UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, Plaintiff, v. PHILIP MORRIS USA INC., f/k/a PHILIP MORRIS INC., et al., Defendants.	)	Civil Action No. 99-CV-02496 (GK)

DIRECT TESTIMONY

OF

PAUL C. MELE, Ph.D.

Submitted Pursuant to Order #471

Q: Please state your name for the record.

A: Paul Camille Mele.

Q: Where do you reside?

A: Olney, Maryland.

Q: Were you served with a subpoena requiring your appearance here today?

A: Yes.

Q: What is your current occupation?

A: I am the Director of Technology Transfer in the Office of Research and Technology Applications at Fort Detrick.

Q: Please describe your educational background.

A: I received a Bachelor's of Science in Biology and Psychology from Union College in Schenectady, New York in 1971. I attended graduate school at Adelphi University in Long Island, New York, where I studied Experimental Psychology in the Behavioral Pharmacology subgroup. I received a master's degree and then graduated from Adelphi University with a Ph.D. in 1980.

Q: What does a course of study in Experimental Psychology and Behavioral Pharmacology entail?

A: That is a research degree where one studies behavior and effects on behavior. My specialty had to do with animal work. I was looking at the effects of drugs on the behavior of rats and trying to get an idea of how those drugs affected the brains of the rats as they altered the rats' behavior.

Q: What type of post-doctoral work did you do?

A: I had post-doctoral training at the University of Wisconsin in Behavioral Toxicology.

Q: What is Behavioral Toxicology?

A: I basically studied the effects of toxic agents and environmental contaminants on rats and monkeys. We examined both the behavior and the brain development and how they were altered by exposure to these environmental pollutants early in life.

Q: What did you do after your post-doctoral study?

A: I went to work for Philip Morris in Richmond, Virginia.

Q: At the time you became employed with Philip Morris, the company was known as Philip Morris Incorporated, correct?

A: Yes.

Q: How long did you work for Philip Morris?

A: I worked with Philip Morris from November 1981 until about December 1984.

Q: Briefly describe for the Court where you have been employed since leaving Philip Morris in 1984.

A: In February 1985, I began working for the Armed Forces Radiobiology Research Institute (AFRRI) in Bethesda, Maryland. This is a Department of Defense lab. I was a Research Psychologist in the Behavioral Sciences Department. In February 1995, I started with the Army Medical Research & Materiel Command at Walter Reed Army Medical Center. In 2000, I went to Fort Detrick, which is where the headquarters of the Command are located.

Q: Please give the Court a brief synopsis of the type of work you have done at each of these positions.

A: At AFRRI, I studied ionizing radiation and radio-protectant compounds, which are drugs to protect soldiers against the effects of radiation. I tested the compounds on animals – rats and monkeys. At Walter Reed and in my current position, I work with technology transfer. I

negotiate and plan research agreements and patent license agreements with partner organizations to develop products for the Army.

Q: Have you testified in previous litigation related to smoking and health?

A: Yes.

Q: **Please identify all prior cases in which you have provided testimony, either in deposition or at trial.**

A: I have testified in only one other case – the Engle case in Florida. I had my deposition taken and I testified at the trial.

Q: Did you testify as an expert in the Engle case?

A: No.

Q: Are you testifying today as an expert?

A: No.

Q: Were you compensated in any way for your work in the Engle case?

A: I was not compensated. I was reimbursed for my travel expenses, but that's all.

Q: Have you been compensated in any way by the United States in this case?

A: No.

Q: Now, Dr. Mele, I am going to ask you questions regarding your employment with Philip Morris from 1981 to 1984. Please briefly describe how you came to be hired by Philip Morris in 1981.

A: Victor DeNoble was working for Philip Morris already. We attended the same graduate program at Adelphi and he was a few years ahead of me. He contacted me about the job at Philip Morris.

Q: Did you interview for the position at Philip Morris?

A: Yes. I met with the members of the Behavioral Research Group. The head of the Group at the time was Dr. William Dunn. I also met with Frank Ryan, Frank Gullotta, and Sandra Dunn, who all worked in the Behavioral Research Group under Dr. Dunn.

