is the percent nicotine times the weight of tobacco, and virtually, there is no difference.

So if one looks again pharmacologically at the amount of nicotine that is potentially available in a cigarette, there is just as much available to the smoker if they can figure out how to get it from a low-yield cigarette versus a high-yield cigarette.

So, clearly, current commercial cigarettes were not a viable option. So the question came up: What about actually reducing the content so that no matter what a person did, then there would be a limitation on how much nicotine one could get. And could that be a basis for making cigarettes non-additive?

(Slide.)

So this concept was developed in our proposal, which was as follows: The goal was primarily to prevent nicotine addiction in youth, to prevent the transition from experimentation to addictive smoking.

The assumption was made that there is a threshold to establish and maintain addiction that was about 5 milligrams of nicotine per day.

The third is that -- again, based on experimental studies that we and others have done -- the most a person can get out of a cigarette no matter how hard they smoke is about 40 percent of the total content. So we assumed a 40 percent maximum bioavailability.

We assumed 30 cigarettes per day, which would mean that the content of a cigarette, if it was limited to half a milligram -- that is compared to 10 milligrams now, so a 20-fold reduction -- would, in theory, be a cigarette that would not sustain addiction, if our assumptions are correct.

And then the final part of this was because there are so many addicted smokers, you couldn't do this overnight. So there would be a gradual phase-down over 10 or 15 years. And if these assumptions were correct, in 15 years, we would have a non-addictive cigarette, that would be the only one available.

Kids might experiment with cigarettes, but not

become addicted, and adult smokers would gradually be weaned off of nicotine over these years and perhaps have a higher quit rate.

This is the proposal. From this, there are five questions that, I think, need to be addressed in terms of the scientific underpinning for this, because there are a lot of assumptions here.

The first one is: Is there a threshold level of nicotine intake that maintains addiction? And that clearly has to be looked at.

The second research issue, or a requirement, is: To do research, we need to have cigarettes of differing nicotine content. And the second question we need to address today is: What should those cigarettes be like?

And that has got to be the first requirement. We have got to contract to have those cigarettes made, so that researchers can use the sort of cigarettes that might be commercially produced in the future with lower nicotine contents.

The third question: What evidence can be found that by manipulating nicotine, we can influence the transition from experimentation to addiction in youth? I think that is an important question. That is another research question.

A fourth research question is: Will tapering

nicotine intake in adults facilitate cessation?

And then a final one, which I think is very important in terms of this, is: With the known compensation behavior, will such a procedure be hazardous? Will people be oversmoking cigarettes to be exposed to more carbon monoxide, more tar, and will this be potentially harmful for already addicted smokers?

So I think if we can answer those five questions, not to find the answers, but if we can generate the sort of research that needs to be done to answer those five questions, then we can go back and address some time in the future the assumptions that underlie this. Thank you.

DEVELOPMENT OF RESEARCH AGENDAS

DR. GLYNN: Thank you, Neal and Jack. It was exactly what we needed to outline the concept and what the questions -- Neal just raised the five questions. The four that you see here -- the fifth question being kind of an overlay of can we develop the research cigarettes necessary to deal with the questions that we raise?

So, from here, what we want to move into is actually addressing the first, third, fourth, and fifth questions that Neal raised, the second one being the -- can we develop the cigarettes, the experimental cigarettes?

Just as a lead into that, in any suggestions you make, please be as specific as possible, remembering that what we are looking for from this is a set of research questions that we then can turn back to the field at some point to see that they get addressed.

So we are looking for four, five, six, seven, eight questions from each of the questions that you see here, which can be addressed by researchers in the field. So when you are making your recommendations, please be specific.

And, also, if you see an area that we don't need to do something in, state that, too, so that we can eliminate that and move on to other issues.

Where we want to end up with this research, with the questions we develop, is either upholding or refining the concept that Jack and Neal suggested or rejecting it, depending upon where the research ends up. But your job that we asking from you today is suggest specific research questions that we can then turn around and give back to the field.

So having said that, the way we are going to try and operate is with each question, I have asked someone to essentially prime the pump, introduce the questions, and then throw it open finally to everyone here who I know is getting anxious to speak.

And we should have about an hour -- except for one, which will be a little shorter -- we should have about an hour and 15 minutes of discussion on each one, given about a 15-minute intro.

So having said that, Jack has agreed to introduce the first one.

WHAT IS THE MINIMAL LEVEL OF NICOTINE IN TOBACCO THAT IS NEEDED TO DEVELOP AND/OR SUSTAIN ADDICTION?

DR. HENNINGFIELD: Is this microphone working now? Great. Could you put the first slide up, please, or do I just do that from here? Make sure that I have got -- that I don't walk around -- two circles.

I learned in the meeting we were at the last couple of days that the only way to make the slide projector work was to walk around in a circle like the little superstitious pigeon, and it did work. And other people tried it and proved it.

(Slide.)

It is interesting, too, coming here after the meeting the last couple of days, which was on the safety and toxicity of nicotine, because there the issue that kept rearing its ugly head every time we turned around was the dose level of nicotine.

What is the dose? Whether you are talking about the effects during pregnancy, cancer, any other issues

that were discussed, dosage is the issue. And, again, thanks to a number of people in this room, it is amazing how far we came in the last couple of decades, but it is amazing how little we yet know.

(Slide)

And what I am going to do is my pump-priming, try to raise more questions and issues. Because the most important product up-to-date, as Tom mentioned, is not answers and working out the details, it is what are the questions? So that we can generate a fruitful research agenda.

In the addition process, just a couple of comments. Saul has published similar data. People start smoking at relatively low levels, and for most people, they start out low and graduate over time.

We don't know much about their nicotine intake per cigarette over time. We just know some very crude things. That cigarettes tend to increase over time.

We also know that there is wide individual variability. That some people stay flat most of their lives, a small percentage. Some people smoke a few cigarettes a day and jump up quickly. Some people escalate more quickly.

The point being is that there is a lot of variability. We don't know much about the determinants of

that variability. We don't know what might protect some people from making the transition. We don't know how the dosage factor might interact.

I love this quote. Ellen Walker, "Well, do you think I chose to smoke? You believe I took a cigarette and said, I think I will smoke this one and then maybe 400,000 more." It is worth keeping in mind, because, again, the perception of young people is that they can do that. They can try them once in a while.

And the other -- there are other data that are relevant here, and that is, that kids discover the problem much more quickly than we anticipated. Around 13, 14 years old, they seem to be spending most of their time thinking about the opposite sex and how to get cigarettes and irritate their parents by smoking them and stealing them from their parents maybe.

(Slide.)

But within just two to three years, as Gallup poll research has shown, other research, and tobacco industry research, the kids figure out that they are dependent, and they start actually trying to quit.

And we have got a lot to learn about this transition process. We don't know any -- almost nothing about stages of change, as we now do in adults.

We don't know withdrawal symptoms specifically.

We know general things. We know there are withdrawal symptoms. But is the withdrawal symptom profile different in kids than adults? How is that related to their nicotine dosage? Is nicotine intake as important?

We know, for example, that sensory factors are important in modulating dependence and withdrawal symptoms. Are they more important in young people, because they are taking in less nicotine? Less important? We don't know.

(Slide.)

Now, when you are thinking about addictive activity, and there are many aspects of nicotine dosing to think about, but we are focusing more on the addictive activity, there are different ways to approach it.

And I am going to raise some of the issues. One issue is that there is the daily dose issue. And the daily dose issue is one way of looking at how much nicotine it takes over the course of the day to sustain dependence.

So, for example, in FDA's current policy, they are looking at ways to make it harder for kids to get that daily 10 to 20 cigarettes per day, but they are not dealing with the dose issues, in part because there aren't much data.

But that was the main feature in the proposal

that Neal and I had made, and the main marker we were using was physiological dependence and indices of physiological dependence.

For those of you that work in abuse liability assessment of drugs in animals and humans, that is not usually the marker you use to determine if a drug is going to addictive or not. It is the one that we were kind of stuck with. So there is a daily dose issue.

Now, the main practical means to control daily dose is unit dose, and so we were working backwards. We were taking the total daily and working backward into the unit dose. The unit dose gets tricky.

In an animal study where unlimited unit doses are available, and the animal presses a lever once, you know, you get a lot of intake. You increase the number of lever presses, you get less intake.

So factors such as ease of use, you can determine how many cigarette, how many units, are you even going to factor into your equation? Are you going to factor in 10 or 20 or 30 or 60 or 100?

Factors such as increased cost, perception of harm, workplace restrictions, those kinds of factors might lead to estimates with fewer doses. So throughout this, we have to be concerned about both unit dose and the total daily dose that results from those unit doses.

