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HEARING OF THE HEALTH AND THE ENVIRONMENT SUBCOMMITTEE
OF THE HOUSE ENERGY AND COMMERCE COMMITTEE

SUBJECT: ANTI-SMOKING BILL AND TOBACCO PRODUCTS

WITNESSES:
DR. VICTOR DENOBLE AND DR. PAUL MELE

CHAIRED BY: REPRESENTATIVE HENRY WAXMAN (D-CA)

ROOM 2123, RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC

THURSDAY, APRIL 28, 1994

REP. WAXMAN: (Sounds gavel.) The meeting of the subcommittee will come to order. This hearing is a continuation of the subcommittee's oversight hearings on tobacco products. The witnesses this morning are Dr. Victor DeNoble and Dr. Paul Mele. Dr. DeNoble worked in Phillip Morris's behavioral pharmacology laboratory from 1980 to 1984. During most of that time, he directed animal research on nicotine and substances that might be substituted for nicotine. Dr. Mele worked with Dr. DeNoble in his laboratory.

On March 31 I released a study that Dr. DeNoble had co-authored with Dr. Mele, and that demonstrated that nicotine has reinforcing properties which the National Institute of Drug Abuse has stated is a hallmark for addiction. The study was accepted for publication in 1983, and again in 1986, but each time Phillip Morris directed Dr. DeNoble to withdraw it. As a consequence, it was never published.

Today Dr. DeNoble and Dr. Mele are here to testify about these incidents and others during their employment at Phillip Morris. To my knowledge, they were -- they are the first scientists to be released from their confidentiality agreements by a tobacco company.

On behalf of the subcommittee, I want to welcome Dr. DeNoble and

Dr. Mele, and to say that we are pleased they are willing to testify in the subcommittee's oversight hearings on tobacco products. But before calling on the two of you, I want to recognize members for any opening statements they wish to make, and to recognize Mr. Bliley first.

REP. BLILEY: Thank you, Mr. Chairman. Today we will hear in greater detail about an issue that was raised at the subcommittee's last two tobacco hearings -- research on nicotine undertaken by former Phillip Morris research scientists in the early '80s, and as with the other tobacco-related issues that this subcommittee has recently considered, this issue already has been aired in the press. It is therefore critically important that once again our deliberations attempt to separate fact from fiction and that we opt for good policy rather than good headlines.

I hope that we approach the proceedings today from the benefit of a wisdom that can only be achieved through experience. In this case, the experience is very recent because we have been down this road before. Just a month ago, allegations were flying in the media about nicotine spiking.

In response, top executives from the major tobacco companies came before us voluntarily and under oath to put these unfounded claims to rest and to set the record straight. Hopefully, the process will allow for a similar fair hearing for all concerned regarding this issue.

In conclusion, I'm here to listen. But because we have the benefit of hearing only one side of the issue here today, additional questions surely will arise. Therefore, this hearing should be viewed as but part of a larger process that allows both sides of the issue to be properly aired.

Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Bliley. I agree with your comments that this is one of a part of a series that will be available for us to get the information for the subcommittee.

Mr. Synar?

REP. MIKE SYNAR (D-OK): Thank you, Mr. Chairman.

As early as 40 years ago, researchers informed Americans of the harmful effects of smoking. The industry continues to deny the deadliness of smoking. On April 14th of this year, the CEOs of our seven U.S. major tobacco companies flatly denied, while under oath, that nicotine is addictive and that smoking causes cancer.

Today, Dr. Victor DeNoble, the former associate senior scientist with Philip Morris, will tell us a different story. It will directly contradict the tobacco executives' statements that nicotine is not addictive, and it shows that companies have proof of nicotine's addictiveness.

Now, why do our executives continue to deny it? Because to do anything else would subject them to expensive and immediate liability. This concealment, coupled with the industry's continued direct targeting of children, is criminal. Americans are beginning to demand some answers from tobacco companies, not to bring back the 8 million lives lost, but to prevent the next generation of children from taking up this addiction that will in all likelihood result in their deaths.

I look forward to this important and sound information that we will accumulate today in this continuing battle to deal with the largest preventable cause of death in our society.

REP. WAXMAN: Thank you very much, Mr. Synar.

Mr. Wyden?

REP. RON WYDEN (D-OR): Thank you very much, Mr. Chairman. I, too, want to commend you for the painstaking approach that you are taking on the health hazards of tobacco. I think this series of hearings is an effort to get at the core of the onion by peeling away the deceptive practices we have seen in this industry layer by layer.

Today's hearing is especially important because we have a respected researcher, a former tobacco industry scientist, who in effect is brought in from the cold. Now, this is no spy novel, but the whole environment of the tobacco industry in its relationship to tobacco consumers very often does read like a cloak-and-dagger thriller. This industry works with secret lists, confidential technologies, and veiled advertising message, and in effect, through these practices, can orchestrate a world-class confidence game. Individuals like Dr. DeNoble who get in their way because of embarrassing information they might have to offer are, in effect,

pushed to the sidelines. And it seems to me the losers are consumers who each day by the tens of thousands decide to take up this deadly habit.

Now, the corporate leaders who run this industry have told the subcommittee in sworn testimony that they have no proof that their products are addictive. Recently, they came before us and said that they are making a safe product that millions of Americans enjoy. In effect, their message was that the United States Congress was the bad guy for trying to dampen enthusiasm for a harmless vice. But the fact of the matter is that all Americans ought to be troubled by what we're going to learn today, which is that, when the tobacco industry does research and the results hurt them, the investigators and their data are buttoned up tight. What we are learning is that tobacco science is politicized science, and it is especially important that we have Dr. DeNoble's message today.

Mr. Chairman, I look forward to pursuing this with you. You have taken, in my view, another important step by bringing Dr. DeNoble here, and I look forward to our questions.

REP. WAXMAN: Thank you very much, Mr. Wyden.

Dr. DeNoble and Dr. Mele, we're pleased to welcome you both to our subcommittee hearing today. You were both employed as research scientists by Philip Morris during the early 1980s, and I understand, Dr. DeNoble, you're going to make a statement, but that Dr. Mele wishes simply to be available to answer questions.

But before we get to your testimony, I want to inform you that the applicable rules of the House and the rules of the committee are in that blue and white pamphlet that's on the table before you. That will inform you of the limits on the power of this subcommittee and the extent of your rights during your appearance today.

Do you desire to be represented by counsel or advised by counsel during your appearances today?

MR. DENOBLE: Mr. Chairman, I do have counsel with me, and I would like the opportunity to talk with him if necessary.

REP. WAXMAN: Dr. Mele?

MR. MELE: Yes, I would likewise.

REP. WAXMAN: Okay. Do you object to appearing before this subcommittee under oath?

MR. DENOBLE: No, sir, I do not.

MR. MELE: No.

REP. WAXMAN: Okay. Well, if you have no objections to appearing before us under oath, I'd like to ask you both to rise and raise your right hand.

(The oath is administered.)

REP. WAXMAN: Please consider yourself to be under oath. I'd like to ask each of you to identify yourself for the record.

MR. DENOBLE: I'm Dr. Victor John DeNoble.

MR. MELE: I'm Dr. Paul C. Mele.

REP. WAXMAN: And would you introduce anyone who is with you today.

MR. DENOBLE: I have with me my wife --

REP. WAXMAN: Would you be sure the mike is turned on? There's a button. Push it forward.

MR. DENOBLE: I have with me my wife Kimi (sp) DeNoble and my counsel -- (name inaudible).

MR. MELE: I have my wife Joy Mele, my son Tristan (sp) Mele, and my counsel Dave Vladik (sp).

REP. WAXMAN: Thank you.

Dr. DeNoble, I'd like to recognize you to make your comments.

MR. DENOBLE: Thank you.

REP. WAXMAN: And would you pull the microphone close to you so we can be sure to get all this on the record.

MR. DENOBLE: Mr. Chairman and members of the committee, I am Dr. Victor John DeNoble, and this is my colleague and friend, Dr. Paul Mele. We are grateful to have this opportunity to talk to you about our research.

REP. WAXMAN: Excuse me, Dr. DeNoble. I'm not sure is your mike on. Is there a light?

MR. DENOBLE: The light is on, yes, sir.

REP. WAXMAN: Well, pull it closer to you.

MR. DENOBLE: My career began in 1976 when I received a Ph.D. in experimental psychology from Adelphi University in New York. After receiving my degree, I began post-doctoral research on the behavioral and electrophysiological effects of alcohol in non-human primates at (Downstate ?) Medical Center in New York. Following this, I accepted a post-doctoral position sponsored by the National Institute of Drug Abuse at the University of Minnesota. At Minnesota I studied the self-administration techniques in rodents and non-human primates. I am currently a senior behavior analyst with the Community Mental Retardation Program for the state of Delaware.

From April of 1980 to April of 1984, I was employed at the Philip Morris Research Center in Richmond, Virginia as an associate scientist and then as an associate senior scientist, a position I was promoted to in 1983. During that time, I established and directed a behavioral pharmacology laboratory to study the behavioral and physiological effects of nicotine in rats. Our goal was to identify the effects of nicotine in the central nervous system and to establish structural activity relationships among organically-synthesized analogs of nicotine.

The purpose of this nicotine analog program was to develop an analog that would retain the physiological effects of nicotine in the brain as well as the behavioral effects but not have adverse effects on the cardiovascular system. Our program was successful in identifying a -- (inaudible word) -- series of compounds which met this criteria.

In order to behaviorally evaluate nicotine analogs, a characterization of the behavioral effects of nicotine in rats using a variety of conditioning procedures needed to be developed. One of the earliest test procedures we used was a nicotine self-administration

test. In this procedure, an animal can press a lever and deliver a drug solution into its vein. If the solution has reinforcing properties or qualities, the animal will continue to press the lever.

We found that nicotine functioned as a intravenously delivered reinforcer in rats in the absence of any inducement conditions. In previous studies, inducement conditions made the analysis of nicotine's reinforcing effects difficult to assess. Our results demonstrated for the first time that nicotine shared common characteristics with other drugs that are delivered intravenously.

In other studies, we also found that rats would develop tolerance to repeated injections of nicotine, and this tolerance was in part behavioral and in part physiological. Following tolerance development, higher doses of nicotine were required to produce the effects that were both quantitatively and qualitatively to before tolerance development.

We also examined the potential of nicotine to produce a physical dependence in rats. In two separate experiments, we were not able to show that nicotine produced a withdrawal syndrome.

There were several other studies performed in the laboratory with nicotine. And although none of these -- very few of these studies were published, almost all of this research has since been replicated, confirmed by other investigators around the world.

In 1982, however, we began to investigate the behavioral effects of another smoke component, and to the best of my knowledge, this research has never been replicated and therefore awaits scientific confirmation.

In our search to identify molecules in cigarette smoke that may have reinforcing properties other than nicotine, we identified a molecule called esanaldehyde (ph). It was in high concentrations in cigarette smoke. Because esanaldehyde could be delivered to the brain in seconds and it's highly reactive with catacolamines (ph), we hypothesized that one esanaldehyde functions as a reinforcer for rats, and two, that possibly interactions with nicotine could be achieved.

Our research confirmed that esanaldehyde was a reinforcer for rats, and the reinforcing properties of esanaldehyde and nicotine combinations would interact, producing additive effects in these animals.

I would like to state that senior research management in Richmond, Virginia, as well as top officials at the Phillip Morris Company in New York continually reviewed our research and approved our research. Senior management also reviewed and made final decisions determining whether data could be published, presented at scientific meetings or even discussed in the scientific community.

With regard to the Phillip Morris press release dated March 31st, 1994, the statements made concerning my research and my assessment of the self-administration experiments are out of context and misleading.

Further, during my employment at Phillip Morris, three manuscripts were approved for publication. Two of these manuscripts were subsequently ordered to be withdrawn by the company after this approval.

In addition, my 1983 scheduled presentation of the nicotine self-administration paper at the American Psychological Association meeting was also blocked by the company.

Finally, without prior discussion or prior warning, the behavior pharmacology laboratory was abruptly closed in April of 1984.

Mr. Chairman and members of the committee, I would like to thank you for reading our statement, and I welcome any questions.

REP. WAXMAN: Thank you very much, Dr. DeNoble. If the members have no objection, we're going to recognize each one in turn for 10 minutes, but since these are our only witnesses for today, if someone is pursuing a line of questioning that might go a little beyond the 10 minutes, I hope we'll be willing to extend the courtesy to continue that line of questioning.

Dr. DeNoble, I want the clerk to give you an Exhibit 1, which is your resume, and I note that you've published more than 20 articles and that you've held teaching positions at seven universities.

Dr. Mele, we're also pleased you're able to be here, and although you didn't present a formal statement, could you tell us about your training, education and employment background?

MR. MELE: Yes. First, Mr. Chairman, let me thank you and the members of the committee for allowing me to be here today. I received

my Ph.D. degree in experimental psychology in 1980 from Adelphi University in the field of behavioral pharmacology. That worked focused on the effects of amphetamine on complex behavior in rats.

Following that work, I spent two years at the University of Wisconsin at Madison, funded under a National Institutes of Health research service award, where I studied the behavioral toxicology of lead and polychlorinated biphenols in non-human primates.

Following that, I went to the Phillip Morris Research Center to work with Dr. DeNoble. That was in November of 1981. And I was there until its closing -- until April of 1984.

Since leaving Phillip Morris, I've been with the Department of Defense at the Armed Forces Radiobiology Research Institute in Bethesda, studying effects of ionizing radiation and radioprotecting compounds on the behavior of laboratory animals.

REP. WAXMAN: Thank you very much, Dr. Mele. Dr. DeNoble, I assume that you're aware that a month ago, Dr. David Kessler, the commissioner of the Food and Drug Administration, testified before this subcommittee that nicotine addiction -- and he also talked about nicotine manipulation. He referred to your article on nicotine self-administration in rats and to the fact that Phillip Morris ordered the article withdrawn after it had been accepted for publication.

Subsequently to his testimony, I released your article. Then just two weeks ago, the executives from the largest tobacco companies appeared before this subcommittee and testified that nicotine is not addictive.

For example, William Campbell, the president and CEO of Phillip Morris USA testified, and I quote, "Cigarette smoking is not addictive. Nicotine contributes to the taste of cigarettes and the pleasure of smoking." End quote.