Q: When you began working at Philip Morris, who was your immediate supervisor?

A: Dr. Victor DeNoble.

Q: To whom did Dr. DeNoble report?

A: Dr. DeNoble reported to Dunn at first, but after I had been at Philip Morris for approximately six months, our lab was transferred to the Biochemical Research Division. Dr. DeNoble's immediate supervisor became Dr. Jim Charles, who was our boss for the rest of our time there.

Q: To whom did Dr. Charles report?

A: Dr. Charles's boss was Dr. Thomas Osdene, the Director of Research.

Q: During your tenure, what positions did you hold at Philip Morris?

A: I was first hired as a Scientist and, after about a year I was promoted to the Research Scientist level, which is the next step up.

Q: What were your job responsibilities when you first started working at Philip Morris?

A: My job at Philip Morris was to plan, design and conduct experiments on the behavioral pharmacology of nicotine and other tobacco smoke components. Our lab was a very "hands on" place and I worked on the experiments with Dr. DeNoble, but I also began supervising other technicians in the lab.

Q: How many other people worked in the lab with you and Dr. DeNoble?

A: At any one time, there were at most four people in our lab – Dr. DeNoble, me and two

technicians.

Q: What direction, if any, did Philip Morris provide to you and Dr. DeNoble with respect to your research?

A: There were basically two main programs that we had at Philip Morris. One was the nicotine analogue program where we set out to identify a compound that would have many of the qualities of nicotine and that could be used as a substitute for nicotine. The second direction was more broad. We basically set out to examine the key components of cigarette smoke for product related development. We studied nicotine and other smoke components to understand more thoroughly the effects on the body and why people smoked.

Q: Dr. Mele, we will discuss each of these research programs in detail, but first, please tell the Court generally what experimental models that you and Dr. DeNoble used to conduct your research.

A: Our studies were all done with rats and were based on well-established models in the scientific literature that are used to study drugs of abuse and abuse liability. We adapted those models to our work.

The main test that we used was the rat self-administration test. In this test, we implanted a catheter into the rat. It's a relatively simple surgical procedure that was performed in the lab. Dr. DeNoble usually performed the procedure because he was very good at it. Once the rat healed, we put him into an experimental chamber and he learned pretty quickly to press a lever to receive a small intravenous dose of nicotine through the catheter. Nicotine has positively reinforcing effects and rats will work for it.

At the same time, we were conducting drug discrimination tests. In the discrimination studies, rats are injected with nicotine, which has positive reinforcing effects for the rats. The

rats then learn to press a lever when they receive a drug that "looks" like nicotine to them, meaning that it has the same reinforcing effects.

Q: Dr. Mele, what do you mean by "abuse liability?"

A: Abuse liability refers to the likelihood that a drug will be used inappropriately by humans.

Q: When you refer to the "reinforcing effects" of nicotine, what specific effects are you referring to?

A: Nicotine is a positive reinforcer, which means that rats will work to get it. Nicotine and other drugs of abuse act as positive reinforcers by acting on the brain. When I say that we studied the reinforcing effects of nicotine, I mean that we studied the characteristics of nicotine as a positive reinforcer – something that rats will work to get – and we studied areas in the brain where nicotine acts to produce its positively reinforcing effects. I am also referring to the fact that nicotine binds in the brain and how nicotine affects the brain.

Q: Why was the focus of your research on nicotine?

A: Nicotine is the primary component in smoke that maintains smoking behavior.

Q: Did you hear other scientists at Philip Morris express this view of nicotine when you were there?

A: Yes. This was discussed at our meetings with supervisors and it was the reason we studied nicotine. No one ever doubted that nicotine was the component in smoke that kept people smoking.

Q: Why were the rat self-administration tests used in your lab?

A: Well, if a rat will self-administer a drug, a human will self-administer a drug. It's a very good predictive model. There are drugs humans will self-administer that rats won't, like LSD.