(Slide.)

When we are looking at the unit dose issue, in determining addictive activity, and addictive activity is, again, the effect we are looking at here, the last few days we are looking at the effects of nicotine, and what the threshold is for producing cardiovascular impacts or problems during pregnancy.

Today, we are looking at what doses are necessary to produce some addictive effect, and how do we predict that? Because some of the perfect studies, giving a bunch of kids different kinds of cigarettes and letting them try it out, we can't do. So how do we predict it? How do we make the best possible predictions?

Well, there are a variety of kinds of methods to look at the reinforcing effects, the effects that will lead the person to keep taking that drug. The effects that they can discriminate, that they can feel, that might control their behavior, subjective kinds of effects.

These things are related, but not one-to-one. The main thing is that they are ways that drugs can affect behavior, and predictors. And they are things that we can study in the laboratory.

Now, one of the many issues is that doses that do not appear to be reinforcing might be effective starting doses. So you get into some real tricky issues.

So, for example, one of the lessons learned with the smokeless tobacco products is that the high dosage maintenance products and higher dosage products that most people in this country are lousy starter doses.

And the smokeless tobacco industry gave itself a huge shot in the arm by introducing products that were extremely low in nicotine dosing, extremely low. So we have got to be concerned about those issues, and how we predict that

The findings with the above kinds of methods, looking at the reinforcing effects, the discriminative effects, the effects that somebody likes, may produce different kinds of values. So I don't think there is any one model that is going to allow us to make accurate predictions.

(Slide.)

And I think, in this room, we are fortunate to have people that work with a variety of different models, because I think it is going to take different models and different approaches.

So what is the threshold dose for an addictive nicotine delivering product? The honest answer is: We don't know. Neal and I made a best guess, and as soon as we did that, we and everybody could see the limitations of it. You heard Neal say "if" about 10 times, and it is a

hypothesis.

And, moreover, probably that specific question is too narrow. Because the absolute dose probably varies across product types, across things that deliver nicotine at different speeds.

The threshold dose for a reinforcing or for a psychological effect of any sort in a nicotine patch, gosh, I don't know what it would be, 40, 50, 60 milligrams per day. But the 22 milligrams per day, people can hardly feel. Yet a half a milligram or so taken in very quickly, people can feel.

I concur with the FDA's Drug Abuse Advisory Committee that a meaningful threshold can be found, but again, the question has to be much broader than just what is the dose.

(Slide.)

It is what is the dose, for which population, for which product, and so forth. So in the next couple of minutes, I am going to conclude this by rather than making an argument for one particular threshold value, to throw out some of the questions and issues that come to mind. And issues that limit our ability to precisely determine the threshold right now.

(Slide.)

Now, one issue to keep in mind is what I am

calling the numerator/denominator concept. The numerator, which is the addictive dose divided by X, the numerator is the number that Neal and I came up with.

It is the best number that science can support. It is the number that when you hit that number, you have got a problem. You have got a biological problem, and in this case, our biological problem is addiction.

So what is the number that we can support? People Neal and I, well, you should have, you know, maybe somebody could get addicted a tenth that dose. Why didn't you use a tenth the dose?

Our answer was: We don't have a general base of knowledge that we could defend. We feel we had a base of knowledge, limited as it was, that we could defend the dose we came up with.

So the numerator is the scientifically determined dose at which the adverse effect, and here we are talking about addictive activity, occurs. And that can be looked at in terms of the total daily dose for tolerance and physical dependence to be sustained, and the unit dose that produces reinforcement, subjective effects, discriminative effects.

Now, the denominator, that is what you divided it by, and that reflects things like population variability, and the notion that 50 percent of the

population -- for 50 percent of the population, a tenth of a milligram might be the cut-off dose. But for 20 percent, maybe it is a hundredth.

So what do you divide by? What do you adjust by? And whenever you are coming up with a denominator, you are entering into unknowns, you are entering in your fear, your concern, with being too high.

On the other hand, you are entering in things like manufacturing costs. Some people say, why don't you just say zero? You rarely say zero, because there is a cost of saying zero. And you have got to be able to defend it.

So some examples of this. Non-alcoholic beer is not no alcohol beer. It is less than .5 percent, which means that you could get a pharmacological effect by drinking five to ten of these beers. But you have to drink five to ten of them.

And somebody could say, well, it should be a tenth, and if the manufacturers come back and say, defend that, you know, that is the interplay that goes on. That is where you need a scientifically defensible dose, and then you come up with some reasonable value.

Coffee. Decaffeinated coffee is not no caffeine. In this country, a decaffeinated cup of coffee contains anywhere from 1 to 5 milligrams of caffeine.

Again, in that case, you probably need five to ten cups to get any measurable effect, but you can do it.

Lead and PCBs in drinking water, it is not zero. They are there. There is a threshold.

For those of who eating doughnuts and things this morning, there is a percentage of rat droppings that are allowed in that flour. Now, there my guess is that the numerator is probably pretty high, and the denominator is much bigger, just because of the public perception and not because of science.

And things like drug discrimination studies can give you information about the numerator. But things like genetic and population variability studies are what enter into the denominator. And your fear of making a mistake enter into the denominator. What is the risk if you blow it?

(Slide.)

What are some factors, some known factors, determining the behavioral effects of nicotine and other drugs? Well, the total daily dose, obviously, but the speed of the nicotine delivery.

That is a big factor. And that is going to be a real challenge to research. Because we can't probably do research where we give the experimental cigarettes that I think we need for some of this research to children. I am

guessing that we can't. That would be tough.

So we are probably going to have to work with models that don't mimic cigarettes precisely like nasal and other forms of nicotine delivery. But we are going to have to be making some predictions, because those forms aren't going to provide adequate models either in a sensory or a speed perspective to perfectly simulate smoke nicotine.

Nicotine tolerance of the individual. How different are people that have never had nicotine? I mean, these issues are really going to be tough ones. You propose research to an institutional review board, and it is oftentimes difficult to test the drug that the people have never had any experience for. So how do we safely do that?

What about other drugs, other behavioral states, that might interact with this? Does it matter if somebody is using caffeine or not? Steve Goldberg is doing animal research that suggests that caffeine intake affects acquisition. What other things should we be looking at like that?

(Slide.)

Just to illustrate the tremendous difference across formulations, nicotine patch, the kinetics are very slow, and again, with 22 milligrams per day, the people

cannot reliably even feel an effect.

Yet with a cigarette, just a few puffs, taking in just a few tenths of a milligram, people can already feel an effect. And this appears to be related in part to the speed of delivery.

But, also, as Jed Rose knows better than any one of us here, sensory factor is associated.

(Slide.)

How do we predict the possibly potentiating effects of sensory factors, or mitigating effects of sensory factors?

The cigarette is producing this incredible arterial spike that -- these are nicotine data in venous blood from somebody smoking cocaine or smoking nicotine, and in arterial blood. The cocaine study that had a lot more data points, the levels were 13 times greater. They didn't last very long.

We don't have any models to my knowledge right now that duplicate that. So we are going to be working with other models and doing the best we can.

(Slide.)

Cost, the cost affects the minimal addictive dose. And this has been demonstrated in animal studies. You know, whether an animal, for example, kills himself by taking cocaine depends on the cost of the cocaine, how

many times the animal has to work for each dose, and the dose available.

So those factors are important factors that interact, and they are important factors in the natural environment, because cigarettes cost something. We already know that young people, in particular, are price sensitive.

(Slide.)

So there are a lot of tricky issues. Here are a couple of research considerations and challenges just in this area that I have identified, and hopefully, we will identify lots more or maybe throw some of these out the window.

Cigarettes provide the most efficient and sensory rich means of dose delivery and thereby might be addictive at doses much lower than those that are determined in studies using nasal, i.v., oral nicotine. Which models are useful? How far can we push them?

My guess is that it is possible to generate valid data with these models, but it is not a simple challenge.

How do we obtain valid data for predicting thresholds for nicotine addictive in naive people? Now, what we probably can't do is allow naive people to become addicted.

So in the absence of that, can something like nicotine -- the threshold for the nicotine behavioral effect that is not necessarily an addictive effect -- as Ken Perkins has worked with the discrimination threshold, the effect at which people can feel it and thereby the drug might control behavior.

Is that adequate? It might be the best we can do. Can we do something else to predict what we can't do in the laboratory?

Obtaining valid data for predicting thresholds in youth. How much can we do in youth? We have got to get some kinetic data in youth, but we probably are going to be very limited on what we can.