Now, you ran a laboratory that was charged with identifying the essential characteristics of nicotine so that a synthetic form of nicotine could be developed. Yet you didn't test for the taste of nicotine. Did you ever hear any serious discussion to the effect that Phillip Morris leaves nicotine in cigarettes for taste?

MR. DENOBLE: No, sir. None at all.

REP. WAXMAN: As I understand it, you were charged with developing a rat model to test nicotine analogs for the effects on the brain in an effort to develop a nicotine substitute. Did anyone at Phillip Morris ever suggest to you during the course of your analog work that you should develop an analog that would duplicate the taste of nicotine?

MR. DENOBLE: No, not at all.

REP. WAXMAN: Are you aware of anyone else doing work on this at Phillip Morris?

MR. DENOBLE: Our laboratory didn't do any work in taste. That could have been done in the other areas of the research center, but I don't have any knowledge of that.

REP. WAXMAN: Prior to your employment at Phillip Morris, what sort of scientific work had you done?

MR. DENOBLE: I was working at the University of Minnesota under a sponsorship of the National Institute on Drug Abuse. My work was with drug self-administration in non-human primates and in rodents.

REP. WAXMAN: You were doing animal tests on alcohol and barbiturates, is that it?

MR. DENOBLE: That is correct.

REP. WAXMAN: Okay. You were previously doing work on drugs for which there is a concern about both dependence and abuse.

MR. DENOBLE: That's correct.

REP. WAXMAN: And at Phillip Morris, you did similar types of animal research on nicotine, is that correct?

MR. DENOBLE: Very similar, yes.

REP. WAXMAN: Could you compare the tests you did on nicotine with the tests that the National Institute on Drug Abuse would do to determine if a drug has an abuse potential?

MR. DENOBLE: Well, they're exactly the same tests. We did not do drug comparisons, but the test models are exactly the same.

REP. WAXMAN: As I understand it, in order to test nicotine analogs, you had to understand the brain effects of nicotine itself. How did you approach this task? Where did you start?

MR. DENOBLE: When the lab existed, we already had one test which identified whether rats could tell us whether they were given an injection of nicotine peripherally in the -- systemically. We -- our first model to get to a direct effect of the pleasurable effects, if you will, was to look at a self-administration model. That was the primary screen.

REP. WAXMAN: I suppose there are many brain effects that a substance might have and many tests that could be done. It's my understanding there are certain tests that qualify as hallmarks of potential drug abuse or addiction. Am I correct that in the early 1980s, the three animal tests that would be done to identify whether a substance was potentially addictive would be self-administration, tolerance and physical withdrawal?

MR. DENOBLE: That is correct.

REP. WAXMAN: And isn't it true that you did all these tests and that they were an essential part of your work at the laboratory?

MR. DENOBLE: That is also correct.

REP. WAXMAN: Now, would you briefly describe for us how you tested for self-administration, tolerance and physical dependence?

MR. DENOBLE: Well, for self-administration, the animals are surgically prepared with a catheter that lodges itself just above the heart. The animals, after surgery recovery, could be hooked up to an infusion pump. If the animal pressed one of two levers, one lever didn't do anything; the other lever would deliver a nicotine solution into the vein.

If nicotine is a reinforcing agent, then the pressing of the lever would increase. And that's what we found. We did several manipulations and several investigations to clearly show that the animal was pressing the lever to obtain nicotine.

In terms of a tolerance, a study design that Paul put together was to repeatedly inject animals with nicotine over several days and

then test to determine whether or not the animal was tolerant to the disruptive effects of nicotine. When you inject nicotine in an animal when he's working on a lever for food, the performance of the animal becomes impaired. That performance impairment goes away as the animal has exposure to nicotine.

We also demonstrated in an experiment that part of that tolerance was physiological and part of the tolerance was behavioral, that is, a learned tolerance.

In physical dependence, we conducted two large experiments in which we chronically administered nicotine to rats over several days, if not weeks. We challenged the nicotine in the animals with an antagonist, mecamilamine. Or in another experiment, we let the -- simply the nicotine -- took it away from the animal. We did not observe any withdrawal syndrome as evidence by changes in food-motivated behavior.

REP. WAXMAN: So of the three hallmarks of dependence, you did find that there was self-administration and tolerance, but you did not find that there was a physical dependence?

MR. DENOBLE: That is correct.

REP. WAXMAN: And did these studies that you did also indicate that nicotine has a potential for drug liability?

MR. DENOBLE: Yes. The self-administration study is a classical hallmark to indicate that a solution or a drug substance has a potential for abuse, yes.

REP. WAXMAN: And what does drug liability mean?

MR. DENOBLE: It essentially means that if you find it in an animal, it has the potential to be a drug of abuse in humans. You need to then go on to do other species and other strains of animals, and also go into the human to determine the final factor.

REP. WAXMAN: Now, on March 31, I released a version of your self-administration study. On that same day, Phillip Morris issued a statement which I would like entered in the record, without objection, as Exhibit 2. And they said, and I quote, "Dr. DeNoble concluded that nicotine self-administration cannot be viewed as a form of drug abuse." End quote.

On the basis of your work at Phillip Morris, did you reach such a conclusion?

MR. DENOBLE: No, sir, I did not.

REP. WAXMAN: At this time, I'd like to show you Exhibit 3, which is a letter from Dr. Alan Leshner (sp), Director of the National Institute on Drug Abuse. That letter states that the findings in your study, quote, "indicate that nicotine has reinforcing properties, one of the hallmark characteristics of addictive drugs." Do you agree with that characterization of your work?

MR. DENOBLE: Yes, I do.

REP. WAXMAN: You were not able to show this physical dependence. Am I correct that later studies did show a withdrawal syndrome in rats on nicotine, meeting the third criterion for addiction?

MR. DENOBLE: That is correct. Those studies were not performed in our laboratory. They have since been performed between 1984 and 1994.

REP. WAXMAN: Why did those studies reach a different result than yours?

MR. DENOBLE: I reviewed those studies, and the conclusion that I can come to is that those studies used very different measures than what we were using, much more sensitive measures than we were using. We modeled our dependent studies after work that I had done with alcohol and barbiturates. So we didn't find it using those procedures, but other people have.

REP. WAXMAN: Now, I'd like to ask you about your study on self-administration. Prior to your work, had anyone ever shown that rats will self-administer nicotine?

MR. DENOBLE: There have been at least a half a dozen demonstrations that rats will self administer nicotine. The problem with most of those studies is that there was a compounding variable of inducement. It was not clear -- you couldn't interpret clearly whether nicotine was a true reinforcing agent, or whether it was coupled to another thing going on in the animal's life.

REP. WAXMAN: So your studies succeeded others that failed. Can you tell us why?

MR. DENOBLE: I think that the main difference between our study and previous studies was the infusion time. Back in the seventies and eighties, it was common to infuse a drug solution into the vein of an animal over a 13 to 15-second period. That's not what happens if you observe a smoker. A smoker takes smoke into his lungs and nicotine is immediately going to the lung and immediately getting to the brain. So we basically shortened our infusion times to less than four seconds. So we were delivering a very quick pulsed infusion. That seems to be the critical factor in our success.

REP. WAXMAN: I'd like to show you some posters if we can have those displayed. The first one, Exhibit 4, is entitled Self Administration Methodology, could you explain it for us?

MR. DENOBLE: Yes, that's a poster -- this is a rat that would be inside of an experimental chamber, and he has a switch -- what I refer to as a lever. The rat is also, as you can see on his back, he's surgically prepared with a catheter that it lodges in his vein or in the atrium of the heart. The rat has the option to go over and press the lever. When he does, it activates some programming circuitry; you record when the press occurred. It also activates an infusion pump, and that pump will then infuse nicotine or whatever solution you have into the animal's vein. Again, if that solution is a reinforcer, the rat will continue to press the lever at reasonably high rates.

REP. WAXMAN: We have another poster, which would be Exhibit 9, and that shows the number of times the rats press the lever for nicotine. Can you explain it for us, and let me indicate, by the way, that both of these posters are furnished to us from your slides -- they were given to us by you.

MR. DENOBLE: That's correct. This is a group data shot. Primarily after the rats are surgically prepared with the catheter, you put them in the box, and they're hooked up to a pump which has saline in it. And the animals don't press the lever very often for saline, In fact, they pressed it less than 12 times. If you now substitute nicotine at a dose of 32 micrograms per kilograms, you can see that after several days an animal will inject itself well over -- almost 90 times per 24 hour session.

If you now remove the drug solution, in this case nicotine, the

animal stops pressing the lever in a series of days. So the nicotine self administration falls back down the original saline levels. Standard control is to reintroduce the nicotine, and that's the second large bar you see, where it says 32. And that's again, the animals will resume pressing the lever once nicotine is again made available intravenously.

REP. WAXMAN: How did you pick the dose of nicotine to give to the rat?

MR. DENOBLE: Well, we looked through the literature at the time, in the early eighties, and it was determined by us that about one to two milligrams of nicotine was coming through in a cigarette. I just simply divided that by a 70 kilogram individual and came up with 30 micrograms per kilogram.

REP. WAXMAN: And is that any relationship to what a human would get?

MR. DENOBLE: It's basically -- it's very difficult to answer that question. It's based upon what a single cigarette delivers to a human, but I don't know if it's any relationship to the physiological affects; I cannot answer that.

REP. WAXMAN: We have the next exhibit, Exhibit 10, it's a little bit more complicated. It's my understanding that it shows how hard the rats will work for nicotine. Could you explain that to us?

MR. DENOBLE: Yes. Could I walk over there? Or is that hard to do?

REP. WAXMAN: It's going to be a little difficult to get this on the microphone.

MR. DENOBLE: Okay, that will be fine. If you look at what's called fixed ratio size, that is how many times a rat has to press a lever, and if you look at the unit number one, he gets a single press, he gets a single injection. If you now say to the animal, I'm going to see how hard you'll work for it, I'm going to ask you to press the lever twice. The animal -- and again -- this represents and animal pressing the lever twice for nicotine.

What's interesting, this dotted line tells you how many infusions the animal is taking. So here he's taking a stable level of

infusions. If you ask him to double his work output. You can ask him to triple it, quadruple it, etcetera. The animals will continue to work and press the lever to get nicotine up to about a fixed ratio of six or seven, and then it begins to fall off. The cost is just too high. Two points about this slide. One is, animals will work for nicotine; and second is, animals will maintain a constant level of nicotine infusion over different work schedules.

REP. WAXMAN: At our April 14th hearing, Phillip Morris' chief executive officer testified that you had quote, 'concluded that nicotine is a reinforcer in the class of non-addictive chemical compounds such as saccharine and water.' We asked Phillip Morris for these and other relevant documents, but they were unable to provide them prior to this hearing. Is Phillip Morris correct that you concluded after you did this work, that nicotine is a reinforcer comparable to saccharine and water?

MR. DENOBLE: No, not at all.

REP. WAXMAN: What would be the difference?

MR. DENOBLE: Well, water is a reinforcer, but you need to be food deprived or very nervous to drink it. Food is a reinforcing agent, but you need to be hungry, or it needs to taste good; it requires tongue. Nicotine was being injected directly into the vein. We went on to use a series of blocking agents to show that it was the brain activity of nicotine -- not its effect on the periphery, not its effect on taste systems that determined its reinforcing affects. An animal doesn't have to need nicotine for it to be a reinforcer, all it has to do is experience it.

REP. WAXMAN: Now, you said food. Would that also apply to saccharine, you need to taste saccharine --

MR. DENOBLE: Saccharine is very -- yes. The reinforcing effects of saccharine are clearly mediated via its interactions with the taste system in the mouth.

REP. WAXMAN: Now, if you ran the kind of tests you did for nicotine on saccharine, what would you find?

MR. DENOBLE: That saccharine is not self administered intravenously to the best of my knowledge.

REP. WAXMAN: So you have an intravenous feeding of this nicotine that's going right to the brain. If you put saccharine intravenously, there would be no taste, there would be no reason why they'd want to go back to it.

MR. DENOBLE: I don't know of any experiment that's ever demonstrated it, no.

REP. WAXMAN: Finally, I want to ask you about a statement in the 1983 version of your unpublished article on self administration that doesn't appear in your 1986 version. In the 1983 version of the article, you state that nicotine quote, 'may be a weak reinforcing agent' end quote. What was the basis for this statement, and why did you take it out in a later version of the article?

MR. DENOBLE: In the earlier version of the article, I was doing some literature comparisons between nicotine and other intravenously delivered reinforcers, specifically, psycho-stimulants like cocaine and amphetamine. And if you look at just how hard an animal will work for these substances, nicotine looks like a weak reinforcer. And I made that statement that I think that was a fair assessment at that time. As we begin to think and know more about the reinforcing effects of these drugs, we also found that rat models do not necessarily predict how reinforcing something will be in a human.

For example, alcohol is not a very good intravenously delivered reinforcer in rats, but alcohol is a very powerful reinforcing agent in humans. So, I did not put that in the second article, simply because I didn't think my data was strong enough to make that statement.

REP. WAXMAN: Put this all in a historical context for us. Your work on nicotine at Phillip Morris, what significance did it have at that time frame, and how should we view this -- (inaudible) --?

MR. DENOBLE: The work that we did with nicotine was clearly some years ahead of the external community, scientific community. It wasn't until 1989 that Bill Corgal (sp) demonstrated that nicotine would function as an intravenously delivered reinforcer for rats, using the same models that I used -- that Paul and I used. Interestingly enough, he found the same dosing schedules to be effective. The work that we did on self administration, on dependence, on tolerance, on frustration, clearly would have moved the scientific community much further along than it had been moved by that

work not getting out.

REP. WAXMAN: Dr. Mele, do you want to add anything to this?

DR. MELE: Just that this work -- some of these studies were the first to be done with nicotine. I have no doubt that other people would have performed these studies subsequently just as has been done recently in Toronto. But they weren't being done at the time, and to quote a recent review article in science -- a news story that -- it basically took six or seven years for the nicotine self administration model to be developed and come out. Whereas, it would have been out much earlier had this work been allowed to go out and stay out.

REP. WAXMAN: So your work at Phillip Morris indicated the reinforcing nature of nicotine; information that didn't come out until years later and led to the Surgeon General report -- I guess it was 1988 or 1989, when the public was finally informed by the chief medical officer of this country that nicotine is an addictive substance in cigarettes.

MR. DENOBLE: That's correct. I think the significance of the self administration is in part because it was a rat model. And if you're going to understand the biochemistry of this system, if you're going to understand how drugs interact in the brain, you need to run dozens if not hundreds of animals. So the significance -- other people had already been doing this from '84 on. But the rat model wasn't developed until 1989.