Rats don't like LSD and hallucinogens. But rats will self-administer drugs like cocaine, heroin, morphine, and PCP. So, a rat is a conservative measure of what a human will do. If a rat will work to self-administer a drug, a human will, but not necessarily the other way around. I am not aware of any drug that a rat will work for that a human will not self-administer.

Q: Dr. Mele, can you please tell the Court whether your research demonstrated that rats would self-administer nicotine?

A: Yes. Dr. DeNoble had already established nicotine as a reinforcer prior to my beginning work in the lab. The self-administration studies that continued certainly demonstrated that nicotine has reinforcing effects. This is the animal model that you could use to obtain data relevant to the question: "will someone smoke a cigarette to get nicotine?"

Q: To your knowledge, were the nicotine self-administration studies that were performed in your lab at Philip Morris novel?

A: The nicotine self-administration tests beforehand were not as reliable. Dr. DeNoble made the test better, with better controls, and used that as a baseline for our research. Our research showed that nicotine was a positive reinforcer for rats – that it has effects in the brain.

Q: Let's talk separately about each of the research programs that you mentioned earlier. First, how was the nicotine analogue program designed?

A: Nicotine is a simple molecule that can be altered. Philip Morris had a very good group of organic chemists in the research center. The organic chemists made nicotine analogues, which were molecules that were chemically related to nicotine but altered in some way. The goal of the nicotine analogue program was to identify a compound that maintained the reinforcing effects of nicotine but that had fewer of the toxic effects on the cardiovascular system.

Q: What are the adverse effects on the cardiovascular system that Philip Morris sought

to address through the nicotine analogue program?

A: The negative cardiovascular effects that we were aware of at the time included increasing heart rate and increasing blood pressure.

Q: What was your laboratory's role in the nicotine analogue program?

A: The organic chemists sent out the nicotine analogues for several stages of testing. I believe we were the last stage of testing, or close to it. Outside people, consultants at the Medical College of Virginia, tested the analogues for cardiovascular effects. Dr. Leo Abood, a consultant who worked at the University of Rochester, studied the brain binding capability of the analogues. Dr. DeNoble and I did the behavioral analysis. We tested the analogues to determine whether an analogue maintained self-administration and would therefore maintain smoking behavior. We were testing to see whether the analogues had the same reinforcing effects as nicotine.

Q: Why was Philip Morris interested in finding a nicotine analogue?

A: Jim Charles informed us that a successful analogue, which had reduced cardiovascular effects, would be a future benefit to the company when needed. We discussed this at our regular meetings with Jim Charles and other Philip Morris scientists regarding the nicotine analogue program. We also discussed whether the analogue would be put into cigarettes, and if so, would the FDA regulate. As researchers, though, we were not making those decisions regarding the product.

Q: Did your research result in the development of any nicotine analogue that satisfied the criteria of having the same reinforcing effects of nicotine but fewer cardiovascular effects?

A: Yes. 2-prime-methylnicotine and 4-prime-methylnicotine were identified as successful

nicotine analogues. 2-prime was an especially effective reinforcer in rats. The analogue maintained self-administration as well as, if not better than, nicotine. In the discrimination tests, the results showed "yes, this looks like nicotine." Also, there were fewer cardiovascular effects associated with 2 prime.

Q: Were 2-prime-methylnicotine and 4-prime-methylnicotine tested in the self-administration studies?

A: Yes.

Q: Did you and Dr. DeNoble keep your supervisors apprised of your lab's work in the nicotine analogue program, including the testing of the 2-prime-methylnicotine and 4-prime-methylnicotine?

A: Yes, in several ways. We had master data sheets, which we provided to our supervisors. Once an analogue was tested, we would record the results of the tests on the data sheets. Jeff Seeman, one of the organic chemists, would plug our results into a spreadsheet, which showed all of the analogues and their effects. Periodically, everyone would receive copies of the spreadsheet. We could see everyone else's data and they could see ours. We then discussed our results at the nicotine analogue meetings that were held almost monthly to determine what compounds were either good or bad. Dr. DeNoble and I also reported our results in our annual reports.