Individual and population variability due to genetic and environmental factors. Genetic factors are clearly there. Population factors that may not -- that may differ, but may not be related to genetics. What about people that are exposed, or animals that are exposed, prenatally to nicotine? Are their dose thresholds different?

Again, the reason you need this is to find out if there is some important 10 or 20 or 30 percent -- we don't know -- segment of the population that is going to be sensitive to a much lower dose than the mean.

What is the contribution of sensory factors to

the addictive potential? Do other tobacco additives, such as acetaldehyde or ammonia compounds -- the revelations that ammoniated compounds are used in tobacco were really interesting to those of us that have been working in the cocaine area.

Because, essentially, that is the procedure for making crack. That you increase the amount of immediately volatile and free cocaine to be absorbed. How does that affect -- you know, if we have got a model that doesn't incorporate that, are we missing the boat?

What is the relationship between the cost of the dose and the threshold? A variety of other factors are -- you know, ethnic differences.

Most of our focus has been on cigarettes. We should at least, it seems to me, at this time in history, not forget about cigars and other forms of tobacco as much as we did over the last 20 years.

It is amazing how little data we have on smokeless tobacco. And, cigars, I did just a little analysis of -- I spent $40 on a half a dozen cigars, answering a little JAMA thing on -- somebody wrote in and said, are cigars addictive, too?

And we just wanted to illustrate the variability. We found a range of nicotine content of the cigars in just this little sample, ranging from 10

milligrams to over 400.

Now, the 400 milligram thing was one of those suckers that you could use for baseball, but there were some that were much smaller than that that were several hundred milligrams. We don't know anything about those formulations.

(Slide.)

Now, some of the issues and challenges. Now, as an NIH person, quite honestly, the threshold hypothesis, the policy aspects of that, they are not on the FDA radar screen. They are not on my radar screen. We learned that there aren't the data there.

If our nation is going forward with comprehensive tobacco control policies, however, 5, 10, 15 years from now, it is at least going to need information to fill in some of these important gaps, to even contemplate.

What if a manufacturer came up and said, oh, you have got this addiction warning on cigarettes. I think I should be exempt because I don't have any nicotine. The next question is: Well, what is no nicotine? We don't know.

So I see this as potentially a rich program of research regardless of whether or not this hypothesis, this policy issues, is just throw out the window. Some of

these research challenges are already being investigated, fortunately. We are not at ground zero.

Ken Perkins, for example, is looking at thresholds for discrimination in different population groups right now. So for those of you that don't live on the NIH campus, IRP, that is me, the Intramural Research Program, and those of you who get grants are ERPs.

So a lot of this research, it is already being done. I think it makes a lot of sense to continue and to build on.

But other work could be initiated and accelerated that I think could yield work of much broader importance, work that would be relevant to developing more effective medications, work that would be useful in prevention efforts, work that would be useful in treatment efforts. Like what happens when you cut down the nicotine intake of people?

And I guess that is just a handful of the questions that I could think of, and now our task is to give some thought to some of these issues. One of the important issues are tools.

And one of the tools that I think that we clearly need are research cigarettes that are actually palatable research cigarettes and include placebos.

A number of us are lamenting the fact that we

didn't buy boxcars full of Philip Morris's Next when it came on the market. I have been told that RJR bought a boxcar full of them, and they use it, because they think it is a good placebo.

We have a contract to have a pilot group of cigarettes, as I mentioned earlier. As soon as we get them, we will give them to everybody. But this was just sort of a shot in the dark just to get the ball rolling.

One of the issues today would be just discuss some general parameters, not the details, but some general parameters, that should be considered in a contract that the Institutes would then develop and provide.

DR. ROSE: Jed Rose. I just wanted to mention on that point. I learned something very interesting a couple weeks ago. That Philip Morris still markets Next. They are required to in order to maintain their trademark. So we are exploring to find out exactly where that ---

DR. HENNINGFIELD: It is one 7-11 in Canada. If you find it, let us -- we were told that our purchase of one batch resulted in the product being on the market a few months longer.

DR. ROSE: It is actually in the Caribbean.

DR. HENNINGFIELD: I will go. Tom, what is the best way to ---

DR. GLYNN: (Inaudible) -- research questions.

He has also given one factor. If nothing else, we can walk away today knowing that there are rat droppings in our flour.

What I would like to do from this point, and this would hold for each of the four questions is, finally, with all the pent-up issues that you have and just urge you again to be realistic in any of the research questions you suggest. A 15-year longitudinal study is really nice and probably would answer a lot of questions, and it won't be done.

So make suggestions that are realistic. On this one, we have about 15 minutes left. Go to work. Saul.

DR. SHIFFMAN: I am going to do an unusual thing. I am going to use an overhead for a comment.

DR. GLYNN: Okay. As I mentioned, Ovide also is going to be showing a couple of slides, mentioned to me, but I am going to be really, as I mentioned, vicious about this. All right. That is long enough.

DR. SHIFFMAN: He has got a 400 milligram cigar. I will try to be very brief. I guess I want to raise two questions, one obvious and one only mildly obvious, about the extrapolation from our work on chippers to this issue of an addictive threshold.

Let me first raise the obvious, and I think Jack already really did. This is some retrospective data on

smoking rates in chippers over 20 years and in regular smokers over 20 years.

Two points, one of which I am going to leave for my introduction, the key one is that everybody starts out as a chipper, that is, everybody at some time, from what we know, was smoking at these very low, what we are presuming ar sub-addiction, thresholds.

So the question really is: Which came first? And that relates to the question of how does addiction develop? Clearly, it develops starting from fairly low doses. So I think the issue is: Which comes first, the dose or the addictiveness?

The other issue has to do with the patterning of doses over the day.

(Slide.)

This what a chipper's nicotine levels look like throughout a day, and this is a mix of real data and made-up data. Can I say that? The ---

DR. GLYNN: Simulated data.

DR. SHIFFMAN: Simulated data. There we do. The real data is about the smoking patterns, and then what we did with Neal Benowitz is use a pharmacokinetic model, assuming a 1 milligram nicotine input per cigarette, to model what that would do to nicotine levels.

So this is what a chipper looks like. We have

actually systematically selected a day in which the pattern of smoking is very even, and the thing that is striking is you have huge variability and a lot of deep troughs trending to zero.

(Slide.)

Not all chippers look like that. You will see why that is important in a moment. Some chippers look like this.

That is, here is someone that doesn't smoke until 9 o'clock at night and then smokes intensively at that point. So spending most of the time at zero, but getting fairly high nicotine levels acutely during the day.

(Slide.)

You will see that this resembles real data. This is similar modeling of a real smoker's data over the day, and you can see that, first of all, the nicotine accumulates and that you have a trough level up there at 15 to 20 nanograms per mil.

DR. BRESLAU: (Inaudible.) [Not at microphone.]

DR. GLYNN: Please remember to use ---

DR. BRESLAU: I was interested in the diurnal changes. Is there some -- is this pattern consistent ---

DR. SHIFFMAN: It is generally consistent, but of course, it depends most heavily on the input. So, for

example, this person happens to smoke a run of cigarettes at about 5:00 p.m. Maybe they just got off work.

So the diurnal pattern is going to depend heavily on the pattern of input, but will tend to have a rising trough simply because people are smoking -- this is about 30 cigarettes a day -- you are smoking fast enough to exceed steady state.

So you are taking in nicotine faster than you can process it out, and overnight, you will tend to process most of it out.

(Slide.)

Now, essentially, what is proposed is to lower the input per cigarette, and assuming that pharmacokinetics remain the same, this is what it would look like to smoke those same cigarettes in that same pattern, but delivering -- I have simply calculated one-sixth the nicotine as the input.

The point is that, yes, that, in some aggregated sense, the same amount of nicotine as a chipper, but the pattern is hugely different. So here we see all three; that is, this is 30 a day at 1 milligram; this is five a day at 1 milligram; and this 30 a day at a sixth of a milligram.

I guess to translate it into a question, the question is: Is the total daily dose the right metric, or

is it important to look at frequency and pattern?

So, for example, what is the rate of development of tolerance that arises from these two different patterns, and of course, ultimately, the issue of dependence.

It is very striking that this person maintains some sort of threshold hypothetically, where chippers generally do not. That is, they have frequent drops to zero, and we think that adolescents, of course, smoke more like this initially anyway.

So, again, the question is: Is it total dose, or do we need to be at least as concerned with patterning over the day? I took longer than I expected to, but ---

DR. GLYNN: But you did exactly what we need, which is a statement of the problem, and then come up with a researchable question. So that is actually was precisely what we do need. So either build on that or other questions.