REP. WAXMAN: Thank you very much. Mr. Bliley?

REP. BLILEY: Thank you, Mr. Chairman. Dr. DeNoble, Dr. Henningfield (sp) and the Surgeon General have testified before this subcommittee that nicotine use creates a physiological dependence. They have testified that such dependence is important because it shows that nicotine use is addicting. Isn't it true that while you were working at Phillip Morris, you told your superiors that your experiments showed that nicotine use does not create a physiological dependence.

MR. DENOBLE: That's true. We demonstrated that in at least two separate experiments.

REP. BLILEY: Thank you. Dr. Henningfield (sp) works at the National Institute on Drug Abuse. In 1979, NIDA published a report

titled, National Institute on Drug Abuse Technical Review on Cigarette Smoking as an Addiction. Isn't it true that while you were employed at Phillip Morris, you reported to your superiors that most of the evidence in this report was fanciful fantasy, unquote, rather than fact, and that NIDA had chosen the research it used in this report in a biased way so that NIDA could claim publicly that cigarette smoking was an addiction?

MR. DENOBLE: I don't know that I said that. If I have a doc -- it's very possible that I reviewed those documents, but I don't know that those are my words.

REP. BLILEY: After this report by the NIDA came out, you did your experiments in which you carefully examined whether or not nicotine use created a physiological dependence. And you found that nicotine use did not create a physiological dependence? You then reported this to Phillip Morris?

MR. DENOBLE: That is correct. The models we used were, at the time, in the eighties, were excellent models. The animals are very highly motivated in these models, and the animals clearly would show a physical dependence to things like alcohol and barbiturates, but we did not find it with nicotine.

REP. BLILEY: You also did experiments while at Phillip Morris to determine if -- I'll try this word -- Acetaldehyde (ph) use caused physiological dependence, and you found that Acetaldehyde (ph) use did not create a physiological dependence?

MR. DENOBLE: Yes, we used the same experiments that we did with nicotine.

REP. BLILEY: You also did experiments at Phillip Morris to determine whether injections of Acetaldehyde (ph) and nicotine mixed together caused physiological dependence. And you found that Acetaldehyde and nicotine mixed together did not cause a physiological dependence?

MR. DENOBLE: That is correct.

REP. BLILEY: We have been told by other witnesses that because animals will self administer nicotine, this is proof that nicotine is addictive. Isn't it true that while you were working at Phillip Morris, you told you superiors that animals will self administer

saccharine?

MR. DENOBLE: No, sir. I never said they will self administer saccharine. They will work for saccharine. You can press a lever and get a food pellet or get saccharine, and that is a self administration procedure. The difference between self administration of saccharine and food, and nicotine is that one is delivered intravenously, the other one goes through the peripheral system. So saccharine, yes, you can self administer it, but only through the oral route. It will not go intravenously.

REP. BLILEY: Isn't it true that you concluded from your research at Phillip Morris that behavioral factors are primarily responsible for tolerance to nicotine?

MR. DENOBLE: No, I'd like to defer that to Dr. Mele. Paul is -- was an expert -- is an expert in tolerance and nicotine.

DR. MELE: Well, I ran the tolerance studies anyway. Yes, we did determine that under certain conditions, behavioral factors contributed heavily to the development of tolerance to nicotine. Behavioral factors were not the only component, there was also, at least back then, what was termed a physiological or metabolic component. So there was a dual role in our studies.

At least in the first study we ran, the behavioral component was much larger.

REP. BLILEY: And you reported this to your superiors at Philip Morris, both of you?

MR. MELE: Yes.

MR. DENOBLE: Yes.

REP. BLILEY: Isn't it true that you also concluded from your research at Philip Morris that if there is a physiological tolerance to nicotine, it is like that developed to saccharine or caffeine?

MR. DENOBLE: I don't know that tolerance develops to saccharine. I do know that tolerance does develop to caffeine, yes.

REP. BLILEY: And you reported that to your superiors?

MR. DENOBLE: Tolerance to saccharine -- I'm sorry; tolerance to caffeine, tolerance to nicotine, tolerance to alcohol (phenobarbital?). It's pretty much the same; different mechanisms, perhaps, physiological mechanisms, in the liver. But the general conditions are the same, yes.

REP. BLILEY: This subcommittee has been told by some witnesses that the evidence is clear that nicotine alone is an addicting substance, in part because ceasing the use of nicotine causes physiological withdrawal symptoms. Isn't it true that while you were employed at Philip Morris, you told your superiors that your research showed that stopping nicotine use does not result in physiological withdrawal?

MR. DENOBLE: In rats, yes.

REP. BLILEY: While you were employed at Philip Morris, you also did experiments to determine if stopping acetaldehyde caused physiological withdrawal symptoms. And while you were working at Philip Morris, you told your superiors that your experiments found no physiological withdrawal symptoms resulted from stopping the use of acetaldehyde. Isn't that correct?

MR. DENOBLE: Yes, in our experiments with rats.

REP. BLILEY: While you were working at Philip Morris, you also did experiments to determine if stopping the use of acetaldehyde and nicotine mixed together caused physiological withdrawal symptoms. Again, while you were employed at Philip Morris, did you not tell your superiors that your experiments showed that stopping the use of acetaldehyde and nicotine mixed together did not cause physiological withdrawal?

MR. DENOBLE: Yes, we did.

REP. BLILEY: Am I correct that all of your experiments at Philip Morris were with rats and that none of your experiments involved people?

MR. DENOBLE: That is correct.

REP. BLILEY: Doctor, 40 million Americans have quit smoking. Isn't it true that while you were working at Philip Morris, you advised your superiors that the relative ease with which people can

stop smoking without formal treatment identified smoking behavior as fundamentally different from addictive behavior?

MR. DENOBLE: It's not fundamentally different, but it clearly is different than if you were going through an alcoholic or if you were a heroin abuser. That is correct.

REP. BLILEY: Is that what you advised your superiors?

MR. DENOBLE: Yes, that's true.

REP. BLILEY: Am I correct that acetaldehyde is something that results naturally from burning tobacco?

MR. DENOBLE: That is, yes, correct.

REP. BLILEY: Nicotine, of course, is also a natural part of tobacco, isn't it?

MR. DENOBLE: Yes, it is.

REP. BLILEY: Dr. DeNoble, I now want to ask you about your research paper on rats' self-administration of nicotine that was submitted to psychopharmacology and withdrawn. As I recall, the title of that paper was, quote, "Nicotine as a Positive Reinforcer in Rats, Effects of Infusion (Dose?) and Fixed Ratio Size," unquote. According to both the abstract and the first page of your manuscript, your research found that "even the termination of prolonged access to nicotine under which it functions as a positive reinforcer does not result in physiological dependence," unquote. Is that right?

MR. DENOBLE: That is a correct observation, yes.

REP. BLILEY: The amount of nicotine injected directly into the rats' veins in this experience were much higher than the amount of nicotine a smoker receives. Isn't that true?

MR. DENOBLE: The amount of nicotine injected at the 32-microgram dose is roughly the equivalent of one cigarette. But what we did was we did a spread of ranges of doses so we showed at 32, 16, eight and four. Eight and four were not as reinforcing as 16. So we did branch the range. So it is roughly the equivalent of a single cigarette or less in a rat.

I also might add, sir, that animals have been shown to be either more sensitive or less sensitive to drugs, depending upon the drug class. So it's very difficult to make a direct comparison to the human.

REP. BLILEY: You reported, I believe, in this paper, as you told your superiors all the time that you were employed at Philip Morris, that there was no evidence of physiological dependence to nicotine in the experiment and there was no evidence of physiological withdrawal from nicotine in the experiment. Is that true?

MR. DENOBLE: That is correct, yes. We were unable to find it using a model in which an animal is a highly motivated animal. The model is you deprive the animal of food and the animal has to work for food, and then you have it being administered nicotine. Pull the nicotine away and the animal -- your evidence of physiological dependence is that the food-directed behavior is changed in some way; is altered. We did not observe that. We did not see an animal sort of show physical dependence withdrawal syndrome in that particular model.

REP. BLILEY: This subcommittee has been told that the evidence has been clear for some time that nicotine itself is an addicting substance, that the use of nicotine alone creates a physiological dependence, and that stopping only the use of nicotine causes physiological withdrawal symptoms. Isn't it true that while you were employed by Philip Morris you told your superiors that your research at Philip Morris showed that nicotine is not addictive, that nicotine does not create a physiological dependence, and that stopping the use of nicotine does not create physiological withdrawal?

MR. DENOBLE: Yes, we did. In the same way, we also said to them that self-administration in the rat does not necessarily predict the amount of self-administration in the human. Gentlemen, you have to be very careful about predicting from rats to humans. What the animal data shows you is that there's something to look at. And when you see self-administration, you need to go further. When you fail to find physical dependence, you need to go further to determine whether it's really going to be generalizable to the population.

REP. BLILEY: Mr. Chairman, I assume I'll be allowed to go on. Doctor, isn't it true that, to your knowledge, Philip Morris never used any of your research to change the acetaldehyde or nicotine content in any commercial cigarette?

MR. DENOBLE: Yes, I have no knowledge of that.

REP. BLILEY: Isn't it true that to your knowledge Philip Morris never used your research to create a new commercial cigarette?

MR. DENOBLE: That is correct.

REP. BLILEY: Dr. Mele, if I might, isn't it true that while you were working at Philip Morris, you advised your superiors that your experiments showed that nicotine use does not create a physiological dependence?

MR. MELE: No, I don't recall that at all.

REP. BLILEY: You didn't --

MR. MELE: Only as part of possibly a co-author on some of Dr. DeNoble's. I know the tolerance work I was working on that involved chronic administration for over 100 days. We did not find a physiological dependence in that study, but I don't recall specifically discussing that with anybody at Philip Morris. It may be in the manuscript; it may not. I just don't recall it.

REP. BLILEY: Isn't it true that while you were employed at Philip Morris, you advised your superiors that your experiments showed that acetaldehyde use does not create a physiological dependence?

MR. MELE: Yes, under the conditions which we ran the studies, which were very limited, we did not find a physiological dependence.

REP. BLILEY: Isn't it true that while you were employed at Philip Morris, you also did experiments to determine if discontinuing the use of nicotine or acetaldehyde created physiological withdrawal symptoms and that you told your superiors at Philip Morris that your research showed that discontinuation of nicotine or acetaldehyde did not cause physiological withdrawal symptoms?

MR. MELE: Yes, again, under the conditions of those circumstances, we could not identify any physiological withdrawal

REP. BLILEY: And you did all of your experiments, of course, with Dr. DeNoble, with rats.

MR. MELE: Correct.

REP. BLILEY: Isn't it true that some rats in your experiments at Philip Morris liked nicotine more than other rats?

MR. MELE: Some rats may administer higher doses or have different dose response curves than other rats. That is very typical of any drug effect in any rat or any animal. There are individual differences.

REP. BLILEY: Isn't it true that albino rats did not seem to like nicotine as much as hooded rats?

MR. MELE: I didn't work with albino rats at all when I was at Philip Morris.

REP. BLILEY: Though you didn't work with albino rats, but isn't it generally true that albino rats don't seem to like nicotine as much? Dr. DeNoble?

MR. MELE: I'm not sure. I can't answer that question.

MR. DENOBLE: Yeah, I can't answer that question either. I'm not sure where that data is coming from.

REP. BLILEY: Well, isn't it true, Dr. DeNoble, that you decided to use hooded rats in your experiments because hooded rats were easier to get to self-administer?

MR. DENOBLE: No, that's incorrect. There was a paper published in the early '80s, I believe around 1980, actually, which demonstrated that the albino rat was not a prototypical animal to do drug research because it had an altered biochemistry, because it is an albino. The hooded rat has an intact, more generalizable biochemistry in the brain, so that a hooded rat's biochemistry is much closer to that of a monkey's and it's closer to that of a human. So we elected to do all of our studies in hooded rats, whether it be self-administration tolerance, dependence, because their brain biochemistry represented more what a normal animal is.

REP. BLILEY: Thank you. Thank you, Dr. DeNoble. Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Bliley. Mr. Synar?

REP. MIKE SYNAR (D-OK): Thank you, Mr. Chairman. First of all, believe it or not, I think Mr. Waxman, Mr. Wyden and I all believe or we do understand why the executives of these seven major tobacco companies came in here a couple of weeks back and, in the face of overwhelming historical and medical evidence, denied the addictiveness of nicotine. I mean, they have been counseled by their attorneys that an admission of that part would increase their chances of liability.

But Dr. DeNoble, you don't have that same responsibility. You're a scientist. And I want to ask you, do you agree with the statement we heard from the executives under oath that nicotine is not addictive?

MR. DENOBLE: I'll answer that in 1994, not 1984. I think there's an overwhelming body of evidence that nicotine does produce an addiction in the human. That overwhelming body of evidence does not come from a single rat study or (Paul's?) study on tolerance. So my opinion in 1994 is yes. I think in 1980, '81, '82, '83 and '84, I think there were some doubts in my mind because the data wasn't there.

REP. SYNAR: So what you're saying is that your study didn't definitively prove that nicotine was addictive, but it predicted that this was as serious a problem as you had seen, and therefore caused further study and review. Is that basically what you're saying today?

MR. DENOBLE: It certainly did indicate that nicotine had (an abuse?) liability and we needed to look further to determine other factors, yes.

REP. SYNAR: Okay. Now, Mr. Johnston, the chairman of RJR, during his testimony a couple of weeks back, said that nicotine is comparable to saccharine and chocolate. Your study doesn't support that proposition, does it?

MR. DENOBLE: No, sir, it does not.

REP. SYNAR: In fact, that's a little bit stretching the truth to say that we could compare nicotine to saccharine and chocolate.

MR. DENOBLE: Experimentally, scientifically, I believe that's correct, yes.

REP. SYNAR: Now, you've testified this morning, Dr. DeNoble,

that one purpose of the analogue research study was to find a synthetic form of nicotine with reduced cardiovascular effects. Now, why were your superiors at Philip Morris concerned about that cardiovascular effect of nicotine?