Q: Who attended these nicotine analogue meetings that you have mentioned?

A: In addition to myself and Dr. DeNoble, there was Jim Charles and Ted Sanders, who was the head of the Chemical Research Division. Chemists, like Jeff Seeman and Charles Chavdarian, would also attend the meetings regularly. Tom Osdene, Director of Research, attended occasionally and his assistant, Bob Pages, attended the meetings regularly.

Q: To your knowledge, what, if anything, did Philip Morris do with the discovery of the 2-prime-methylnicotine and 4-prime-methylnicotine analogues?

A: I have no idea what they did. They had the technical ability to replace nicotine in tobacco with these compounds, or to add these compounds to tobacco as a supplement to nicotine. One of the questions that we always asked at our meetings was would Philip Morris want to put it in commercial cigarettes at some historic point in time. There were no answers to the questions.

Q: How do you know that Philip Morris had the technical ability to utilize the nicotine analogues?

A: The work that Frank Ryan was conducting was manipulating the nicotine levels in test cigarettes to test the response in human studies. The test cigarettes used in Ryan's studies were manufactured at Philip Morris. They could add more nicotine to cigarettes. They could also remove nicotine entirely or remove some of the nicotine from cigarettes. Also, the working hypothesis for the nicotine analogue program was that one or more of the analogues might someday be put into tobacco products.

Q: How are you aware of Frank Ryan's work?

A: Frank Ryan was a scientist in the Behavioral Research Group when I started work at Philip Morris. The Behavioral Group had regular meetings where the member scientists discussed our respective research projects. I had regular contact with Frank Ryan throughout my time at Philip Morris and we frequently discussed our research projects.

Q: Earlier you stated that you were using scientific models established for studying drugs of abuse and abuse liability. In addition to the self-administration and discrimination tests that you described, can you outline briefly any other tests that you were using in your research at Philip Morris?

A: Drugs of abuse are measured in three ways. Self-administration is one. Physical dependence as shown by withdrawal is another and tolerance is another. Physical dependence, or withdrawal, and tolerance can be shown in drugs of abuse and in compounds that are not drugs of abuse. Self-administration only appears in drugs of abuse. We studied all of these in relation to nicotine and other smoke components at Philip Morris.

Q: Now Dr. Mele, you previously mentioned that a second purpose of your lab was to examine cigarette smoke and nicotine more thoroughly and to understand its effects on the body. What studies did you and Dr. DeNoble perform pursuant to this objective?

A: We used the drug discrimination studies and we also looked at tolerance and withdrawal, which are two classic measures in the literature for drugs of abuse. I was mainly involved in the tolerance studies, which examine the effects of chronic nicotine administration and what happens after you stop the chronic administration.

Q: Dr. Mele, please briefly describe the tolerance studies that you performed.

A: To study tolerance, we used the two primary criteria that have been well established in the field of pharmacology for many drugs of abuse. First, we looked to see whether there was a lessened effect with repeated administration, meaning the effects of nicotine are lessened the more it is given. Second, we studied the "shift in dose response," which is that higher doses are necessary to produce the initial effect. You can recapture the original effect of a drug and overcome tolerance, but you have to give more of the drug to do it.

To begin, we first administered nicotine to the rats once a week to see if they had an initial sensitivity to nicotine that caused a behavioral or physiological effect in the rat. Then we administered nicotine every day for 30 days. What we saw was that the first few times the rats received nicotine, their daily behavior in the test chambers – rats were pressing a small lever to

obtain food pellets – was severely disrupted. After nicotine injections, the rats stopped responding for large portions of the 30-minute daily test session.

We then began administering nicotine injections to the rats every day before the behavioral test session. We saw that the rats gradually started behaving normally – that is, the initial effect of the nicotine went away with repeated administration. After 30 days of daily nicotine administration, we administered several different doses of nicotine to establish a "dose response curve." We saw that we could recapture the disruptive effects of nicotine by administering higher doses of nicotine.

Q: Did these studies demonstrate tolerance to nicotine?