DR. ROSE: In answer, or potential answer, to Saul's question, and I think most of us would agree, that, yes, pattern is important.

One observation that is, I think, extremely relevant to that is what happens to smokers when they are going through a smoking cessation treatment program using the nicotine skin patch. There, it is generally not very

difficult to wean people off of nicotine skin patches.

In other words, a steady delivery of nicotine that does not entail rapid peaks like a cigarette and does not entail the behavioral and sensory aspects either seems to be, and there need to be more control data on this, but the initial impression from clinical trials is that that does not maintain the dependence very well, to have just a steady level of nicotine.

But can I suggest an experiment, as just a -- one way of answering the question that is being raised is -- and this is actually very related, this question 1 and then question 3 ---

REPORTER: Excuse me, you need to be at a mic.

DR. ROSE: Okay.

DR. GLYNN: I am sorry about ---

DR. ROSE: I am trying to shout, but ---

DR. GLYNN: I am sorry about the taping, but you can see that the day is going to go fast, and if we don't have the tape -- the transcript -- we just will lose way too much.

DR. SHIFFMAN: It keeps us from being able to say, oh, I didn't say that.

DR. ROSE: Okay. I just want to use the -- is this okay? Let's go to yet another modality here.

The question of how much nicotine it takes to

sustain dependence and the question of whether reducing nicotine to a threshold will facilitate smoking cessation, those are very closely related, because the notion of addiction is intimately tied up with whether people can stop smoking or not.

So this may be relevant to the later question, too, and you can put it where you want. But here is a simple experimental design, where you take some huge number of smokers, not too huge, but at baseline, and then randomly assign, let's say, to several groups.

You can add your own groups, but just to put a few of the critical groups, let's say they were assigned to smoking cigarettes that deliver -- whose maximum bioavailability of nicotine was along some range -- you know, let's say, just to take for the sake of argument, four -- from .12 milligram nicotine up to 1.0 milligram nicotine,

And you had them smoking these cigarettes for, say, a period of four weeks, or let's say, eight weeks, you know, some period of time, to where they would become accustomed to them.

Now a critical feature here would be the problem of self-selection, because you don't want people differentially -- differential attrition into different groups.

But Dave Gilbert has used a procedure at the University of Illinois, where he pays people rather large sums of money, at least for individuals, several hundred dollars, and gets enormous compliance with even smoking cessation for periods of weeks.

So if there was a high monetary incentive to stay on these cigarettes, and if there was a biochemical method, such as Neal may be able to comment on, for looking at the ratio of, let's say, nicotine to different tobacco-specific alkaloids, maybe anabasine or something, to where you could see whether people were smoking real cigarettes or not or just maybe nicotine levels would be up.

In any case, monitoring compliance during that period, and then at the end of that period of time, having everybody quit cold turkey and observing, what are the success rates in smoking cessation when people are maintained on these different regimens?

And the prediction would be: When you are at or below the threshold for addiction, if you assume that all these people have been to comply with this, they should have now reduced their dependence and addiction and should be able to quit smoking with a very high success.

So that is just a basic model that I was thinking of for a type of experiment.

DR. GLYNN: Thank you. That is exactly, again, what we need. That is exactly the type of thing that we need, which is to give us some very specifics. Ovide.

DR. POMERLEAU: I would like to make a few comments that expand the denominator issues. If you could start the first slide, please, while I attempt to wire myself up.

(Slide.)

I want to start with a few points that are fairly obvious and -- that what we have in the United States and Canada, and the United Kingdom, and several Western countries, is a very aggressive antismoking policy. We are, in effect, conducting an experiment in selecting population differences.

It, in a sense, what has been happening here in this more recent era, where there has been a lot of pressure against smoking, is that the easy quitters have been removed from the smoking populations.

And what I would like to argue is what we are seeing is a different population in the '90s than we saw in the '70s, and certainly in the '60s, before the Luther Terry report. Next slide, please.

(Slide.)

And that population differs in several ways. I am not going to dwell on this. This is in the literature.

Most of you are very familiar with it. As a matter, some of you generated the data, or similar data, to the one I am going to present.

I need to make two points. Among the things that characterize the smokers that we see in the '90s are people who have what could be comorbid conditions, cofactors, that really overdetermine their smoking habit.

And here is just an example. These are women hospitalized at the University of Michigan clinical studies unit with major depression. That is, you can see that women with this diagnosis are about twice as likely as -- smokers are in red -- about twice as likely to be smokers. Okay? Next slide, please.

(Slide.)

Similarly, this is something that came out of our clinic. Just looking at adult attention deficit disorder -- this is something that -- observations more recent -- but, again, people who have this particular diagnosis are about twice as likely to be smokers as people who do not have this diagnosis. Next slide, please.

(Slide.)

Another element that I think we need to take into account are individual differences in sensitivity to nicotine. This is something we are just starting to

develop the tools to examine.

These are three sets of populations that we examined sometime ago, never smokers, being compared with light smokers and being compared with heavy smokers. We administered nicotine intranasally, which allowed us to get nicotine in all three subsets.

This is something that has only recently been feasible, since, obviously, the never smokers do not take in nicotine very effectively from cigarettes. Also, there are ethical concerns about that.

So as you can see in the bottom panel, here they getting a dose of nicotine, about 8 nanograms per ml that is comparable. What is interesting is that after overnight deprivation -- you all know that heavy smokers are more tolerant to nicotine. That is not news.

But even after a short interval of overnight deprivation, it is possible to remove a sufficient amount of nicotine so that the influence of acute tolerance from current nicotine has been taken away. And at that point, it looks as though we are unmasking basic sensitivities to nicotine.

This is just looking at heart rate, and as you can see, this is the inverse of what you would expect for chronic tolerance. What you are seeing here is that the most reactive, physiologically reactive, subjects are the

heavy smokers.

The lighter smokers are less, or immediately reactive, and the least reactive are the never smokers. Now, to tie all this into a question, what I would like to point out is that by focusing the determination of the threshold on chippers, we are looking at a 5 to 10 percent part of the smoking population.

To use that to define a minimum threshold makes certain key assumptions that I think should be explored vigorously in research.

The first is the obvious. We should not assume that smokers are randomly distributed. That they are selected randomly into their smoking status. What I would like to suggest is that there are powerful selection factors that are biological, environmental, and possibly constitutional, having to do with neonatal exposure to nicotine, that will determine the effects of nicotine.

Whether it will be reinforcing. Whether it will have a powerful impact or, as these data suggest, a minimal impact. The smokers, the chippers, belong somewhere between here and here.

They don't seem to develop the tolerance very much. Rather they have tolerance. They are insensitive to nicotine. They don't seem to develop withdrawal when you take away the nicotine. They can take it or leave it.

They seem to be -- the evidence would suggest they are biologically different.

So, to sum up, what I would like to point out is that the two assumptions that are made when one looks at the threshold question by focusing only on dose are that there will be no differences in functional sensitivity to nicotine, that is, the intrinsic reactivity to the substance, and also that there will be no differences in metabolism of nicotine.

I would like to suggest that we mount a vigorous research campaign to obtain population data on individual differences in nicotine metabolism and on functional sensitivity to nicotine.

Functional sensitivity can be defined in a variety of ways. We chose measure of convenience, which is heart rate, but obviously, many other measures need to be included.

I would also like to suggest that we not limit ourselves to phenotypic expression of such. That we also examined genotypic, that is, the genetic control of these mechanisms, and that we attempt to integrate the behavior and the underlying biology.

That is my request. And I think in just a couple of years, we have the answers, Jack.

DR. GLYNN: Thank you again. Again, that was

good modeling there. We got some specific research questions out of it. Mike.

DR. FIORE: Jack made the point that one of the challenges is going to be to address this whole dosing issue in children and adolescents, and how do we get such proposals through IRB boards, not to mention all the ethical issues of looking at the issue of starting individuals on cigarettes.

And I guess I would just like to make a plus that included among the proposals would be to urge epidemiologic studies to go forward, and that really is similar, to some degree, with what Ovide just mentioned.

At the University of Wisconsin, what we have done for the last five years now under Tim Baker is just to follow adolescents as they come into college and to see -- to follow chippers, in essence.

This is actually based on some stuff that Saul did, and we now have five years of data on them and have seen that once they get out of school, the chippers truly are different in their separate population, some of which chose to quit smoking, some of which go on to be regular smokers, and some of which stay chippers for the long term.

And to try to get to some of the psychosocial factors that influence and contribute to that, we have

populations out there through epidemiologic studies that I think we can get better to the issue of what a threshold is.

Because we have populations out there that are already playing with their threshold, and clearly, there are different groups of people that go on to be regular smokers, and you can get a lot of information from them.