MR. DENOBLE: That program was in existence actually before I got to Philip Morris. The nicotine analogue program, I know, was there before I got there because the analogues were there and they also had some animal experiments ongoing. The discussions around nicotine in the '80s, the late '70s, early '80s, was that there was a cardiovascular risk. Clearly nicotine has effects on the cardiovascular system. It was also clear that that effect on the cardiovascular system could be related to increased heart disease, so the objective of the program was to come up with a molecule that would mimic nicotine's effect in the brain and not affect the peripheral nervous system and therefore not have cardiovascular liability.

REP. SYNAR: So beyond addictiveness, nicotine has other consequences with respect to the health of a person.

MR. DENOBLE: Yes.

REP. SYNAR: Now, Dr. DeNoble, could you outline the official policy at Philip Morris with respect to documentation of studies? What I'm interested in is how were the original papers that you worked on archived? How were the documents maintained? Where were they kept? Was there periodic destroying of those documents? Is there a master index of those studies and working papers?

MR. DENOBLE: The laboratory would write annual reports every year. They -- (inaudible) -- and Paul and I would put them together. All data, all original data, would be archived in an annual report and sent to -- would be distributed throughout the research center and then sent to central file. We kept all our original data in notebooks which would also go to a central filing unit. I know of no instances in which data had been destroyed, at least not while I was there up until April of 1984.

We also gave interim reports which would be considered pharmacology reports. Or if we were to try to write a manuscript, that manuscript would also be distributed through the research center.

REP. SYNAR: Okay. Now, did any other researchers at Philip Morris conduct research on humans while you were there?

MR. DENOBLE: On humans?

REP. SYNAR: On humans.

MR. DENOBLE: Yes, there was one laboratory that conducted electrophysiological studies of humans, looking at the effects of cigarette smoking on electrical brain activity, and also looking at the effect of flavorants added to the (nasal?) cavity and looking at the effects on brain activity.

REP. SYNAR: Okay. Now, let's talk about the article which has been really the focus of the controversy. Did Philip Morris orally request that you pull your article from the magazine, or did they send you a correspondence requesting that?

MR. DENOBLE: I never received the correspondence. I was just asked to remove it by our manager. We tried very hard to convince him that we shouldn't remove it from publication, but we lost that battle. So we were told to pull it from the journal.

I immediately called Herb Barry up and told Herb of the situation and sent him off a note as an official record that we needed to withdraw the paper.

REP. SYNAR: Okay, just for the record, Doctor DeNoble, once again, why did you leave Phillip Morris?

MR. DENOBLE: I left because the lab was closed down. It was abruptly closed down in April of 1984.

REP. SYNAR: Did they give you a reason that they couldn't find another position for you?

MR. DENOBLE: Actually, they never said they couldn't. They just said that it wouldn't be to the caliber of the position that we had, that clearly it would be a step down in pay as well as visibility. And I think clearly that we needed to leave.

REP. SYNAR: Now, did you look for other jobs in the tobacco industry?

MR. DENOBLE: No, we're not allowed to do that. Part of your contractual agreement with Phillip Morris is that you cannot work for

a competitor, and I don't remember the timeframe, I think it was seven years, something like that.

REP. SYNAR: Okay. Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Synar. Mr. Greenwood.

REP. GREENWOOD: Thank you, Mr. Chairman. Back to the purposes of the study, and Congressman Synar mentioned that in your testimony you referenced the goal of this program was to identify a nicotine analog that would have central nervous effects without effects on the cardiovascular system.

We understand that now. What were the practical implications of that and has -- first off, let me ask you this -- has such an analog ever been discovered, to your knowledge?

MR. DENOBLE: We did discover a lead series of analogs which had met the criteria of reduced cardiovascular effect and maintained the brain effects. So yes, we were able to identify at least two analogs that would meet that criteria.

REP. GREENWOOD: So what are the practical implications of that, and what uses have been made, if any to your knowledge, of these analogs?

MR. DENOBLE: I don't think any use has been made of it. In fact, it was basically put on the shelf. There was not to my knowledge any activity around these analogs.

REP. GREENWOOD: Are these analogs found in nature or are they synthetic?

MR. DENOBLE: They are synthetic. They are organically synthesized.

REP. GREENWOOD: And was the goal to somehow remove the nicotine from tobacco and substitute this synthetic analog?

MR. DENOBLE: That was exactly the goal, to remove nicotine from the tobacco and have the analog be a substitute so that you would produce a safer cigarette.

REP. GREENWOOD: And the analog that you were searching for and

that you say has been found, does it have -- is the idea for it to have the same habit-forming qualities of nicotine without the health risks? Is that the idea?

MR. DENOBLE: That's a very difficult question to answer when you talk about habit-forming. If you're asking me, would it maintain self-administration, would it act as a reinforcing agent, would it maintain the brain receptor qualities, the answer to that is yes. That's correct.

REP. GREENWOOD: Do you have any information as to why if that synthetic analog has been discovered, that it hasn't been utilized in the production of tobacco products?

MR. DENOBLE: No, I don't. I have no idea, but I also want to mention that the analog that I'm talking about, or the series of analogs meets the criteria, but before you could actually use that, you would have to go through a whole series of other testing, and that testing was never done.

REP. GREENWOOD: Would it have to be approved by the FDA?

MR. DENOBLE: I guess that would depend upon how you put it in tobacco. You could theoretically genetically engineer plants to grow it, it's just a simple molecule, but that's far beyond my expertise.

REP. GREENWOOD: Was your research -- were you asked to devise the format of this research, or were you brought on to Phillip Morris and you were directed by superiors as to how your research was to be conducted?

MR. DENOBLE: No. The goals of the laboratory were pretty straightforward. It was an analog program. We put together the screening procedures with the exception of the drug discrimination procedure, which was there. We determined the direction of the lab in collaboration with management. I met with my manager weekly to discuss research directions and data. So it was really a collaborative arrangement. The people in Richmond are good scientists, and it was a good exchange of ideas.

REP. GREENWOOD: Now, if I understand your testimony, the reason we've heard very different kinds of answers to different questions directed by different members of the panels is that when Chairman Waxman or Mr. Synar have asked you questions about the addictive

quality or the reinforcing qualities of nicotine, you have really relied on information that's been brought forward by other researchers in the past 10 years. When you've been asked to give information based on your own study of 10 years ago, you had different information.

So on the one hand, you said, yes, my study didn't demonstrate that nicotine was addictive or reinforcing; however, we now know that it's the case. Does that correctly summarize --

MR. DENOBLE: Let me see if I can clarify it. The work that was done in '81, '82 and '83 on nicotine self-administration clearly shows that nicotine is an intravenously delivered reinforcer. That is a characteristic of a drug of abuse.

When you talk about addiction, you're talking about a human condition. Rats -- we can't predict that nicotine is addictive in humans based upon that single observation in rats. So my studies stand -- our studies stand as this is a characteristic of the drug; it's definitely a substance that could have an abuse liability. That ends right there.

From '84 on, there have been numerous studies demonstrating in humans as well as in monkeys that nicotine has qualities that the committee calls addicting.

REP. GREENWOOD: Now, there are -- we've talked about other substances throughout these hearings, everything from saccharine and caffeine to alcohol, amphetamines to heroin. Is it possible to place the qualities of nicotine on some sort of a spectrum? Is it more like caffeine or is it more like heroin in terms of its effect on either mice or humans?

MR. DENOBLE: Well, in humans I think the data indicates that it's more like cocaine and amphetamine. Those are the liking studies that have been done back in the late '80s. In the animal, you have to do direct comparisons, and very few of those studies have been done.

In the rat, nicotine is probably like alcohol if you want to talk about weak reinforcing effects. But in the human, I think the data indicates it's more like a stimulant.

REP. GREENWOOD: Well, caffeine is a stimulant, right?

MR. DENOBLE: Caffeine I think is classified as a weak stimulant, yeah.

REP. GREENWOOD: A weak stimulant. So is it more -- you're saying it's more like cocaine than it is like caffeine?

MR. DENOBLE: That would be the data that -- that's the research, yes.

REP. GREENWOOD: Okay. What's the difference between a -- there are lots of pleasurable responses that you can get both rats and humans to work for, push pedals for or whatever else they do. What's the difference between that and addictive behavior?

MR. DENOBLE: Not much. The difference is that the animal is going to control the experimental procedure and you're controlling variables. When a human self-administers a drug, it's the same situation. The human has to go buy it, he has to work to get it. I mean, the comparisons are very, very -- the similarities are astounding.

So they are very similar. Self-administration techniques predict what humans will do.

REP. GREENWOOD: And there's been probably too much made about the food comparisons to cigarettes. But there are people with eating disorders who seem by a lot of measures to be as addicted to foods as people are to substances. Is that the same -- are we talking about the same range of human behavior?

MR. DENOBLE: Not really, because things like bulimia or people who have food addictions may in fact be driven by biochemical imbalances in the brain. That may in fact be a psychiatric disorder. You don't have to have a psychiatric disorder to be addicted. The addiction, or the self-administration, is cued by the drug in the brain. So they're really very different things.

REP. GREENWOOD: Okay. And finally, your testimony in this hearing has been fascinating in terms of science and understanding your experiments and the experiments that followed and the various qualities that are found in nicotine. But we are here to make public policy, so I guess I have to ask you this.

What are you here to tell us in terms of public policy? This is

all very interesting science, but what should we take from your testimony? What do you want us to do in response to your testimony in terms of crafting public policy?

MR. DENOBLE: Well, I'm not here to make public policy. I'm here to tell you of the science that was done between 1980 and 1984. I'm here to position that science as to its relevancy in reference to other science that's been done from '84 on.

I'm not going to be so bold as to tell you what to do with public policy. I can't do that.

REP. GREENWOOD: Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Greenwood. Mr. Wyden.

REP. WYDEN: Thank you, Mr. Chairman. Let me, if I could, Dr. DeNoble, go back to the point of Mr. Bliley because Mr. Bliley was talking specifically about nicotine effects and showing withdrawal in rats.

Now, you testified that subsequent studies showed nicotine does cause withdrawal in rats. What was it about these studies that made it possible to identify withdrawal symptoms?

MR. DENOBLE: Our study, as I mentioned, relied upon a very strongly motivated behavior. If the rat didn't press the lever, it didn't eat. And that is a very strong drive.

These later studies use very subtle measures, whereas a rat doesn't necessarily have to press the lever to eat, but maybe to deliver itself a glucose-sweetened solution. So it's a reward, if you will, a candy.

Under those conditions where the rat is not so strongly motivated, people have shown that nicotine will disrupt those measures. So the difference is ours is a highly motivated animal. If you don't press, you don't eat. And the other one is, if you don't press, well, maybe you don't get your glucose.

REP. WYDEN: Let me turn now to an area that Chairman Waxman I think has really focused on very correctly, and that's this matter of secrecy in the tobacco industry. I mean I just look at the events of what went on in your situation and many others as sort of like a spy

novel, with all this cloak-and-dagger kind of activity.

And I wanted to ask you about some of the details of your situation. When you were hired in 1980, did you discuss whether you would be able to publish the results of your research at Phillip Morris?

MR. DENOBLE: Yes, I did, and as with most companies, it clearly depended upon the proprietary position. I do -- when I went there, it was clear to me that I would not be able to publish everything when I wanted to, but eventually we thought we'd be able to publish everything. So yes, they were very clear on that.

REP. WYDEN: Did Phillip Morris try to keep your work secret?

MR. DENOBLE: During the first two years of the laboratory's existence, the lab was really quite secretive. The animals would be brought in at night or very early morning under cover so that -- people knew we had animals in the building. They couldn't not know, but they didn't know what we were doing with them, and we weren't permitted to discuss our research at any of the research meetings for the first two years or so.

REP. WYDEN: So the animals were brought in and they were covered up?

MR. DENOBLE: Yes, that's correct.

REP. WYDEN: And when the rats had died, were they taken out after hours and that sort of thing?

MR. DENOBLE: Usually they were incinerated, yes.

REP. WYDEN: And nobody was allowed into the laboratory without management's permission?

MR. DENOBLE: That is correct.

REP. WYDEN: What would you say if another scientist working in the building asked you about your work?

MR. DENOBLE: We'd tell them that we were just doing some experiments in the nicotine analog program. Everybody knew about the analog program, but the animal research was not a very well known

commodity.

REP. WYDEN: Who told you to follow all these secrecy procedures?

MR. DENOBLE: They were laid out to us by our management when I was hired.

REP. WYDEN: And that was Mr. Dunn and --

MR. DENOBLE: Dr. Dunn, Dr. Osdine (sp).

REP. WYDEN: Okay. Now, in the fall of 1982, as I understand it, you submitted a manuscript to Phillip Morris on the self-administration matter. You wanted permission to publish the paper. We can give you that exhibit. Who reviewed this paper and whether approval was given?

MR. DENOBLE: This paper was reviewed by my immediate management, which was -- I think it was Jim Charles at the time, although it might have been Dr. Dunn. I don't remember exactly when we changed. It was reviewed by them, then sent to the director of research, Dr. Osdine. From there, it gets kind of fuzzy. I don't know where it goes, but it comes back about two weeks later. It was a yes or a no.

REP. WYDEN: And approval was given to submit it to the "Psychopharmacology Journal"?

MR. DENOBLE: To "Psychopharmacology" as well as to the American Psychological Association meeting in Anaheim coming up in 1983.

REP. WYDEN: All right. Let me ask you, if I might, about some later events at Phillip Morris. You were promoted in 1983?

MR. DENOBLE: Yes, I was.

REP. WYDEN: And your supervisors evaluated your performance and gave you favorable marks overall?

MR. DENOBLE: Yes. We were given evaluations each year that we were there.

REP. WYDEN: Did you get raises?

MR. DENOBLE: Yes, we did, every year we were there.

REP. WYDEN: And how about your associate, Dr. Mele?

MR. MELE: Yes, same thing.

REP. WYDEN: All right. Now we're also interested in some developments in middle '83, where you and some researchers flew form Richmond, Virginia, to New York City to brief the senior management on your work. Can you walk us through what happened on some of those key events that started back in Richmond?

MR. DENOBLE: Sure. We were notified by our senior management that we were going to be going to New York, corporate headquarters, to give a presentation on the activities of the behavioral pharmacology laboratory. We were taken to the airport, put on a company jet, flown up to New York, and one of the PM1 limousines met us and took us over to the corporate headquarters.

At that point, we gave a presentation to several members of New York corporate staff, entertained questions, had lunch in the corporate executive dining room, and then were flown back that evening on the company jet.

REP. WYDEN: What kinds of questions were you asked at the New York briefing?