A: Yes. Using the two primary criteria that I mentioned, we showed that tolerance to nicotine occurs.

Q: Just so the record is clear, Dr. Mele, were your studies at Philip Morris the first to show that nicotine administration results in tolerance?

A: No. Tolerance had already been reported in the literature, but we extended the study. Our studies showed both physiological and behavioral tolerance.

Q: Can you briefly describe what physiological and behavioral tolerance are?

A: Physiological tolerance is how the body adjusts to the effects of a drug when a drug is given repeatedly. One example of physiological tolerance is when the body metabolizes - or breaks down - a drug faster after the drug has been given repeatedly. Faster metabolism causes the drug to have a shorter acting effect, or a smaller effect. Behavioral tolerance occurs when tolerance develops to a behavioral effect of a drug. More specifically, in our studies with nicotine, tolerance developed to a greater degree when the subjects were allowed to perform or "practice" the behavior under the influence of the drug. This "practice effect" is what we refer to

as behavioral tolerance. For example, studies have shown that when people practice a task under the influence of a drug, they learn to overcome the disruptive effects of the drug on the task being performed. As reported in the literature, behavioral tolerance is a characteristic of most other drugs of abuse. Our study demonstrated that nicotine shares this characteristic with most other drugs of abuse.

Q: What was the scientific importance of your findings with respect to the tolerance studies conducted by you at Philip Morris?

A: For one, we extended the studies in the literature. Our studies showed the behavioral tolerance component, which really hadn't been done before. Also, tolerance is a characteristic of drugs of abuse. Our studies showed that nicotine has effects similar to other drugs of abuse.

Q: Were your supervisors aware of the fact that you were studying tolerance?

A: Yes. For all of my studies I submitted a proposal in writing to my supervisors. They knew that we were studying tolerance in our lab.

Q: Did you report the results of your tolerance studies to your supervisors?

A: Yes. I submitted reports that discussed both types of tolerance.

Q: To your knowledge, was it important to Philip Morris that this research on tolerance occurred in a Philip Morris lab?

A: Yes.

Q: Why was this important?

A: It was important because of the implications of the work and the fact that it was being done at Philip Morris. At that time the Diagnostic and Statistical Manual version III (DSM-III) published by the American Psychiatric Association (APA) stated that dependence on a drug was evidenced by the occurrence of *either* tolerance *or* withdrawal. For this reason, the company did

not want to be establishing tolerance to nicotine and, thus, dependency on its product.

Q: Did you ever seek to publish the research on tolerance?

A: Yes. In early 1983, I submitted an abstract of the tolerance studies to Jim Charles and asked that a manuscript be submitted to a journal to try to get it published. A couple of weeks or a month later, I was given a decision.

Q: What was the decision regarding the publication of your study on tolerance?

A: Jim Charles told me that the tolerance study could not be published because the study showed tolerance and physical dependence to nicotine. Philip Morris was worried about it. Charles made it clear that they could not have Philip Morris demonstrating dependency on its products. Charles said that they would allow me to write an internal paper for Philip Morris.

Q: What was your reaction to this decision not to publish your work on tolerance?

A: I was disappointed. One of the reasons I decided to work for Philip Morris was that I thought I could publish. Dr. DeNoble had already published one brain sites paper prior to my arrival, so I thought that I would be able to publish some studies as well.

Q: Dr. Mele, I am showing you U.S. Exhibit 20,100, which has been admitted into evidence. Do you recognize this document?

A: Yes.

Q: What is it?

A: It is a copy of the Behavioral Pharmacology lab's annual report for 1983.

Q: If you turn to Section V., "Tolerance to Chronic Nicotine Administration: Behavioral vs. Metabolic Factors," which begins on page 31 of the report (Bates ending 3919), is this a report that discussed both types of tolerance to nicotine, as you just described?

A: Yes it is.

Q: And does this report represent the basis of your abstract on tolerance that you submitted to Jim Charles for consideration to be published?

A: Yes.

Q: Dr. Mele, who at Philip Morris received copies of your annual reports?