DR. GLYNN: Good. John Hughes.

DR. HUGHES: [Not at microphone.] I am going to propose research that is going to bore talent -- (inaudible) -- without you chirping up, I will be doing well.

I think the question, the way the question is worded now, may cause confusion, and the questions were: What is the minimum level of nicotine in tobacco that is needed to develop and/or sustain addiction? I think the word "addiction" should be replaced with the word "supplemental expression" (?).

Let me tell you why. Two reasons. One is measuring addiction is very difficult. I have been in debates about DSM-4 or FDND, first time a cigarette, and al that sort of stuff. But the more important is this (?).

We have done studies in which you take people who have self-selected to stop drink caffeinated coffee

and moved to decaf coffee. Their intake does not change.

So if there were something bad in coffee other than caffeine, there was a nitrosamine in coffee, and we told everybody to go to decaf coffee, amount of nitrosamine exposure would not change one iota.

So I think we have to focus on intake or self-administration, not addiction, as our attending verb (?).

DR. HENNINGFIELD: I think that ---

DR. GLYNN: Jack Henningfield.

DR. HENNINGFIELD: Oh, I am sorry.

DR. : I will try and do that.

DR. HENNINGFIELD: I think it is a wonderful idea. I just suggest expanding it, though. One, because I think we should be precise than that. I am in complete concurrence, and maybe make it self-administration and dependence, because, again, that is what we really care about. Kids self-administering, but also then making the transition to dependence.

DR. HUGHES: The other concern I have is almost an ethical one. Are we condoning non-dependent use? That is, Naomi has found in 50 percent of her 20-30 year olds, they are non-dependent cigarette smokers. We found in adults about 15 percent.

So are we saying that a program that says -- that we are only concerned about decreasing addiction. If

you can use without being addicted, then this research program has nothing to do with you, and we are not concerned much.

DR. GLYNN: Neal. Neal Benowitz.

DR. BENOWITZ: I think that natural experiments have addressed that in that cigarettes that don't contain much nicotine do not maintain self-administration.

So you may have someone who smokes one or two cigarettes per day, because they like the smoking process, and that is probably not going to be a major health problem.

But it is hard to imagine that many people smoking 30 cigarettes a day without any nicotine-mediated reinforcement. There is no evidence that people have ever done that.

DR. HUGHES: I agree with that. I think there may one flaw in those experiments, and that is, that experiment has always been done when there is the alternative of high nicotine cigarettes.

If you had only low nicotine cigarettes available, I am not sure how they would sell. If the only cigarettes you could get were these really low nicotine ones, I don't know.

DR. BENOWITZ: That is an important research question. I agree.

DR. GLYNN: Jed Rose.

DR. ROSE: A little bit of data that may shed a little bit of light on that question again. We have just completed study where we have given people denicotinized cigarettes in a laboratory, so admittedly, an acute paradigm.

And they either smoked denic cigarettes or they didn't smoke anything. Then they were either infused intravenously with nicotine or not -- this was NIDA funded research -- and we duplicated the exact dose that each smoker self-administered voluntarily baseline when they were allowed to smoke freely, and we measured their nicotine levels and their smoke intake.

And then gave them puff-sized intravenous injections to duplicate that own person's preferred level of nicotine. And when we looked at craving reduction -- we can argue about what craving means -- but we found a really interesting interaction, which is basically that if they were not smoking anything at all, but just getting an infusion, craving was high, because they were overnight abstinent and remained high whether they receive nicotine or saline infusion. So there was no effect of the pure nicotine on cravings.

However, if they smoked a denic cigarette, denicotinized cigarette -- this was the Next Philip

Morris brand cigarette, then the cigarette itself did produce an immediate relief of cravings, to a certain extent, on its own, meaning with saline infusion, accompanied by saline infusion.

But if the denic was accompanied by a nicotine infusion, there was a dramatic lowering of craving. So there was a clear interactive effect of the denicotinized cigarette with the pharmacology of the intravenous nicotine.

And that could either be because of a conditioned sensory/pharmacologic interaction or perhaps other components in smoke that pharmacologically interact. I mean, that opens a lot of questions.

But you could argue -- use that data for either side -- but I think it would tend to argue more for the -- and together with the naturalistic experiment -- that people will probably not get much long-term out of denic cigarettes alone. But they will get a little, at least initially, in terms of craving relief.

DR. POMERLEAU: John, I would like to ask you, what would you project ---

DR. GLYNN: Ovide Pomerleau:

DR. POMERLEAU: Ovide Pomerleau. Yes. What would you project as an extension of these curves if this were done chronically?

DR. ROSE: Well, you know, we have been trying to do -- get enough denics that I could do that study, and we just had a few to anecdotally give them out.

We gave a pack denics to a smoker recently and switched for a day or so. His report was, well, he had a couple in the lab. Yeah, they tasted fine, you know, satisfied him. And then when he home, he went back to his own brand.

And that is puny anecdote -- in terms of data, we need controlled studies. But, you know, my guess would be like Neal. That it is going to extinguish over time. We have more ---

DR. SHIFFMAN: Philip Morris did the experiment.

DR. ROSE: Well, that is true, but there was the alternative of other cigarettes.

The other experiment we have done, which gets around the difficulty John raised of alternative cigarettes is the studies that we are doing that I have talked to some of you about, where we have administered nicomelimine (?), which is essentially a reactive nicotine blocker, which essentially converts every cigarette to a denicotinized cigarette.

Unfortunately, it is not as simple as that, because nicomelimine also blocks endogenous cholinergic nicotinic activity. So each manipulation draws in other

compounds.

But what we have been finding is that, and there is probably not time to go into the complexity of it, but there are certain pharmacologic treatments we can give patching nicotine patch with nicomelimine, which blunts sensitivity to cigarettes, and people show an extinction pattern. But they don't go down to zero.

So, again, it is an interesting model to start to look at these things, but doesn't have the definitive answer at the present time.

DR. GLYNN: Jed, just the price of speaking, can you turn that quickly into a research question on the threshold?

DR. ROSE: Well, the research question, which is actually -- well, it is very similar to the model I proposed before -- is to experimentally put randomly assigned people into groups, enforcing, in some sense, different nicotine deliveries, you know, leading up to a quit smoking attempt.

Ethically, these people could all eventually get the effective pharmacologic treatment for smoking treatment, if that is a problem.

And then empirically see how many will continue to use, for four or eight weeks or longer, a cigarette that delivery minimal levels of nicotine. I think that is

even better than using a pharmacologic blocker like nicomelimine. But both approaches might have different pros and cons.

DR. HUGHES: But, Jed, wouldn't a better experiment be if you did the first part of yours, and you just ran it out long enough. Because if there is a threshold, and you are below that threshold, the behavior should extinguish. Right? If you are below the threshold of dependence, the behavior should extinct.

DR. ROSE: Yes.

DR. HUGHES: So you don't need to quit smoking.

DR. ROSE: Yes, it would an alternative, yes.

DR. GLYNN: Let's go to Jack and then Jack Henningfield and then Saul Shiffman.

DR. HENNINGFIELD: Rather than spend too much time on this study, I would like to just convert it to a research question.

And I think the research question, because John is right, we don't know the answer to, is what happens when only a low, very low nic cigarette is available? And there isn't anything else available. And that nicotine cigarette is highly palatable.

And some of the studies -- (?) -- classic study. They have funny cigarettes. Others of us have worked with lettuce cigarettes. That is not a good model.

So I think the really important question is: What happens? And if people drop out, will only smoke a few cigarettes, that is maybe not such a bad option. We are not talking about condoning here or anything.

But if a lot of people, or the majority of people smoke 20 or 30 of those things, we haven't gotten much benefit. And the truth is, John is right. We don't know.

And I think Jed has discussed a couple of ways to get at that. They all have limitations. But I think that is what then the R01 process is for, to -- but I think that John has hit the important question on the head.

DR. GLYNN: Saul.

DR. SHIFFMAN: I would just like to make an argument for making a distinction between maintenance of addiction and an addicted smoker and the development of addiction.

And as I understand, the policy question is really focused on deterring and preventing the initiation of addiction. In some ways, I mean, almost everyone around this table is a researcher on adult-dependent smokers. So we tend to think that way.

And there is also a significant deterrence to studying initiation, because of the ethical issues that I

think we have all raised.

But what I am proposing is that we not take for granted that what we observe at the far end, that is, the maintenance or discontinuation of addiction, will apply to the initiative of addiction.