MR. DENOBLE: I was only asked one question.

REP. WYDEN: What was that?

MR. DENOBLE: I can't quote it, but I'll paraphrase it, and it's basically, why should I risk a billion-dollar industry on rats pressing a lever to get nicotine?

REP. WYDEN: And this was a Phillip Morris executive who asked you that question?

MR. DENOBLE: Yes, it was.

REP. WAXMAN: Will the gentleman yield, please?

REP. WYDEN: I'll be happy to yield.

REP. WAXMAN: Could you tell us who was at this meeting?

MR. DENOBLE: I've been wracking my brain and I can't. There is only one individual that I can remember who was there, and that was a lady named Carolyn Levy, Dr. Levy.

REP. WAXMAN: Were these top management people?

MR. DENOBLE: Yes, they were.

REP. WAXMAN: Thank you, Mr. Wyden.

REP. WYDEN: Would it be fair to say that the senior management people were troubled or worried about the work that you were doing?

MR. DENOBLE: From that meeting, I didn't think so. In fact, on the way back in the plane, we all thought things went very, very well. However, subsequently, after that meeting, we were told that our laboratory might be shut down, but they wanted to continue the research, and the possibility was that we would set up a laboratory in Lusanne, Switzerland, to continue the research.

REP. WYDEN: Let me ask you about -- specifically about a matter a couple of weeks after the meeting. Were you told a couple of weeks after the meeting, by several of the Philip Morris management, that your lab was generating information that the company did not want generated inside the company?

MR. DENOBLE: That is correct. Apparently, at the time, some litigation had come out, some law suits, and we were told that the data we were generating, the types of studies that we were doing would not be favorable in that litigation.

REP. WYDEN: Were you told them that the top management was looking at a couple of specific options -- one of them was releasing you and your associate from employment and possibly trying to look at some other arrangement?

MR. DENOBLE: Yes, it was -- two options were discussed. One was to release us from employment, but employ us as contract individuals somewhere in Richmond or somewhere close to the research center -- because the scientists at Philip Morris down in Richmond felt the research should continue. Then there was the idea -- the discussion that that really doesn't remove it from the company as much as they would like it, so they talked about sending us to Luasanne,

Switzerland at a contract facility.

REP. WAXMAN: Will the gentleman yield?

REP. WYDEN: I'd be happy to yield.

REP. WAXMAN: Let me get you on the record, who was telling you these things?

MR. DENOBLE: Dr. Jim Charles and Dr. Tom Osdine (sp).

REP. WAXMAN: They were with you at Philip Morris in Richmond?

MR. DENOBLE: Yes. Dr. Charles was our immediate supervisor. He was the manager of the biochemistry group. Dr. Osdine (sp) was the research director and reported to the vice president.

REP. WAXMAN: And both those options were to have you out -- do the work, but not in-house? Did they --

MR. DENOBLE: That is correct.

REP. WAXMAN: Did they give you a reason?

MR. DENOBLE: They just said that if the work were removed from the company connecting it back to the company would be, you know, more difficult to do than if it's being done right in the company itself.

REP. WAXMAN: That's what we call deniability -- although, I guess that's a --

MR. DENOBLE: I'm sorry, sir. I don't know.

REP. WAXMAN: Yes.

Mr. Wyden?

REP. WYDEN: Dr. Mele, can you confirm that these discussions took place?

MR. MELE: Yes. They did.

REP. WYDEN: All right. Let's turn, if we could now, to August of '83. The company was involved in the Chipolone (ph) case, sued,

one of the claims, of course, was that cigarettes were dangerous because they were addictive. Now, to begin with the self-administration paper that you submitted to pharmacology, I understand that in August of '83, about the time of the lawsuit, this paper was accepted for publication, but at essentially that time you were told that you could not publish it?

MR. DENOBLE: That is correct. I was told to withdraw it.

REP. WYDEN: And, let us now make sure we understand the status of that paper, because, you know, to me, this is one of the kinds of key concerns I have because right at a time when the public -- the company has some exposure and there is independence science generated within the company, the company is still trying to push it aside, and I'm curious about the status of the paper. At that time, has the paper gone through peer review at this particular journal?

MR. DENOBLE: Yes, it had been reviewed by Dr. Barry and two anonymous reviewers.

REP. WYDEN: So, it had been officially accepted for publication?

MR. DENOBLE: Yes.

REP. WYDEN: And were you told by management that you would have to withdraw it?

MR. DENOBLE: Yes, I was.

REP. WYDEN: Did management say that it could help plaintiffs in litigation if it was published?

MR. DENOBLE: I don't believe they said that, but they did say that if it were -- actually, they said that, "If it were published, it wouldn't be good for litigation.

REP. WYDEN: And you protested at that time?

MR. DENOBLE: Yes, we both did, very much so.

REP. WYDEN: You said that, in effect, you were a scientist and you had an obligation to let science go forward unfettered and it would be embarrassing to retract a paper after acceptance?

MR. DENOBLE: I would love to say I said it that way, but basically --

REP. WYDEN: Don't let me characterize.

MR. DENOBLE: -- protested --

REP. WYDEN: You say it.

MR. DENOBLE: I basically protested and felt that the paper was released, it had been approved, it should have been published, that there was no doubt about that. We protested both to our immediate manager, Jim Charles, and also to the director of research, Dr. Osdine (sp).

REP. WYDEN: And you wrote in August of 1983 to the journal withdrawing publication? You said you were withdrawing the manuscript due to factors beyond your control?

MR. DENOBLE: That is correct.

REP. WYDEN: All right.

Mr. Chairman, I would like that letter introduced into the record as Exhibit 12, and note that my time has expired, and yield back.

REP. WAXMAN: Without objection, it will be in the record as Exhibit 12. Does the gentleman want additional time?

REP. WYDEN: Yes. If that'd be acceptable, maybe a couple more questions at this point would be helpful, Mr. Chairman.

Now, Dr. DeNoble, you were scheduled to go to California to present your work before the American Psychological Association. This was supposed to be a process, a program, a poster presentation. What is that and what happened to your presentation?

MR. DENOBLE: Well, a poster presentation is very much like the posters you have over here. You would take an introduction of what the experiment was, a title, you put all your results up, and you put your conclusions up. And it's basically a three hour poster session in which you stand by the presentation for at least an hour -- a minimum of an hour, and discuss your research with other scientists who were at the meeting.

REP. WYDEN: Were you told by the top management at Philip Morris that you couldn't make a poster presentation?

MR. DENOBLE: Yes, we were. I was --

REP. WYDEN: And did they tell you why you couldn't make a poster presentation?

MR. DENOBLE: It had to do with the facts that this would not look good in current litigation.

REP. WYDEN: Okay. At that time, did you get a visit from a small battalion of lawyers from Philip Morris over at your lab?

MR. DENOBLE: Well, a couple of them came. Yes, we did get visited by several attorneys.

REP. WYDEN: Okay. Three or four, or how many?

MR. DENOBLE: Give me a second, please? There were at least three attorneys.

REP. WAXMAN: Okay. And they basically set up shop next to your lab and brought their Xerox machine and started rummaging around your documents and files?

MR. DENOBLE: They did go through my files. They went through Paul's files as well. They took documents and placed them in red folders. These red folders were then documents that they would photocopy. They did not remove anything from the lab, they just photocopied everything they thought was important.

REP. WAXMAN: Will the gentleman yield to me?

For the record, do you recall the names of any of those attorneys?

MR. DENOBLE: Yes, there was Fred Newman (sp), and I believe he was a corporate attorney from New York, Rhonda Fosset (sp), who was from an agency called Chicardi (sp) and Bacon (sp) in Kansas City, and her two supervisors -- and I do not remember their names.

REP. WAXMAN: She was from a law firm that --

MR. DENOBLE: She was from a law firm in Kansas City.

REP. WAXMAN: And two of her supervisors from the law firm?

MR. DENOBLE: Yes.

REP. WAXMAN: Okay.

REP. WYDEN: Let me, if I could, possibly understate this, Dr. DeNoble -- isn't it a little bit unusual to have a paper like this, after it has been peer reviewed, accepted for a journal, suppressed, a poster presentation canceled, and then to have a visit by three or four lawyers? Isn't that a little bit unusual?

MR. DENOBLE: Yes, sir. It is.

REP. WYDEN: Mr. Chairman, thank you.

REP. WAXMAN: Thank you, Mr. Wyden.

I want to recognize my self for another round of questions.

Let me just see if I understand the chronology here. You went to work in 1980. You were doing work in '80, '82. By June of 1983, you went to New York and you met with some of the top executives of Philip Morris. You're telling them what you were doing in your lab work. That was June '83. In August, you wanted to publish your paper. You were told when you were hired, you could publish paper, and now you were being told you couldn't publish this paper or make a presentation to the American Psychological Association. That August '83 is a significant time as well, because in August 1, 1983, the Chipolone (ph) case was filed. The Chipolone (ph) case was a case of going against Philip Morris for liability for a death resulting from cigarette smoking.

Now, you -- Mr. Wyden indicated -- started to get more concern expressed by people at Philip Morris. People were suggesting -- your supervisors were suggesting perhaps you ought to go outside of Philip Morris and do your work. Go to Switzerland and do an independent lab from where you were, and then you next had visitors from these lawyers that came by, and they were looking very carefully at your work.

I'd like to jump ahead two months to November of 1983. Your

laboratory had a visit from Shep Pollock (sp). According to Moody's (sp) Industrial Manual from 1983, Shep Pollock (sp) was an important person at Philip Morris. In fact, he was the president and chief operating officer of Philip Morris USA. He was also on the board of directors of the parent company, Philip Morris, Incorporated.

Who was -- who visited the laboratory with Mr. Pollock (sp)?

MR. DENOBLE: He was accompanied by Mr. Fed Newman, the attorney I mentioned previously.

REP. WAXMAN: And --

MR. DENOBLE: Also by -- I'm sorry -- also by Jim Charles, I believe, or Dr. Osdine (sp), but they didn't tour the lab, just Mr. Newman and Mr. Pollock.

REP. WAXMAN: And what happened at that meeting?

MR. DENOBLE: We toured the laboratory facility. We set up a demonstration for Mr. Pollock (sp), that he would actually see the animals working for food or -- and pressing the lever for nicotine.

REP. WAXMAN: You had a demonstration of the rat actually self-administering?

MR. DENOBLE: Yes. It was easy to do. The lab was situated such that if we stood in the operating room, we could see the self-administration room, and those doors could be left open, and we could also sit and look into the experimental room where the animals worked for food, and those doors -- we had to train animals to actually work -- (inaudible).

REP. WAXMAN: Just so we can understand this, I think we have a photograph of what that cage looked like. That was, without objection, Exhibit 8, earlier referred to but not shown to the committee.

So what happened?

MR. DENOBLE: That's a single experimental chamber in our self-administration room. As I indicated, there's a little lever or switch, and you can see levers in the boxes. The animal has access to water and food. There is a pump on top of the box, and there is a

solution of -- behind it probably of either nicotine or acid-aldehyde. The animals hooked up to the tether that hangs down in the box and can press the lever to deliver the solution into its vein.

REP. WAXMAN: So, you're there with the president of Philip Morris showing his how these rats self-administer nicotine

MR. DENOBLE: That is --

REP. WAXMAN: -- in their brain?

MR. DENOBLE: In their heart.

REP. WAXMAN: This is in their heart?

MR. DENOBLE: Yes.

REP. WAXMAN: And that this is a reinforcing agent? I assume you went through all of that?

MR. DENOBLE: (Inaudible) -- yes. The interesting thing was, I mean, the question brought out, of course, was, you know, is this addiction. And what --

REP. WAXMAN: Who asked that question?

MR. DENOBLE: Mr. Pollock (sp). And I went into my routine. It's not addiction. It's a reinforcing agent. And it predicts abuse liability. So, it was an opportunity to do some educating.

REP. WAXMAN: And what did Mr. Pollock (sp) say about that?

MR. DENOBLE: Oh, he accepted the answer. We chatted about that, and we moved forward.

REP. WAXMAN: Yes. What about Fred Newman -- he was the lawyer? Did he ask any questions?

MR. DENOBLE: Mr. Newman asked if this test procedure was the same test procedure that a government agency would use to demonstrate addiction. After I corrected him about addiction, I did say it's the exact procedure that NIDA would use to demonstrate abuse liability, yes.

REP. WAXMAN: And NIDA is?

MR. DENOBLE: The National Institute of Drug Abuse.

REP. WAXMAN: Okay. And what was his reaction to that?

MR. DENOBLE: He was not very happy with that reaction. He basically shook his head and walked off.

REP. WAXMAN: Dr. Mele, can you confirm these -- this report of this meeting with Shep Pollock (sp), the president of Philip Morris, in visiting the lab in November of 1983?

MR. MELE: Yes, he did visit. He toured the lab. And he did ask the question about addiction, and it was responded just as Dr. DeNoble says.

REP. WAXMAN: Well, let me make an observation about the significance of what you're telling us, because, to this day, Philip Morris has maintained that nicotine is not addictive and it is in cigarettes only for its taste, yet it is now clear that, 10 years ago, the president of Philip Morris, the president of the company visited your lab and actually witnessed a rat injecting himself with nicotine. This rat was not doing that because of the taste of nicotine, and the rat wasn't pressing the lever to get more nicotine because of peer review -- the rat was pressing this lever in order to self-administer nicotine because this was something that rat physiologically wanted. And he was told by you that nicotine is a reinforcing drug that has an abuse liability. Is that a correct statement?

MR. DENOBLE: That is a correct statement.

REP. WAXMAN: What was the immediate result of the visit by Shep Pollock (sp)? Were you told to continue your research?

MR. DENOBLE: Actually, yes. Two weeks later, we were given the green light to just go ahead. We -- actually, I think we actually hired another person and a contract person. We were told that everything was fine and just to run full force -- and we did. So, we just kept doing experiments.

REP. WAXMAN: This was the end of the year, beginning of 1984. In April of 1984, Philip Morris made a decision to close down the laboratory. Could you please recount for us the closing of the lab?