A: We had a restricted distribution of our research, at least at first. For the first year or so I could see that our annual reports were highly restricted. Only people like Tom Osdene, Jim Charles, and Bob Pages reviewed the reports. The distribution list on the 1983 annual report shows the widest distribution throughout the Research Center that our annual report achieved. This occurred less than one year before our lab was closed. The recipients of this report include the Vice President of Research and Development, the five directors of the Research Center and several project leaders in the Biochemical Research Division.

Q: How did the internal distribution of your lab's annual reports compare to the distribution of reports for other labs in the Research Center?

A: Our distribution was much more restricted than any other projects in the Biochemical or Chemical Research Divisions. I can't say that it was the most restricted in the entire Research Center; however, we were the most restricted of the two research divisions. At its severest, only those with a direct "need to know" received our reports - Charles, Osdene, Bob Pages, Judy John (Page's assistant), Ted Sanders and maybe one or two other Principal scientists with a medical scientific background. I do not know which reports were sent to upper management in New York.

Q: What was the review process for outside publication of research conducted at Philip Morris?

A: Normally, we would submit proposals to Jim Charles or we would ask Bob Pages to review something we were writing. Charles would discuss our work with Osdene and they would determine whether to send the work to New York for legal review. Fred Newman's name was mentioned a lot. Newman was an attorney for Philip Morris. I always thought it was interesting that the attorneys were reviewing the science.

Q: In addition to the tolerance studies, you testified that you performed studies on withdrawal. How were those studies structured?

A: We did at least one study of physical dependence, which is shown by withdrawal. We administered nicotine every day in a similar way as in the tolerance studies. Once daily nicotine administration ceased, we looked for withdrawal signs.

Q: What did those studies demonstrate?

A: In this study, we were not able to demonstrate withdrawal.

Q: Did you report these findings to your supervisors at Philip Morris?

A: Yes. We submitted written reports and an abstract for publication. Philip Morris was happy about this result and our supervisors allowed us to submit the paper to a journal for publication. The journal had contacted us during the review process and asked us to do some further experiments. When someone wants to publish a negative result, meaning a result that something doesn't happen, then you must reassess the set of studies. We were going through the review and analyzing data at the time our lab was closed, so we never finished or published the study.

Q: You previously testified that your research had "restricted distribution." How was the distribution of your research restricted?

A: When I first started at Philip Morris, the managers would always say that the research in

our lab was distributed to others, even within Philip Morris, on a "need to know" basis. Everything was "need to know." I think the Biochemical Research Division knew that there were studies being done with rats, but it wasn't something we discussed openly. Our rats were brought in with a sheet over the cart. As I mentioned earlier, our annual reports were highly restricted for the first year or so. We also did not give presentations to the entire research center the way other scientists at Philip Morris did.

Q: Other than the people who actually worked in your lab and your direct supervisors, who, if anyone, had access to your lab?

A: We were allowed to have very few visitors, but occasionally we had project leaders from the Biochemical Research Division and important visitors, like senior managers, who wanted to take a look at our lab. On one occasion a Senior Manager from the Operations Center, Jim Remington, came for a tour of our lab. There were other occasions when Philip Morris executives came to the lab as well.

Q: Did there come a time when the restriction on distribution of your research changed?

A: Yes.

Q: What changes to the restricted distribution policy did you observe?

A: In the summer of 1982, there was the first lifting of the veil of secrecy when Victor DeNoble was permitted to give a presentation of our work to the five directors. The directors, people like Osdene, met weekly and sometimes scientists were asked to present their research at those meetings. After that, we were permitted to present our work to the Biochemical Research Division, which was about 40 people. Then, some time later, we were allowed to give a talk to the whole Research Center at one of the periodic scientific seminars.

Q: So far you have discussed your studies on nicotine self-administration, nicotine analogues, tolerance, and withdrawal. While you were at Philip Morris, did you ever conduct research on things other than nicotine and nicotine analogues?