And this is, I would say, before Tom cuts me off that it is a research meta-question, in a sense; that is, that every research idea that we put forth be sensitive to the issue of whether we are studying maintenance in addicted smokers or initiation and development of addiction in new initiates.

DR. : What is the generality of any of our questions to youth ---

DR. GLYNN: Let's go. Martin Jarvis and then Naomi.

DR. JARVIS: Can I just echo Mike Fiore's plea for more natural history studies, looking at the process of acquisition of smoking in existing adolescents.

You know, I think that is a researchable issue. We can use models like salivary cotinine to track the way that nicotine intake develops. We can also look at measures of subjective dependence, intake per cigarette, and try and see how those relate to each other temporally. Which comes first and which follows.

We can look at -- even with existing cigarettes

on the market -- how the development of intake and dependence relates to the choice of cigarette and the yield of the cigarettes that adolescents are smoking.

We have got some preliminary data on that, which suggests that at least in the range we have got in the U.K. at the moment, although children who start smoking on lower yielding brands have somewhat lower intakes, if you look at them over time, their increase in intake is no different from children who are smoking high-yielding brands.

So I think that the natural history studies, the epidemiological studies, are crucial for getting a understanding of what is going on there in the world as it is at the moment.

DR. GLYNN: Mike has suggested some good populations to work with. Naomi, did you have something -- Naomi Breslau.

DR. BRESLAU: I would like to emphasize also the need to separate the questions on the maintenance and the potential for cessation among addicted smokers and the process of becoming addicted.

I think that the combination of the two together makes it sort of hard to think of specific research strategies.

In regards to development of addiction, I think

it is also important to keep in mind at what age, because we -- despite the fact that we all have this kind of model that kids start in their early teens -- we have data which showed that some proportion of the population started their first cigarette after age 17. And I think that is a very different population.

In terms of even ethical issues, might be a better population to do studies on, if you take kids over 18, and looking at how they develop, especially experimentally.

In regards to this issue of looking at the development of smoking behaviors, I think it is, especially epidemiologically, I would like to emphasize another issue. This is, we have very crude definitions of what we mean by smoking initiation and the whole issues of measuring this progression.

I see it all the time. We really don't know what we mean by initiation. Does it mean the first cigarette? Or does it mean when you start smoking pretty regularly? This whole question needs to be standardized.

DR. GLYNN: Thank you. Michael Russell.

DR. RUSSELL: I think we are quite right to focus on the unit dose rather than the overall daily dose, and I think we have all agreed that Saul's chippers would probably not bother to put a 5 milligram patch on each

morning to get their usual nicotine intake.

Now, I think also that how much do Saul's chippers actually need that milligram of cigarette -- milligram of nicotine per cigarette. He might have already undertaken these studies.

But I think it would be quite useful to look at the sort of threshold of reduction that Saul's chippers would (a) tolerate. Would they up-regulate?

And you could get a sort of guidance from the steps in lowering that might make a difference or not by looking at the reaction of Saul's chippers to them and also, obviously, compare it with other sort of more regular smokers.

So I think that is sort of an initial approach. I would be very interested to know if Saul's chippers are happy without their nicotine.

And the other thing, I would like to support Ovide Pomerleau's plea for the kind of studies he wishes to look at with sensitivity to nicotine after elimination of acute tolerance by -- usually 48 hours abstinence is better.

We did one study like that, and we got smokers to abstain for 48 hours. The intake subsequently, and the response to the first cigarette of that period, it was the ones who found the 48-hour withdrawal most difficult, had

more withdrawal symptoms in it, who actually had a far greater response to the first cigarette after that period.

Some of them even felt dizzy and slightly nauseous afterwards. We concluded that this was due to the fact that they had up-regulated nicotinic receptors, more empty nicotinic receptors, and were certainly more reactive subsequently, when they got the nicotine to fill up all those empty receptors.

DR. GLYNN: Saul Shiffman.

DR. SHIFFMAN: You were asking whether chippers are happy without their nicotine. Research on happiness would be a whole area I am not sure -- but what I can tell you -- let me bring forth two facts which, I think, address that.

One is we have done an experimental study, which was published fairly recently, looking at whether chippers develop withdrawal symptoms when we, as it were, force them to stop, and the answer was unambiguously no. Their subjective state and their cognitive performance remained exactly the same. So that is fact one.

Fact two is a sort of natural history fact, which is that when you interview these people, you become very aware that they undergo a lot of voluntary casual abstinence.

We see that formally when we ask them how much

they smoked each of the last 30 days. There are lots of gaps, days they just didn't smoke, and we see it, I think, more powerfully ethnographically in that when you talk to people, and you are getting a history, they say, oh, yeah, that was the summer I was traveling with my cousin Harry. He didn't smoke, so I didn't smoke either, because it bothered him.

And if you gave that account to a confirmed dependent smoker, they would look at you like you were from Mars. The answer is, I think, they genuinely seem to be able to do without.

On the other hand, given their druthers, they continue to self-administer. So they are getting something out of it, but it is not compulsive. I agree with you. It would be quite interesting to see ---

DR. RUSSELL: -- that the nicotine from the cigarettes that they do smoke for some reason.

DR. SHIFFMAN: I agree completely.

DR. RUSSELL: -- make a difference.

DR. SHIFFMAN: I agree. They may be examining, for example, purely for the sensory.

DR. GLYNN: Neal has a follow-up to that, and then I have a note to myself, make sure everyone is involved, and I have been ignoring people who are not in my immediate sight. So let's go over to the side.

DR. BENOWITZ: A comment about Saul's -- (inaudible) -- question. It was clear that the nicotine increase after smoking a cigarette was identical in chippers compared to regular smokers. So there was no difference.

The question I have for Saul is: Did you look at the relationship between machine yield versus nicotine or cotinine levels in the chippers versus non-chippers to see if they have the same sort of regulation type behavior?

DR. SHIFFMAN: The question is actually implicitly answered in the study we talked about, because we matched our subjects on FTC nicotine yield of the cigarettes. So having observed identical biological yields, that says that they don't extract different proportions of nicotine. So the relationship seems to be the same.

DR. BENOWITZ: So it seems to me that if they are smoking to obtain the same amount of nicotine, then they must not be smoking purely for the habit of smoking. That there must be ---

DR. : That doesn't follow.

DR. SHIFFMAN: No, it could still be that if we remove the nicotine, this might the market for that.

DR. BENOWITZ: But if they were just smoking by

a mechanical way the way a machine would, then people who are smoking low-yield cigarettes should have a lower nicotine intake.

The fact you found no relationship in chippers, just as you find no relationship in the regular smokers, argues that they are smoking for the nicotine rather than just the mechanical way the machine would smoke a cigarette.

DR. ROSE: But there are other sources of variability besides in the delivery. In other words, it does not imply a deliberate attempt to compensate, just because there is no correlation between FTC nicotine delivery and blood levels. There could be a lot of other problems.

What I think is that population would be an excellent population to switch in any kind of study to denic cigarettes.

There is one point that has to be addressed in such a study, or in similar studies, with dependent smokers, in anticipating what the tobacco industry, one of their many objections, arguments, is going to be -- one of them is typically the fact that they say nicotine is an important component of taste or flavor.

So what would be important is to demonstrate, and it might have the best chance of succeeding in the

chipper population, is to come up with a denicotinized cigarette that basically they cannot distinguish in terms of taste from a high-nicotine cigarette.

And then that would essentially demolish the argument that nicotine is a flavor instead of making it additive.

DR. GLYNN: And that goes well with Jack's need, or suggestion, that we need to focus on development of the experimental cigarettes. Nancy Geller.

DR. GELLER: I wanted to make the observation that some of the studies you propose really can be done only in the laboratory.

When you take these things out to population studies, whether they be clinical trials or epidemiological studies, you have certain problems you have to face, and the biggest one is non-compliance.

I guess if I think about doing the epidemiological study on youth, I found that attractive. I guess I would go to the school yard to find them and see the kids who were smoking and ask them if they could be followed.

But, you know, the kids who are smoking are already very good at lying, because their parents don't know they are smoking. So I don't understand why they should tell you the truth about their cigarette intake any

more than they would tell their parents.

People who want to quit are an interesting population to study, because at least they are motivated to comply to begin with. But in any study you design which involves people who want to quit, you had better build in non-compliance anyway.

It is going to be very difficult to measure. I mean, you can do it by taking serum cotinine. That should help. But, still, if you really want to get some assessment on how much non-compliance you have, I suggest it might be more a function of a tapering rate. If you tried to taper too quickly, you would get more non-compliance.