MR. DENOBLE: I believe it was the second Thursday? It was April 5th, the first Thursday in 1984. It was at 3:00 in the afternoon and Dr. Charles, Jim, called me to his office and was telling me what a great job we had done for the company. Quite frankly, I thought this was great and we were getting a lot of accolades. I was getting a lot of accolades, and Paul. And he said, "But, however, we are discontinuing animal research beginning now." I was told that Paul had to come up and talk him, and I was told to basically shut the equipment off, terminate the experiment -- even if they were ongoing, and to kill all the animals the following day, and that was the end/

We were -- our badges were discontinued access to the research center. I believe, the following Monday, we couldn't get back in. We were provided offices. We were provided secretarial support. We were provided funds to look for other jobs. Quite frankly, the company was very gracious to us during that time. But the lab was literally shut down in --

REP. WAXMAN: When you were told they were shutting down your lab, what was your reaction? What did you say to them?

MR. DENOBLE: Why? I mean, you know, why? You know, all of a sudden everything is going down the tubes, and the response that I immediately got was, "It was a business decision." I mean, that's the only thing they said to us during the first couple of weeks we were shut down.

REP. WAXMAN: Did you ask for at least a short period of time to complete some of the work that was ongoing?

MR. DENOBLE: To do anything -- I mean, just to complete manuscripts, we were not able to do that. We were unable to continue.

REP. WAXMAN: Is it accurate that you asked for at least another day to get some more data that --

MR. DENOBLE: We did. We were able to get that Friday to -- right. That's right. We went back the next day, on Friday, and we did kill all our rats, and at that point, the lab was over. It was ended.

REP. WAXMAN: Did you ever --

MR. MELE: May I add something here?

REP. WAXMAN: Yes, Dr. Mele.

MR. MELE: Just because we're -- I was going through this recently. We did -- that Friday was a critical day to end one study. I don't remember what the study was, but it was a final manipulation of a long series of manipulation, and we did ask for permission to at least finish that study, and that was denied.

REP. WAXMAN: What do you mean "manipulations?"

MR. MELE: Oh, it was a chronic dosing study, and this was the day where the animals would have been tested to see how they responded. I don't remember again the details of the study, but we did try and get that one final data point, and they didn't even want us to continue that much. It wasn't of much interest to the company, it was of interest to us.

REP. WAXMAN: Did you ever go back to the labs?

MR. DENOBLE: I had the occasion to go back to the lab a few days later, the following week, because I had the combination to a safe where we kept some controlled substances, yes.

REP. WAXMAN: And what did you find?

MR. DENOBLE: The lab was gone, everything was gone. The equipment was gone, the cages were gone, the animals were gone, all the data was gone. It was empty rooms.

REP. WAXMAN: Was it as if there had never been a lab there before?

MR. DENOBLE: Well, you would probably think there was, but there was no evidence there was any behavioral lab there. The only thing that was there was the safe. Everything was just gone.

REP. WAXMAN: Mr. Bliley.

REP. BLILEY: Dr. DeNoble, if you could clarify one point for me. Something you said earlier about lawyers from Philip Morris being in your lab in 1983. Isn't it correct that they were in your lab to collect documents to be placed, produced in a law suit, perhaps the

Tripelon (sp) case?

MR. DENOBLE: I believe that's correct, yes.

REP. BLILEY: Mr. Chairman, could we keep the record open so that we could submit some questions in writing to these two gentlemen?

REP. WAXMAN: Without objection we will keep the record open and members of the subcommittee may have additional questions they will want you to respond to in writing for the record, and we would ask you to make those responses.

REP. BLILEY: Thank you, Mr. Chairman, I have no further questions.

REP. WAXMAN: Thank you, Mr. Bliley. Mr. Synar.

REP. SYNAR: Mr. Chairman. Doctor, let me move on to this issue of your termination of employment. After the lab closed, what clear options did Philip Morris give you?

MR. DENOBLE: There were three options that were offered to us. One was to stay with the company. The second was to receive a cash payout. And the third was to continue on the payroll until we located new positions elsewhere.

REP. SYNAR: And what option did you take?

MR. DENOBLE: Well, originally we took the option of staying with the company. We wanted -- we figured times were tough in the 1980s and jobs were very difficult to come by, so we said well, we'll stay with the company. And we were then informed that if we did do that that significant reductions in salary as well as position -- there was even discussion of well, you may in fact have to go sweep the floors somewhere if we stayed with the company. So it was clear that they didn't want us to be there. So the second option we both elected was to continue to be on salary until we located new positions.

REP. SYNAR: So what -- so ultimately what happened?

MR. DENOBLE: Ultimately we both found new jobs.

REP. SYNAR: Okay. And when you left Philip Morris were you free to talk about your work or were you covered by a secrecy agreement?

MR. DENOBLE: Well, I think we were still covered, we were still covered by that agreement, so we kept it pretty low profile at the time, at least we thought it was low profile. We were pretty upset about this so we didn't talk about it very freely.

REP. SYNAR: Well let's move this story on beyond that. It didn't end after you left Philip Morris. In 1985 and 1986 you both made various efforts to publish and present some of your work. I'm told, for instance -- and we have a letter and an article that you sent the journal in December of 1985 -- that letter I think is Exhibit 13 -- I ask unanimous consent that it be made part of the record.

REP. WAXMAN: Without objection.

REP. SYNAR: And the article is Exhibit 14. Now this article is a revised version of a self-administration paper that Philip Morris suppressed in '83. Now I understand that you sent that self-administration paper to the Journal in December of '85 without first getting a consent from Philip Morris. Some might say that this is a violation of your secrecy agreement. Did you take that risk?

MR. DENOBLE: Yes, I did.

REP. SYNAR: And why did you take that risk?

MR. DENOBLE: It's one thing for industry to hold back scientific information because they are involved in the development of a product. It's another thing to say we need to get the patents done. It's done all the time in the drug industry. Scientists aren't free to publish right of way. Usually you have to get the product out or you have to get a position in the marketplace. You know there are valid reasons to do that for market reasons. This had nothing to do with the product. This information wasn't going out simply because the company didn't like what it said. And that was unacceptable. In 1986 people still weren't close to doing this kind of research. They still hadn't picked up, so we took the risk.

REP. SYNAR: Now I understand that in April of '86 you and Dr. Mele went to St. Louis to present a paper on tolerance to nicotine before the Federation of American Societies for Experimental Biology. What was the response by Philip Morris to that?

MR. DENOBLE: They sent us a letter indicating that that was a

violation of our agreement and that they would not tolerate that kind of conduct in the future.

REP. SYNAR: I would like to enter into the record Exhibit 15 if I could, a copy of that letter. Dr. DeNoble, I understand that in August of '83 you and Dr. Mele spoke at a convention of the American Psychological Association in Washington, DC about another aspect of your work with Philip Morris. What was Philip Morris' response to that appearance?

MR. DENOBLE: Well, that was quite interesting because they actually had somebody out there taking pictures of us. They sent one of their people out to take a picture and they sent us another letter indicating that -- a little stronger this time -- that action would be taken against us. At that point, I called Mr. Tassig (ph) who was I think the Assistant General Counsel to discuss with him -- well actually, kind of to let him know that we had submitted two manuscripts for review and one was going to be published and the other one was accepted and was going to be published. And that led to him telling me that if these articles were published that they would be suing us and it would be very long and costly.

REP. SYNAR: So that was the action to be taken, they were going to sue you?

MR. DENOBLE: That is correct. They also indicated that if they could they would try to bring an injunction against the Journal to prevent publication of the self-administration paper. But that did not occur because I was able to pull it out.

REP. SYNAR: Now I have -- now was this in writing?

MR. DENOBLE: No, sir, it was not, it was a phone conversation.

REP. SYNAR: Okay. Now I have a copy of that letter sent to you and Dr. Mele dated September 10th -- Exhibit 16. I would ask unanimous consent that it be made part of the record.

REP. WAXMAN: Without objection.

REP. SYNAR: Now, doctor, in this letter that you have before you Philip Morris says, and I quote, "The company cannot tolerate this kind of conduct. Any further breach of your agreement will result in action being taken." And that was signed by Eric Tassig (ph) the

Assistant General Counsel for Phillip Morris. So what happened next was that he called you and then --

MR. DENOBLE: No, sir, I called him to let him -- because when I got this letter we had already sent out two more publications. I called him to let him know that they had gone out.

REP. SYNAR: And you got a harsh lecture based upon that conversation?

MR. DENOBLE: Yes, sir.

REP. SYNAR: Did you contact, based upon that conversation, the psycho-pharmacological magazine just to see what you could do?

MR. DENOBLE: Yes, I called Herb Barry up and asked him what the status of the two papers were. The first paper, which was a brain-sight (ph) paper had already gone to press. It was out, there was nothing we could do. The self-administration paper, I believe your Exhibit 14, was in press, but it had not gone to proof. so we were able to again -- the second time in three years, unfortunately -- tell Herb that we had to pull the paper back.

REP. SYNAR: All right, I have a copy of the letter that you sent the Journal editor, Herbert Barry, it's Exhibit 17. I would ask unanimous consent that it be made part of the record.

REP. WAXMAN: Without objection.

REP. SYNAR: Now this was a letter from Barry to you and I want to quote from it. "I share the distress you expressed in your phone conversation of the 18th of September that the Philip Morris Company has issued a conjunction against the publication of this paper." And, Dr. DeNoble, you've worked for other companies since Philip Morris, how do you compare these types of actions which we've just gone through, and their efforts to keep your work confidential, with other companies you've worked with?

MR. DENOBLE: Before I answer that let me just say this. There is an error in the letter. The company never issued an injunction, they just told me they would if I couldn't get it out. So that's an error.

I have never had this happen to me. I've never heard of it

happening to any other scientist that I've ever talked to. This is very, very unusual. Paul -- I don't know if Paul has --

I don't know of anyone else who has tested the water and gone against an agreement like this like we signed. I mean it was clearly --

REP. SYNAR : Let's talk about that agreement because you obviously have a confidentiality agreement that lasts 10 years. You haven't been free to talk publicly about your work. There's got to be other researchers in that same situation. How do these agreements work at a practice? Are they in effect a complete bar to getting information to the very people that the information is supposed to serve?

MR. DENOBLE: I've never had an agreement with anybody else like this; this is the only agreement I've ever had.

REP. SYNAR: So this is unique to the tobacco industry?

MR. DENOBLE: No, sir, it is not -- industry has agreements that you will not divulge proprietary information, that you will not take data with you when you leave, every company has. This agreement was probably similar to those agreements, but it was being enforced in quite a different way. This was used to prevent us from publishing information that did not relate to a product, did not relate to a market issue. It didn't relate to anything like that, it was just science. What we found wasn't liked.

REP. SYNAR: Let me move on to another question if I could, the issue of tolerance. Instead of moving on to that area, let me conclude with just this general question, Dr. DeNoble, if I could. You are presently employed where?

MR. DENOBLE: I work with the Department of Mental Retardation with the state of Delaware, servicing folks who have -- citizens who are mentally retarded.

REP. SYNAR: And Dr. Mele, you are where?

MR. DENOBLE: I work with the Defense Department.

REP. SYNAR: Okay. What has this told you about the tobacco industry, this experience, over the years that you've had to deal

with. What does it tell you about the character and the trust worthiness of this industry? More importantly, what did you feel like on April 14, 1994 as you watched, as the rest of America did, the testimony of the seven chief executives of this country, on the issue of whether or not one, tobacco was deadly and secondly, that it is not addictive. What did you feel like at that moment when you saw that?

MR. DENOBLE: That's a very difficult question to answer. You know when I first agreed to appear before this committee, I promised that I probably would not go out and make public policy. It is difficult to watch those hearings and to feel good about what happened to us. I would very much like to stick with the issues surrounding the laboratory and very much like to stick to the issues in the data, and would very much not like to personalize this. That's the best answer I can give you sir.

REP. SYNAR: Dr. Mele.

MR. MELE: It just brought back to me the amount of data and type of data that we had collected and that was going nowhere. And in a very limited sense, that data should be out. I don't know about broader public policy issues, but we put a lot of effort into collecting that data, they asked us to collect it. They suppressed it, it remains suppressed right now. It may be of use to the world, it may not. That should be put out and let the scientific community judge.

REP. SYNAR: Thank you both.

REP. WAXMAN: Mr. Synar, if you could just yield to me, not only did they suppress the data, but due to these agreements, they with you as researchers, and I assume they had this with all their researchers, they have been able to keep people who work for them from coming forward to talk about what they know and what they've done, even as employees of the tobacco industry. I want to tell you that I think you've come to us in good conscience, concern and with a great deal of courage, to make this presentation. And I hope others will be coming forward as well.

REP. : Mr. --

REP. WYDEN: Mr. Chairman, thank you. I am going to go back to the laboratory in just a second, Dr. DeNoble. But, Mr. Chairman, I would like to enter into the record at this point the Wall Street

Journal article, February 11th, 1993. And what this article really does is make it very clear that what Dr. DeNoble and his associate are talking about is not some kind of isolated case. What you are describing, according to the Wall Street Journal, not exactly an organ of anti-business kind of thinking, has gone on on a number of occasions.

So I am going to take you back to the laboratory, Dr. DeNoble, and I understand that you would be more comfortable there. But I think that the American people need to know that publications like the Wall Street Journal are outlining some specifics, the kinds of things that you've described very clearly today.

REP. WAXMAN: If you would yield --

REP. WYDEN: I would be happy to yield, Mr. Chairman.

REP. WAXMAN: I commend it people to read it. But as that article indicated a multi-decade period effort by the tobacco industry to sponsor research and then to suppress research, to make sure that what they knew didn't get out, so they would always have that deniability. And not only deniability, they use their research findings to try to make things look as if they were still open questions rather than concluded scientific issues. So I thank you gentlemen, again, for raising that article and I think it's appropriate to have in the record.

REP. WYDEN: Dr. DeNoble, Dr. Mele, let's talk about this matter of tolerance for nicotine. My sense is you all understand the science better than we do, of course. Does the tolerance imply that an animal or a human being gets a diminished effect with repeated doses of the drug, and it's one of the indicators of a potential abuse liability or its addiction.

Now, Dr. Mele, I guess maybe we'll start with you on this. Did your work find that rats developed a tolerance to nicotine?

MR. MELE: Yes, we did.

REP. WYDEN: Now, we've got a manuscript that you wrote with Dr. DeNoble entitled "Development of Behavioral Tolerance Following Chronic Nicotine Administration." Mr. Chairman, I would ask that this be entered into the record, as well.

REP. WAXMAN: Without objection, that'll be ordered.