A: Yes, we studied other components in cigarette smoke, like formaldehyde and acetaldehyde. Both are found in cigarette smoke. Acetaldehyde, in particular, is released in high quantities in cigarette smoke and we studied the more prevalent compounds found in smoke. Acetaldehyde is a metabolite of alcohol also. DeNoble had experience with alcohol work before coming to Philip Morris. I had experience with amphetamines and I also studied brain dopamine systems, which alcohol affects. So, it made sense for us to look at acetaldehyde.

Q: What studies did you perform using acetaldehyde?

A: We tested acetaldehyde on clean, naive rats using the same types of studies we did for nicotine- self-administration studies, and we found acetaldehyde to be reinforcing. We also did drug discrimination and withdrawal studies with acetaldehyde. Basically, instead of using nicotine in the studies, we just plugged in acetaldehyde.

Q: Can you please tell the Court what you mean by "clean, naive rats?"

A: These are rats with no experimental history. Rats that have never been used in experiments.

Q: What, specifically, were the results of those studies using acetaldehyde?

A: With drug discrimination, we were not able to get the rats to discriminate acetaldehyde. With the withdrawal studies, we could not demonstrate physical dependence of acetaldehyde as indicated by withdrawal. We did find that rats would self-administer acetaldehyde. We then studied the combination of acetaldehyde and nicotine together. This combination produced a "super-additive" effect, or a synergistic effect, meaning that there is a greater response than the

sum of those two things when each is given alone.

Q: Did you and Dr. DeNoble report the results of the acetaldehyde work to your supervisors?

A: Yes.

Q: How did you report your results?

A: We had regular meetings where we discussed our research, including our nicotine/acetaldehyde work. We would have also reported the acetaldehyde results in our annual reports.

Q: Who participated in these meetings regarding the acetaldehyde work?

A: Besides me, there was DeNoble and Jim Charles. Jim Charles was a very "hands on" supervisor.

Q: What value, if any, did the discovery of the super-additive effect of acetaldehyde and nicotine potentially have for Philip Morris?

A: There was a practical aspect of the super-additive quality of the reinforcing effects of nicotine and acetaldehyde. Jim Charles discussed with us the importance of finding the optimum ratio of nicotine and acetaldehyde that was reinforcing in the self-administration test. We looked at a number of different ratios that potentially could be used in a commercial cigarette.

Q: Do you know whether Philip Morris ever pursued research or product development to make a commercial cigarette using your discovery regarding nicotine and acetaldehyde?

A: I don't know. This discovery was at a time shortly before our lab was closed, so any product development stages would have to have taken place after we left.

Q: Did you seek to publish the results of your acetaldehyde studies?

A: No. We felt there was never any hope of getting these results out. This was such a

potentially new and blockbuster finding that never in our wildest dreams did we believe they would let us put it out.

Q: Other than the tolerance study and the withdrawal study that you discussed previously, did you seek to publish any other papers during the time you were employed by Philip Morris?

A: Yes. Dr. DeNoble and I did.

Q: How many?

A: One other paper.

Q: What was the topic of that paper?

A: The paper was based on one self-administration study that we performed for the first time where the data was collected with a number of appropriate control procedures. We found that rats indeed self-administered nicotine. We also found that there is an optimal dose for self-administration and then it falls off because the nicotine becomes too toxic. For control measures we used a drug blocking technique where we injected a nicotine blocker, one that readily enters a rat's brain, to see if it really was nicotine acting in the brain that had the reinforcing effects.

Q: When did you submit the self-administration paper to the review process at Philip Morris?

A: Some time in 1982, maybe late 1982.

Q: What was Philip Morris's decision regarding the self-administration paper?

A: They did allow us to send this out for publication and it was accepted by the journal Psychopharmacology.

Q: In addition to the journal publication, were you and Dr. DeNoble given permission to present the results of the self-administration study outside of Philip Morris?

A: Yes. We planned to present a poster of the self-administration study at the American Psychological Association (APA) meeting in Anaheim. The meeting is held every year in August, so this would have been for August 1983.

Q: Was the self-administration study actually published?

A: No.

Q: Why not?