So I think designing a clinical trial might be a little premature, because there are a lot of questions about tapering we need to answer, and quit rate is a great outcome, because, you know, you just say I want to find out how long people quit after a certain point. So that is a good outcome. Or you just measure yes or no if they quit for a certain length of time.

But non-compliance is the bane of taking the studies out to the field.

DR. GLYNN: Let's go to Norm Krasnegor and Dorothy Hatsukami.

DR. KRASNEGOR: Thanks. Norm Krasnegor. I have

been listening a long time here, and of course, my own interest here has to do with kids. And I think that is the interest of many of you.

One of the points I would raise is that I think it would be useful to convene a panel of ethicists who would be able to at least give you a sense of what would be acceptable in the real world, either in laboratory studies or in the environment, and I think that would help give you the baseline.

It wouldn't be the whole thing. But it would be very important for human subject studies if you are going to do an R01 -- might say, yes, no.

The other thing is behavioral history is extraordinary individualistic, but it doesn't come out of nowhere. Some people who are perhaps loners and start smoking early have lots of other behaviors that are atypical, get them into all kinds of trouble, and we are interested in risk taking in general in our Institute.

That is one population that would be very interesting, that is, people who start on their own, versus people who are taught. And the people who are taught have different behavioral histories, because they have a different kind of a teacher.

I think kind of separating those things out might give you the way people who pick it up and begin

inhale first versus those who become president and just never did, so to speak.

So I think it is very important to try to get those kinds of things in. That may be just a questionnaire more than it is an observational kind of thing, to get a feel for how those things might have happened, which might give you a sense of which kids are the most vulnerable. Thanks.

DR. GLYNN: Thank you. Dorothy.

DR. HATSUKAMI: I am just speaking as an advocate for human laboratory models, and I think that is still one area that we need a lot of development in is in trying to develop human laboratory models of self-administration of nicotine to determine thresholds for self-administration.

By developing these human laboratory models, then you can systematically start taking a look at what are some of the issues that might manipulate increased or decreased self-administration of nicotine, including cost, different sensitivities to nicotine, perceptions of the effects of nicotine, and so on. So I think that is an area that we need to ---

DR. GLYNN: Thank you. Let's go to Ken Perkins, Ovide, and Sharon Hall will have the last word for this session.

DR. PERKINS: [Not at microphone.] I just wanted to reinforce what Dorothy was talking about, and it also feeds off what Jack was talking about before: to do basic laboratory research on thresholds for discrimination and self-administration.

We have been starting some pilot (?) to look at this with non-smokers, and you can -- that with -- discriminate -- at least -- 1 microgram per kilogram versus 0. That translates out to about .07 milligrams, so substantially below .1 milligram versus smokers, who are up anywhere from about 4 to 10 micrograms per kilogram discrimination.

And then we have other data on tolerance also. But I think that it is feasible to do that kind of work, fairly quickly, too.

DR. GLYNN: That is a good point, too, in terms of trying not to make sure that everything is done in six months, but where we have the possibility of turning things around quickly, I think it will help, given, again, not that we are making policy and so on, but given the climate of the possibility of change, the sooner we can get data, the better -- that are good data. Ovide. Sharon.

DR. POMERLEAU: Yes. Just a quick comment to make Nancy Geller's life more interesting, I should point

out that it is possible to get reasonably accurate samples of cotinine deposited in hair, and that those hair samples could be used as measures of compliance.

So maybe this barbershop research could be undertaken, which, of course, will make Norm's call for ethicists all the more important. Because now you will never know what is lurking in barbershops.

DR. KRASNEGOR: But John and I can't do that kind of study.

DR. GLYNN: Sharon.

DR. HALL: I would just follow up partly on Dorothy's comment. I mean, it is very important that we are looking at laboratory models, and actually also field models, in initiation to look at the effects of whether self-administration of other substances and also changes in food intake is a factor that modulates what you want to call the addictive dose or the self-reinforcing dose.

Because at the time a lot of kids are starting smoking, they are starting to use other drugs also. And they may influence the denominator there.

And there are also -- particular young women -- sometimes will be undergoing severe food deprivation for long time periods in an attempt to keep their weight down. We already have some data in these areas, but I think it is important to study further.

DR. GLYNN: Thank you. I said Sharon would have the last word, which is true. Jack is going to have the last picture.

DR. HENNINGFIELD: One of the tools that we clearly need for some of this research are a range of different cigarettes that actually do vary in nicotine delivery and other things and different placebo cigarettes, not lettuce cigarettes.

And, again, we will have some pilot cigarettes that we will make available as soon as we get them. I can't tell you if they will be worthless or useful, but it will help jump-start.

But any of you should give thought to what your ideal range of cigarettes would be, and for the time being, feel free to send to me or Tom. I am not sure what the process will be, but clearly -- and everybody has their different wish list.

For example, just in a placebo, you know, it is kind of obvious you have got a cigarette that is highly palatable and no nicotine. Do we actually want or need a placebo that is menthol?

Should we have somebody put money into developing a placebo cigarette that only delivers peripheral nicotine? In principle, that should be pretty easy.

DR. BENOWITZ: (Inaudible.)

DR. HENNINGFIELD: Nicotine that is not centrally active or centrally absorbed. There would be several ways of doing that. But, for example, the D isomer of nicotine would be -- right now, I don't want to even address the different ways. But I assume that it can be done, and I assume that there are a variety of ways to do it.

But that is just -- it seems pretty obvious that when we have placebo, that that is not a simple question. That, potentially, we need different kinds of placebos. So send us your ideas, and we will get back to you.

Then what are the other things in the series of cigarettes? What is the range of nicotine dosages? These are the kinds of things that then go into contracts for people to develop them. What other things should we be varying? Tar? Or what is more specific than tar? Maybe some critical component.

You know, we are not going to be able to develop a thousand cigarettes, and no trials will be useful if everybody is using 10 different series. But, clearly, it is not as simple as I have done just to get the ball rolling in my lab, which is give some crude specs to somebody and let them do it.

So rather than try to work it out now, I have

already gotten some ideas on my list from this discussion. Send us more ideas.

DR. GLYNN: Thank you.

DR. BENOWITZ: Tom, I think this is the absolutely critical thing that has got to come out of this meeting -- research. We have to have a decision about what cigarettes get manufactured.

Do you think it would be worthwhile for us to try to deal with this in a more concrete way, at least in terms of the different nicotine contents, to agree, so that a contract could be let as soon as possible.

DR. GLYNN: Okay. Why don't we set aside, say, 20 minutes after -- I am going to eat into Harry's a little bit and just push that back a little and spend about 20 minutes specific to the questions that Jack just raised and where we go with that.

You have already suggested enough research to spend the combined budgets of all four Institutes that are involved here. So we are onto a good start. Let's take a 15-minute break and reconvene at 10:20. Thanks.

I realize that the real work is getting done at the break, but -- I didn't want to put little microphones on everybody. A couple of things before we get started.

There is a complimentary shuttle to Dulles and to National, and if you can get the front desk know by

2:00 whether you and when you need it, that would be helpful.

DR. RUSSELL: [Not at microphone.] (Inaudible.)

DR. GLYNN: Is Pat here?

MS. DONOVAN: Yes.

DR. GLYNN: Do you know what time check-out time is?

MS. DONOVAN: (Inaudible.)

DR. GLYNN: We will stop in time for you to -- the way lunch is going to work is lunch is going to be brought in, and it will be very informal. Give you eight or nine minutes to eat, and then we will get back.

I want to make sure everyone is involved. Again, I apologize for the table, but don't hesitate to just jump right up to the table, grab a microphone if you have a question or comment.

I also realized that a lot of the of these four questions that -- these four questions, and five including the experimental cigarettes, are not discrete. Clearly, there is a lot of overlap among the questions, and while I kept on saying the word "threshold" in terms of your research questions, it is not going to be easy to stick entirely within, but to the extent possible, if we can.

I also just want to point out that, at least to this point, the tobacco industry is not here. We did have

inquiries yesterday afternoon. I spent part of the afternoon determining what our ability is to keep the meeting closed, and to this point, it is closed.

If there are people here at any point, I will let you know, because to this point, I know everyone. But there was an interesting set of discussions that went on yesterday afternoon. Terry.

DR. PECHACEK: To that point -- Terry Pechacek -- (?) and I were putting our heads together. Actually, a research issue that is relevant that Mike Cummings, a colleague -- friend and colleagues of mine from Buffalo, who I worked with the last two years, pointed me to a very important issue that I would point you to.

That, of course, the tobacco industry has answered about half the questions that you want to answer already -- (inaudible).

DR. GLYNN: Right. Sherry leaned over to me as we were talking before and said, Philip Morris has the answer to that.