REP. WYDEN: Now, you've indicated that your work shows that rats did develop a tolerance to nicotine. We've indicated that this is one of the warning signals of potential abuse, liability, or addiction. I'm curious -- my understanding is that you submitted this particular manuscript that I've cited to the management of Philip Morris. You were seeking approval to publish the results. When you asked them for approval to publish those results, results that to me seem important for the public, were you denied the right to publish them?

MR. MELE: Yes.

Let me just say two things about that work first. We were certainly not the first to demonstrate nicotine tolerance. That's been shown for a long time. This study identified certain behavioral parameters that contribute to nicotine tolerance. So after conducting this study and asking to get it out and submitting it, we thought it was a relatively benign study, because although tolerance is a characteristic of many drugs of abuse, it is not necessarily a predictor of abuse, but it is a characteristic of many compounds. So we thought it was relatively benign.

The companies thought it very threatening, because the word "tolerance" was appearing at that time in the diagnostic and statistical manual of the American Psychiatric Association as a criterion or an indicator of drug dependence. By using that criterion, they felt that this work was too dangerous and, one, would not let it go out and, two, did not want further tolerance work to continue.

REP. WYDEN: So in effect what you're saying is because you were showing that -- these studies were showing a tolerance for nicotine, this would establish a drug dependence and this was, again, defined by a major health group, the American Psychiatric Association -- this would be damaging to them.

MR. MELE: Well, let me clarify. I think Philip Morris's assessment of the work was wrong. I don't think tolerance, again, identifies necessarily dependence-producing agents. It is a characteristic of many of those, but it is not a single identifying characteristic. But they misidentify it in the DSM manual and (in behavior judgment ?)

REP. WYDEN: In addition to saying that you couldn't publish the tolerance paper, did the management there take other steps to curtail your research into tolerance?

MR. MELE: Well, they preferred that tolerance work did not continue.

REP. WYDEN: So you were --

REP. WAXMAN: If the gentleman would yield, if I might just get names, if we could, for the record. Who were these people --

MR. MELE: Dr. Jim Charles was the one who came to my office with the manuscript review request and asked me to write an internal document but that it could not go out because it demonstrated tolerance and, in his mind or somebody's mind, it indicated a dependence-producing situation.

REP. WYDEN: In terms of what happened after they said you couldn't publish the paper, did you communicate to the management, Mr. Charles specifically, that you wanted to examine whether rats can develop tolerance that would cause them to suffer physical withdrawal symptoms and then the management said, "You are not allowed to do this work"?

MR. MELE: Not specifically in that way. Our plan was with these data to pursue the role of tolerance in other aspects of nicotine use --

REP. WYDEN: All right.

MR. MELE: -- to see how tolerance would influence health administration, to see how tolerance would influence physical dependence. We weren't able to pursue those studies as a result of this study.

REP. WYDEN: But the management said that you could not pursue that additional work.

MR. MELE: I don't recall specifically talking to them about those specific studies, but just tolerance in general was not sometime they wanted pursued.

REP. WYDEN: All right. Dr. Mele, do you know Kathy Ellis (ph),

Dr. Kathy Ellis?

MR. MELE: Yes.

REP. WYDEN: Now, Dr. Ellis testified about the tolerance issue at the hearing on April 14, when she appeared with the CEO of Philip Morris, Mr. Campbell. Let me read you what she said to our subcommittee then. She said, and I quote, "The strict pharmacological definition of addiction involves three different criteria. They are intoxication, physical dependence, and tolerance, and to my knowledge, there is no evidence that nicotine or cigarette smoking plays in any of these definitions."

So it seems to me what Dr. Ellis did was, in effect, deny the very work that you did at Philip Morris.

(Whispering off mike)

MR. MELE: I don't know what access she had back then to our work. I would assume currently, in her current position, she would have been aware of it. So, yes, she was not recognizing that nor recognizing a large body of literature on nicotine tolerance.

REP. WYDEN: And she was a colleague of yours at the Richmond research center, isn't that correct?

MR. MELE: Correct.

REP. WYDEN: Mr. Chairman, again, I think what we have here is another example of a serious misstatement by the Philip Morris Company. Now, contrary to the findings of Dr. Mele's report, Dr. Mele, of course, has indicated that he was a colleague of Dr. Ellis's at the Richmond research center. What Dr. Ellis said to the subcommittee is that Philip Morris has no evidence that nicotine causes tolerance, so I would hope that before too long, we ask for further information on this matter, because it appears to me to be yet another serious misstatement by the Philip Morris Company.

MR. MELE (?): Congressman, I would just like to add and clarify that. Kathy Ellis (ph) did not work in our laboratory. She had her own laboratory, but we were part of the same division.

REP. WYDEN: Mr. Chairman, I yield back.

REP. WAXMAN: Would you have had -- would she have had access to your work?

MR. MELE: In the beginning, I don't know. I don't think so, because it was kept very secret, although at one point, once we were allowed to present our data to the division and to the rest of the research center, she would have been familiar.

REP. WAXMAN: Thank you.

REP. WYDEN: Mr. Chairman, I yield back.

REP. WAXMAN: Thank you, Mr. Wyden. Mr. Kreidler.

REP. KREIDLER: Thank you, Mr. Chairman.

You have said that the purpose of the analog program was to develop a nicotine analog that had the brain effects of -- that had the brain effects of nicotine but not the heart effects, if I recall correctly. Was the initial idea, as far as you understand, to develop a safer cigarette?

MR. DENOBLE: That's correct, yes, sir.

REP. KREIDLER: Mm-hmm (acknowledgement). Where were the analogs developed.

MR. DENOBLE: They were synthesized at the Richmond Center organic laboratory.

REP. KREIDLER: And do you know which clinical group -- who headed that clinical group?

MR. DENOBLE: Dr. Jeff Seaman (ph) headed the group. Chuck Shaverian (ph) was also another chemist in the group.

REP. KREIDLER: They were at Philip Morris then?

MR. DENOBLE: Sir, they were back in 1984. I don't know whether they are now.

REP. KREIDLER: Okay.

It is my understanding that part of the analog testing was done

in Rochester and part in Richmond. Can you tell us what the relationship between the work in Rochester and the work in Richmond was?

MR. DENOBLE: Yes, the analogs would be synthesized in Richmond, Virginia, and they would first be sent to Rochester, Dr. Leo Bood's (ph) laboratory. What Leo would do would be screen the analogs in a receptor binding assay to see whether the analog recognized the nicotinic receptor in, you know, in the brain. He was using torpedipus (ph) membranes, but it's the same thing.

At that point, we would determine whether or not it had the -- whether the receptor said, "Gee, you look like nicotine."

REP. KREIDLER: Mm-hmm (acknowledgement).

MR. DENOBLE: We would then get some data on whether or not it produced contractions of guinea pig ileum, which would be a predictor of cardiac activity. At that point, that data would be sent back down to us in our laboratory, and we would screen the compound -- if it was good data, if it met the criteria of good data, we would screen the compound in our tests in animal behavior to determine whether it looked like nicotine.

REP. KREIDLER: Mm-hmm (acknowledgement). So it was at least the tobacco version of nicotine that was causing the cardiovascular type of reaction, then, as far as you could determine?

MR. DENOBLE: I'm not sure I understand --

REP. KREIDLER: The cardiovascular responses of nicotine were associated with the tobacco form and there were perhaps some other forms of nicotine --

MR. DENOBLE: There's a couple of different forms of nicotine, but the depressor effect you get is with the inhaled form of nicotine, yes.

REP. KREIDLER: I see.

I would like to distribute Exhibit 18-A, which was part of the 1980 memorandum explaining the work of nicotine receptor programming in Rochester, Mr. Chairman, if that's all right.

REP. WAXMAN: Without objection, that will be submitted for the record and identified as the next exhibit in sequential number.

REP. KREIDLER: I find the first sentence of the memo particularly interesting. It states, "Nicotine is a powerful pharmacological agent with multiple sites of action and may be the most important component in cigarette smoke." This certainly paints a different picture of nicotine than the picture painted by the tobacco company executives two weeks ago. Do you have a response to that?

MR. DENOBLE: That statement was a misstatement, that it is a powerful pharmacological agent. It justified much of the research at the research center. I mean, the whole thrust of research of this program was work on nicotine not as a flavorant, but as a pharmacological agent.

It was our belief back then and my belief today that nicotine is an agent in cigarette smoke that is reinforcing and it is a contributor to why people smoke. That was the premise of our whole program.

REP. KREIDLER: Mm-hmm (acknowledgement).

Now I would like to show exhibits 19, 20, and 21, which are the pictures of rats in the analog program.

REP. WAXMAN: Without objection, those photographs will be accepted for the record in next sequential order.

REP. KREIDLER: Doctor, would you please tell us what we're seeing in these pictures here?

MR. DENOBLE: The poster on the -- my right is a picture of an animal who has been anesthetized, and we are placing a cannula -- basically a needle -- into different areas of its brain.

The work that came out of Leo Bood's lab in Rochester indicated that if you placed nicotine directly in the brain, that the animal would have a particular behavioral response, and he went on to show, very elegantly, that that effect was only produced with nicotine-like drugs. So we went back to our lab, cannulated animals to see if we could replicate and extend his findings and use it as a tool.

The animal -- the center picture is an animal who is reaching up

to grab a pellet of food, and he's got a brain cannula. We injected five microliters of nicotine into his brain, and the animal -- it's the same animal (mutely two ?), and that last photograph you see, he's not responding to the food pellet. That was a syndrome called prostration syndrome. It was unique to nicotine. The animal becomes splayed, he becomes unresponsive for about 12 minutes. We went on to characterize that behaviorally, to show pharmacologically that it wasn't an effect of nicotine on brain receptors, and that was a primary screening tool in our laboratory in the nicotine analog program.

REP. KREIDLER: Did you succeed in developing a nicotine analog that would have the effects that nicotine has on the brain but does not have nicotine's effect on the heart?

MR. DENOBLE: We did identify a series of analogs that had -- that met our minimal criteria for that effect, yes.

REP. KREIDLER: Did Philip Morris ever use the analogs, to the best of your knowledge?

MR. DENOBLE: No, sir, I have no knowledge of that.

REP. KREIDLER: Do you know why not?

MR. DENOBLE: No. We had several discussions about, you know, what we would do with it when we found it, and once we found it, nothing was done with it. The indications were to us is that we'll take a wait-and-see attitude.

Quite honestly, I think that scientifically that was an interesting finding. It could be conceived of as a major breakthrough in my mind --

REP. KREIDLER: Mm-hmm (acknowledgement).

MR. DENOBLE: -- to disassociate brain effects from peripheral effects --

REP. KREIDLER: Mm-hmm (acknowledgement).

MR. DENOBLE: -- but they never chose to follow that through the next logical scientific conclusions.

REP. KREIDLER: Mm-hmm (acknowledgement).

Do you have any suspicions that it might be that that level of research might be something they couldn't keep control of at some point in the future that might have maybe influenced whether they wanted to follow up on these nicotines?

MR. DENOBLE: No, I don't believe that. I think that the research facility was quite capable of following up on those nicotines --

REP. KREIDLER: Mm-hmm (acknowledgement).

MR. DENOBLE: -- and doing a lot more work, and, quite frankly, sir, it may have been done.

REP. KREIDLER: Mm-hmm (acknowledgement).

MR. DENOBLE: I am just not aware of it.

REP. KREIDLER: I see. Sure.

Smoking causes over 150,000 deaths each year from heart disease. Your work at Philip Morris shows that there might be a replacement for nicotine in cigarettes that would duplicate the brain's effects of nicotine but would not have nicotine's effect on the heart, yet after you succeeded in developing an nicotine, Philip Morris's response was to put your discovery on the shelf.

Did you -- presuming that no follow-up was done, does that trouble you at all?

MR. DENOBLE: Well, sure. I mean, it troubles me a lot. I mean, to the best of my knowledge, it was put on the shelf. It may not have been put on the shelf.

Also, recognize that there's a large leap from our laboratory -- from, you know, Rochester data, from in-house data, and going into a product. I mean, this would have to go through -- this nicotine would have to go through many, many, many other tests, and I think it is, from a scientific point of view, it was disturbing that they didn't choose to do those other tests. At least, we have no knowledge that they did them themselves.

REP. WYDEN: Would the gentleman yield?

REP. KREIDLER: I yield.

REP. WYDEN: I thank my colleague. Let me just be real brief. Wouldn't it have been in the public interest right at that point to aggressively have pursued this new research? I mean, here we have a situation -- my colleague has basically said that the evidence looks to us like it was put on the shelf. A situation where smoking causes 150 [sic] deaths as a result from heart -- 150,000 deaths from heart disease. My colleague has pointed out that, you know, here's an opportunity to really do something to help people. Wouldn't it have been in the public interest to have aggressively done the research right at that point so you and other scientists would be able to tell us today what you know about it?

MR. DENOBLE: Yes, sir. Absolutely.

REP. WYDEN: I thank my colleague for yielding.

REP. WAXMAN: Will you also yield?

REP. KREIDLER: Certainly.

REP. WAXMAN: I thought one of the ideas of scientific inquiry is that you go as far as you can go and then other scientists can pick up where you left off, but if this information is never made public or never given to other scientists,, there's no way that some of these advances can be pursued, and I'm hoping that we can follow further this trail, because this is a new revelation that perhaps cigarettes maybe couldn't have been made healthy, but at least could have been made in a way that would have avoided the deaths from heart problems that came from the nicotine. Nicotine we've always heard about as an addictive substance, but now we're learning nicotine is a problem that affects the heart, as well.

Could you give us the name of the compound that might have been a successful nicotine?

MR. DENOBLE: I'm not a chemist, but I can give you -- it was called 2-prime-methyl-nicotine (ph).

REP. WAXMAN: Thank you very much.

Mr. Kreidler, do you want to pursue further questions?

REP. KREIDLER: I think my time has expired. Thank you very much, Mr. Chairman.

(Loud buzz)

REP. WAXMAN: Dr. DeNoble, did you look for other substances in tobacco or tobacco smoke that had effects on the brain?

MR. DENOBLE: Yes, we did. In late 1981 and early 1982, we raised the question of whether or not there could be other things in cigarette smoke that may have biological activity.

REP. WAXMAN: Mm-hmm (acknowledgement). And what did you look at?

MR. DENOBLE: What we did was we did a -- basically a computer search of the components that are identified in cigarette smoke and we looked through the list and we found a compound that stuck out in our mind was acetaldehyde (ph). This is a compound that is a -- it's a reasonably high concentration in cigarette smoke, it's a highly volatile compound, and it was really kind of serendipitous, because the work -- you really wouldn't think this was anything hot, but I had just come off of doing a post-doc where I'd recognized that aldehyde -- acetaldehyde (ph) is a major metabolyte of alcohol, and there were some theories in the '70s that this metabolyte would react in the brain with other chemicals to form other chemicals and that may be the basis for alcohol addiction. Well, that theory did not hold up, but what struck me was -- and it didn't hold up because your liver is making acetaldehyde (ph) and by the time it gets to the brain, it's all chewed up anyway.

But here you have a situation where aldehyde's (ph) going right into the lung, and there are only two ways -- three ways to get things into the brain quickly. One is you put it in the brain, the second fastest way is you put it in the lungs, and the third fastest way is you put it in the heart. So it struck us that this compound was getting into the brain, maybe it's doing something that has reinforcing --

REP. WAXMAN: And I want to show you a chart which I'd like to have entered into the record as Exhibit 22. It's made from a slide of you acetaldehyde (ph) work. Could you tell us what kind of tests you

did on acetaldehyde (ph) and what the graph represents?

MR. DENOBLE: This work was reasonably linked in the development of the acetaldehyde (ph) self-administration procedures. We demonstrated that acetaldehyde (ph), like nicotine, would maintain behavior and would be reinforcing in rats.

This particular slide looks at the interactions between acetaldehyde (ph) and nicotine. If you give a rat -- if you focus on the second bar, where it has 8.0 and below it there's a zero, that's eight micrograms of nicotine, and that will maintain about 100 injections per day. If you go down to the fourth bar, again, the zero and the eight, that's eight micrograms of acetaldehyde (ph). That maintains it looks like around 230, I guess, injections a day.

If you now put them together, as in the first, the third -- pardon me, the first, third, and the fifth bar, they interact, and the animal presses a lot more than it would have pressed for either one alone. This is a demonstration that nicotine and aldehyde (ph) combinations are more reinforcing than either of the drugs alone. They interact behaviorally.

REP. WAXMAN: Well, that's a significant finding, isn't it? It confirms that if you have cigarettes not just with the nicotine but the acetaldehyde (ph) that it's even more addictive than nicotine by itself and that it's reinforcement. Is that a correct --

MR. DENOBLE: Well, it leads to some interesting speculations about the role of nicotine and aldehyde (ph) in cigarette smoke. Importantly, very importantly, all the work that we did has been -- most, if not all of it -- has been replicated by other researchers around the world, even though we had not published it.

This work has never been replicated, so I think we have to look at this as really a scientific inquiry. But it does raise some fascinating possibilities.

REP. WAXMAN: Well, it means that even for animal tests, when looking at the addictive nature of nicotine, that the nicotine with acetaldehyde is even more a reinforced or more of an addicting substance. Is that -- the combination.

MR. DENOBLE: In this experiment, that is correct.

REP. WAXMAN: And Philip Morris, rather than encouraging this kind of finding to be made known to the world, what did they do?

MR. DENOBLE: This was a very high-priority project. We were not allowed to even discuss this outside of the research center. We were permitted to give talks on nicotine but never on acetaldehyde.

REP. WAXMAN: And this has never been published before.

MR. DENOBLE: No, sir, never been published.

REP. WAXMAN: I want to leave the area of the work that you did, the two of you, on nicotine and acetaldehyde. I want to ask you about the work of other scientists that you may have observed or known about at Philip Morris. I want to begin with the dangers of exposure to environmental tobacco smoke.

As you may know, the entire tobacco industry, including Philip Morris, maintains an exposure to environmental tobacco smoke is not a health risk. Dr. DeNoble, while you were at Philip Morris, was anyone conducting research on the effects of exposure to environmental tobacco smoke or also known as sidestream smoke?

MR. DENOBLE: Can you give me a moment, please, sir? May I take a moment?

REP. WAXMAN: Yes.

MR. DENOBLE: We are aware of a research project using a plant called trataskancha (ph). And the goal of that project was to look at the effects of sidestream smoke on the plant's ability to either reproduce or repair itself.

REP. WAXMAN: Do you know who was conducting that research project?

MR. DENOBLE: I don't know the specific name. It was under the control of Dr. Jim Charles in the biochemistry department, but I cannot remember the specific scientist's name.

REP. WAXMAN: Dr. Mele, do you have any information on that?

MR. MELE: It was, I believe, Dr. Teri Lu (ph) or Teri Wu (ph), a female researcher.

REP. WAXMAN: And what do either of you know about this research? What can you tell us about it?

MR. MELE: I remember one briefing of the biochemical research division where slides were presented of these plants in closed containers. The plants exposed to the sidestream smoke were seriously debilitated -- wilted, so forth. Plants exposed to -- it was either mainstream smoke or fresh air -- I believe there was a comparison between sidestream and mainstream -- were less debilitated, indicating the sidestream smoke was more toxic to these plants.

REP. WAXMAN: Toxic. Did it cause any genetic changes or did it simply kill the plant?

MR. MELE: Well, just the way they looked. Just visually they were wilted and falling over and that sort of thing.

REP. WAXMAN: And what happened to the work that you're describing? Did Philip Morris allow this important work to be published, or do you know whether it suppressed publication of that?

MR. MELE: My understanding is that work stopped. If they continued, we didn't know anything about it.

REP. WAXMAN: Well, this is -- let me ask you about other tests sponsored by Philip Morris on the effects of (painting?) components of tobacco smoke on the skin of mice. Tell us about that, whatever you know about it.

MR. MELE: I'm just aware that those studies were performed. Dr. Jim Charles worked with another scientist before I was there, I believe. Those studies were more or less commonly discussed in the cafeteria. I never saw any data or evidence of those studies, and I don't know what happened to those studies.

REP. WAXMAN: Dr. DeNoble, did you ever see a presentation on this research?

MR. DENOBLE: Yes, I did. The research was conducted at a contract laboratory facility outside of Philip Morris. The purpose of the study was to investigate the various components of smoke that had been liquefied on mice skin, mouse skin. It's a test for carcinogenic activity. I'm not a (teratologist?) and I can't interpret that data,

but I do remember seeing the slides and hearing the presentation.

REP. WAXMAN: And what did the mice look like?

MR. DENOBLE: A lot of the mice had fairly open lesions and wounds from a variety of substances placed on their skin, but I do not know what those substances were other than they were smoke components.

REP. WAXMAN: And would nitrosamines have been involved in that?

MR. DENOBLE: Nitrosamines? No, that was a different research project. That was Jim Charles's research project. They were looking at the effects of nitrosamines on the lung's ability to repair itself using a (chromotide?) exchange procedure in the lung. Again, that's out of my area of expertise. I attended some meetings and presentations, but I couldn't give you the --

REP. WAXMAN: And do you recall what the results were from these nitrosamine studies?

MR. DENOBLE: In general terms, that the lung's ability to repair itself was impaired after exposure to various nitromasines.

REP. WAXMAN: An issue that's received some attention recently is whether the FTC, the Federal Trade Commission, test method accurately measures the amount of nicotine consumed by smokers. At our March 25th hearing, Dr. Kessler said that this test method doesn't accurately measure actual consumption because the tobacco companies can manipulate the test. One example of manipulation he cited was putting ventilation holes in cigarettes which are then covered up by the smoker's lips or fingers. Did either of you observe any research conducted by Philip Morris on this issue?

MR. DENOBLE: There was some research that was done. And again, I'm a little vague on the specific results of the research. At the time there was a cigarette on the market that had either ventilation holes or tubes inserted -- not tubes; they were tube-like -- they were channels, channels inserted into the filter. And that would allow a smoking machine to smoke the cigarette without crushing the filter. Research at Philip Morris was done where they actually observed -- they filmed people smoking and they noticed that the people would actually crush these channels as they would put the cigarette to their mouth. Not everybody would do that, but it was evidenced in a fair number of smokers delivering a lot more of the smoke (phase?) to the

lung than would be delivered in the machine.

REP. WAXMAN: Do either of you recall the names of any of the researchers?

MR. DENOBLE: The name was Frank Ryan, Francis Ryan.

REP. WAXMAN: And what they determined was that some smokers did cover up the ventilation holes with their fingers or their lips, so that the FTC test, which didn't do that, might have had a different result than what was the actual consumption of the smoke (given?) the individual involved.

MR. DENOBLE: That was the general conclusion. That work was also under the control of Dr. Gil Dunn (ph).

REP. WAXMAN: Thank you. Mr. Bliley?

REP. BLILEY: Thank you, Mr. Chairman. The only thing I'd like to do -- we've heard a lot of conversation today about contracts. I have an employee agreement here by Abbott Laboratories, and I'd just like to get unanimous consent to insert it in the record and to read just a little bit of it.

REP. WAXMAN: Without objection, it'll be received for the record.

REP. BLILEY: And it goes on to say what the employees will do. In the second paragraph it says, "All memorandas, notes, records, reports, photographs, drawings, plans, papers or other documents made or compiled by or made available to employee during the course of employment with Abbott, and any companies or abstracts thereof, whether or not they contain confidential information, are and shall be the property of Abbott and shall be delivered to Abbott by employee immediately upon termination of employment with Abbott." So I just mention that to say that it's not uncommon to have contracts of confidentiality with employees.

Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Bliley. Mr. Wyden?

REP. WYDEN: One last point, Mr. Chairman. First, let me thank both of you, because I think this has been very, very helpful; ask you

one last question. As I have worked on Chairman Waxman's subcommittee over the years on this issue, we have continually heard that the tobacco industry's position is that smoking is essentially a matter of free choice. I think, you know, we have had some science that has raised questions about that. But certainly at a minimum, if it is a matter of free choice, people ought to be in a position to make an informed choice.

One of the things that has troubled me is it seems to me that if your studies had gotten out at the time that they were written, at a minimum, at a bare minimum, other scientists would have followed up on the research that you had done and then clearly the American people could have made a more informed choice about smoking. Would you agree with that, Dr. DeNoble?

MR. DENOBLE: Yes, I do agree with that. It was the reason that Paul and I took the risk in '86 to try to publish this material and present it. The scientific community had the right to look at this research and to confirm or disconfirm it, and they confirmed it, much of it, but years after it should have been confirmed.

REP. WYDEN: Thank you, Mr. Chairman.

REP. WAXMAN: Thank you, Mr. Wyden. We've referred to a number of exhibits during this hearing, and let me indicate that all of the exhibits were shared with the minority in advance of this hearing. And let me ask unanimous consent so we'll have it on the record that all those exhibits be made part of the record in the sequential numbering order that they've been referred to. And without objection, that will be the order.

Let me also indicate that Dr. DeNoble and Dr. Mele, you not only met with our staff, but you had a meeting with the minority staff as well prior to this hearing. Is that correct?

MR. DENOBLE: Yes, that's correct.

REP. WAXMAN: And that was a private meeting.

MR. DENOBLE: Yes, it was.

REP. WAXMAN: Well, I want to make an observation. And I thank you both for being here. I was taken aback two weeks ago when we had at this very table the seven chief executive officers of the major

tobacco companies in this nation. And they gave us blanket denials, absolute blanket denials, about a number of important issues.

We asked them if they knew whether cigarette smoking caused people harm, and they said they didn't know. But one thing they did know about and could tell us was that cigarette smoking was not addictive. And we went down the line, and each chief executive officer indicated that cigarette smoking was not addictive. They also told us at this hearing that environmental tobacco smoke was not dangerous, that advertising was not intended to influence kids. One of the witnesses even told us that he thought cigarette smoking was not addictive and if it was, it was no more of an addiction than eating Twinkies.

Well, I want to just indicate that that hearing, and compared to this hearing, there's a reason why Congress has got to be involved in the oversight of what is happening with tobacco in this country. We have heard from tobacco executives who I believe are more focused on corporate survival than on corporate responsibility.

Two of the three criteria for drug addiction was known to be present in cigarettes, in animal tests, as early as 1983, according to the two of you in your testimony today, which is under oath. And not only that; the president of Philip Morris was told this information. I think there's a code of corporate conduct which we expect every corporation in this country to follow, and that's not to come before the Congress and deny everything and accept no responsibility.

I expect this is not our last hearing on this subject. I think we need to get for the record a lot of responses to what you've had to say. That's not only the fair thing to do, but I think we've uncovered enough information for which I think we ought to get a response from these companies, and particularly Philip Morris because that's the one you've talked about, but others as well, as to how much they've known, what they knew and when they knew it, to quote a phrase that's recently been in the news again.

I thank you both for being here, and I want to recognize any other members who want to make any other comments. Mr. Bliley?

REP. BLILEY: (Inaudible) -- Mr. DeNoble, if you would. In your testimony, in response to my questions today, you did say that nicotine, as well as acetaldehyde, are reinforcing agents. But you also testified that nicotine is not addictive, I believe. Is that

right?

MR. DENOBLE: No, sir, that's not correct. What I said was that from an animal study, you can't infer addiction. I do think that there's a preponderance of evidence that has come about in the last 14 years to show that nicotine is an addictive substance in humans. Our data back in 1982, '83 and '84 suggested that from rat studies, but you cannot prove addiction in a rat. But you can say you need to look further.

REP. BLILEY: And that was the same thing for acetaldehyde?

MR. DENOBLE: That is correct.

REP. BLILEY: I see. Thank you very much.

MR. DENOBLE: Thank you.

REP. WAXMAN: Mr. Wyden, anything further?

REP. WYDEN: No, Mr. Chairman.

REP. WAXMAN: On that last point, you're saying you can't prove addiction in people by tests on animals. But you certainly can surmise that there's information there that ought to be pursued to determine whether, in fact, addiction is a reality.

MR. DENOBLE: Yes. It's a real strong indicator.

REP. WAXMAN: Let me indicate again the quote from Dr. Ellis, who testified before us, and she said that to her knowledge there is no evidence that nicotine or cigarette smoking -- that nicotine or cigarette smoking plays in any of these definitions. And she was referring to the -- let me read the whole quote. "The strict pharmacological definition of addiction involves three different criteria. They are intoxication, physical dependence and tolerance. And to my knowledge, there is no evidence that nicotine or cigarette smoking plays in any of these definitions." I think that goes beyond that very thin cutting of those words that are so carefully crafted to say something that I believe to be misleading. This is an absolutely untrue statement under anybody's interpretation of the words before us.

Thank you both very much for being here. I want to commend you

and thank you for your courage and willingness to come before us.

That completes this hearing and we stand adjourned.

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