DR. PECHACEK: Yes, and one of the things that we have discovered recently is that a lot of their information that -- of course, we are hope we are going to be able to get out through other types of disclosure mechanisms -- is already available in the patent literature.

I don't know if people are aware of the hundreds of thousands of patents that the industry holds, and the amount of information that they commonly submit as part of their patents. Many of these issues in relationship to formulation of the cigarettes and all of these other types of compounds are in the patent literature.

DR. HOFFMAN: (Inaudible.)

DR. PECHACEK: Uh?

DR. HOFFMAN: We are aware of that. That this is an issue that, I think, should people -- researchable issue of pharmacological analysis of the industry patent literature with respect to a number of these issues and, of course, then other types of disclosure, mechanisms for trying to get inside the laboratory data to give us a leg up on many of these questions.

DR. GLYNN: Okay. Thanks, Derek.

DR. HENNINGFIELD: That could be an R01.

DR. PECHACEK: It could be an R01. Yes -- analysis of the industry patent literature.

DR. HENNINGFIELD: It might be the second one in history to be shut down by Congress.

DR. GLYNN: When I asked Saul to prime the pump of the second queston here, I appealed to him in patriotic terms that he serve his country. So he is not wrapped in the flag, but he has agreed to do this. Thank you.

WILL REDUCING THE NICOTINE CONTENT OF TOBACCO REDUCE THE LIKELIHOOD THAT ADOLESCENTS WHO EXPERIMENT WITH CIGARETTES WILL BECOME ADDICTED?

DR. SHIFFMAN: What Tom isn't telling you is that the choice he gave me was this or Bosnia.

I must say, as many of you know, I am not primarily an investigator of adolescent initiation. So trying to think about these issues has been a challenge and really quite an education. In part, I have been educated and informed by reading some of the work of people around the room.

(Slide.)

The question I was asked to set us thinking about was whether reducing the nicotine content of tobacco would reduce experimentation -- would reduce the development of addiction.

I want to start really with some basic, I think, really obvious straightforward principles. One that we have already stumbled upon is that the impact of the propose policy is not going to be tested directed.

So in terms of eliminating research approaches, we can eliminate that one real quickly, although God knows that policymaking agencies have done such experiments. They don't have to go through the IRB, do they?

That doesn't mean that policy decisions can't be

informed by general knowledge about initiation even if we can't test the specific policy.

I think a very important issue for us to keep in mind that policy initiatives can, and often do, have adverse consequences. So in terms of researchable questions, we need not only to ask: Will the policy do good, but also will it do harm?

And I just ask for -- physician's first rule for policymakers should be: First, do no harm. And, secondly, what we don't know can hurt us. That is, that we need to -- in terms of avoiding incidental harm from a policy, we need to attend not only to what we know, but to what we don't know, which can come back to bite us.

I am going to suggest that we know a fair amount about adolescent initiation, but that our ignorance is also fairly vast.

(Slide.)

This is a brief model of progression in smoking, remembering that what we are interested in development of dependence. I mean, everybody who starts with first use probably goes through a stage of occasional and periodic smoking, progresses to daily use, and then poof, develops nicotine dependence.

I don't know if you are familiar with that Richard Harris cartoon, where there are equations, and

then there is a part that says, "And then magic happens." That is what this is meant to represent.

That is, it strikes me that we know a good deal about this stage of the process, and almost nothing about what happens in here. What we know suggests that social and psychological processes are of primary importance here, and pharmacological processes are of primary importance there with psychological processes perhaps being in the middle.

How we go from this socially driven behavior to nicotine dependence and pharmacologically driven behavior, I think, we really do not understand, and I think that is the key question to be answered in considering the effects of such a policy.

A caveat from sort of my crude analysis of the sociology of this science is, although we think we are convinced that all of this process if primarily social and that is primarily pharmacological, what worries me is that that may be the result of the fact that all this research is done by social psychologists and all this research is done by clinical and psychopharm and psychiatry types.

So, to some extent, we have not -- our ignorance results from the fact that we have basically not asked pharmacologically relevant questions about this part of the process.

(Slide.)

What are some basic things we think we know? Most adolescents try smoking by age 18, and indeed, in those who are going to continue, smoking is often pretty well established.

Psychosocial factors heavily influence initiation. For some, smoking then accelerates in frequency and rate. By frequency, typically, studies are done in terms of how many days per month or days per week you smoke, and by rate, I mean, number of cigarettes per day.

Let me jump down to here to what is a very important fact, which is that the majority of experimenters do not progress to dependent smokers. That is, there is huge drop-off, at least two-thirds, from the earlier stages to the later stages.

So, that (a) there really is a process. It is not instantaneous, and (b) there is population heterogeneity. That is, as you are moving through that process, you are not only seeing a developmental trajectory in individuals, but you are seeing a change in who those individuals are.

And I think that relates to the points Ovide was making, and Naomi was making, or has made in the literature, about the characteristics of people who

persist in smoking.

We do now, and I will show you some data about this -- I think Ann McNeill's studies with Martin Jarvis and Michael Russell stand out as almost the single exception to this rule, that initiation is only studies by -- in terms of non-pharmacological factors.

From her work, we know that nicotine exposure and absorption occurs fairly in the process. So there is a potential for pharmacologic factors to be at work. I will show you those data in a moment.

And we know from Ann McNeill's work, and more recently, from, for example, Gary Giovino's analyses of the TAPS data, that withdrawal and difficult quitting also emerge fairly early, probably within a few years of initiation.

(Slide.)

You have already seen a version of this graph. That there is an orderly progression from first cigarette to daily smoking, and it does seem to take about two-and-a-half years across a number of populations.

Let me comment again that daily smoking has been used as the endpoint in initiation research, and I think that is a huge problem. That as we are going -- we are saying, okay, they are smoking every day now. Now who is a dependent smoker?

In fact, we don't. Because what you see in adulthood is not people smoking one cigarette a day. You see people smoking 20 and 30 and 40. And how we get from here to there is, I think, really quite unknown.

(Slide.)

This is a complex figure based on Ann McNeill's work, looking at smoking rate and cotinine levels, which, of course, reflect nicotine intake in some cohorts that were studied over three years. Let me take you through it, because it is a little bit too complex.

These are the folks who were smoking daily at all three time points. It is longitudinal data. And you can see that they are escalating in rate from about 8 cigarettes a day here to about 10 a day there and a fairly parallel increase in cotinine levels.

This is a group that was smoking occasionally, that is, less than daily at year 1, but progressed to daily smoking at year 2, and you can see that that is associated with a dramatic increase in cigarettes per day and a concomitant dramatic increase in cotinine intake.

Now, this was a fairly small n study, and so there was no difference in the linear progression rate in essentially the cotinine per cigarette that people were taking in.

But the small n is relevant to statistical

power; that is, it does look as though the rate of cotinine increases is going up a little faster than the rate of increasing numbers of cigarettes, which suggests that people are getting better. These kids are getting better are extracting nicotine from cigarettes.

This is a group, very small, I think it may have been something like 12 kids who were not smoking at year 1 and were smoking daily by year 2, and then again at year 3. You can see, obviously and tautologically, an increase in rate, although only to about two cigarettes a day and cotinine levels at about 50 or 60, roughly the level that was described this morning as the threshold for addiction.

In our chippers, we see cotinine levels of about 50 to 60 nanograms per ml. So these folks look like chippers at this stage, and then a year later, are smoking about seven cigarettes a day, but already showing cotinine levels of 115 nanograms per ml, which is much closer to what you see in confirmed smokers.

So there is an escalation in absorption. One of the problems in this study -- I raise it because it is a problem in the whole literature -- is that often the X axis is age, or in this case, it is follow-up time. It is very hard to find data that is denominated in length of time someone has been smoking.

So we have a lot of data on how a 18-year old

looks different than a 16-year old, but you can't translate that into amount of exposure to smoking, either behaviorally or pharmacologically.

(Slide.)

This is retrospective data that I already showed you briefly from our -- it is very retrospective -- it is from our chippers and a matched group of regular relatively heavy smokers, and it look at their first 20 years of regular smoking. So we don't -- this does not even count that early stage before they are smoking regularly.

First, you can see that chippers stay where they were roughly, at least they say they do. One of the things that, to me, is quite striking about this is that regular smokers continue to increase the number of cigarettes, at least throughout the first 20 years of smoking, on average.

So we have to stop thinking of this as a binary process, where one day you are dependent, and now you stay at the same place. There seems to be continual increase, and it does appear that there are some people who initially progress and then turn out to be chippers at the time we see them.

So that is quite an interesting group, particularly because they show that exposure to lots of