A: Jim Charles told Dr. DeNoble to pull the paper. Around this time the Cipollone case had already been filed and Dr. Charles talked openly with us that the company was concerned about this case. Dr. DeNoble, Dr. Charles and I had regular meetings in our lab where this was discussed. Dr. Charles and Tom Osdene told us that we couldn't put out our work at that time. Dr. DeNoble and I were putting pressure on Dr. Charles and Dr. Osdene to let us publish our work and we kept asking when we would be able to do that. I think they were getting frustrated with us, but it's not good for scientists not to publish.

Q: Specifically, what reasons, if any, did Philip Morris give for why you and Dr. DeNoble had to withdraw the publication of the self-administration study?

A: That the Cipollone lawsuit was causing problems.

Q: Did anyone at Philip Morris ever indicate to you that there was any problem with the scientific validity of paper?

A: No, never.

Q: Did you and Dr. DeNoble withdraw the paper in response to the instruction from management?

A: Yes. Dr. DeNoble had all the contact with the journal.

Q: When was the paper pulled from the journal?

A: It would have been around the same time as the APA meeting – August 1983.

Q: Did you and Dr. DeNoble present the self-administration data at the APA meeting in Anaheim?

A: No. There was a last-minute retraction.

Q: What reasons, if any, were you given by Philip Morris for why you could not proceed with the presentation at the APA meeting?

A: I don't recall exactly but the Cipollone lawsuit was being discussed; it was of great concern, and it was clear that we were not going to be allowed to present or publish anything for some time. At some point later someone at Philip Morris questioned whether Dr. DeNoble went through the correct steps in the clearance procedure for the poster presentation. The poster, however, included the same data as in the manuscript that was withdrawn from publication because of the lawsuit.

Q: In the summer of 1983, were any other restrictions placed upon your work by Philip Morris?

A: Well, there were discussions about whether to close the lab in the summer of 1983. There was also talk about moving our lab to Switzerland or moving us off of Philip Morris property.

Q: Who took part in these discussions about closing or moving your lab?

A: Jim Charles discussed this with Dr. DeNoble, who relayed it to me.

Q: Were you told why Philip Morris wanted to move your lab off of the property?

A: I was told that it was to create distance between Philip Morris and the work we were doing in order to reduce the liability Philip Morris would have for conducting such research.

Q: Did any of these possibilities ever come to fruition?

A: No.

Q: To your knowledge, why did these possibilities not occur?

A: I was told that there was not a practical way for Philip Morris to separate the company from the work that we were doing.

Q: Dr. Mele, you previously testified that Philip Morris was beginning to expand the internal audience to whom you and Dr. DeNoble could present your research, such as to the directors, the Biochemical Research Division and the Research Center. Did there come a time when your research was presented to upper management executives at Philip Morris?

A: Yes.

Q: When was that?

A: Some time in either late 1982 or early 1983. It was certainly before our paper was pulled.

Q: Where did the presentation to the executives occur?

A: New York.

Q: Did you take part in that presentation?

A: No, Dr. DeNoble went up in the company jet. I was considered a junior party and I had to keep the lab going. It would have been highly unusual for someone in my position to present to upper management. It was unusual for someone at Dr. DeNoble's level to present to upper management. During the time I was at Philip Morris, I never heard of anyone at Dr. DeNoble's level presenting research to upper management.

Q: Did any Philip Morris executives come to your lab in Richmond to see your research firsthand?

A: Yes. In November 1983, Mr. Shep Pollack, head of Philip Morris, USA, came to our lab with a group of about 4-6 people. Fred Newman, a corporate attorney, was also with them. They

wanted to see the self-administration lab.

Q: What questions, if any, did Mr. Pollack or members of his group have about your research?

A: At one point, Mr. Pollack asked whether nicotine, or maybe tobacco – I can't remember which – was addicting.

Q: Did you respond to this question?

A: Yes, I wanted to give him my views.

Q: What was your response?

A: I told him that a lot more work needed to be done on the self-administration studies. We had the models in place to address the question and we needed to keep going. I believe I also pointed out that while physical dependence can be measured in animals, addiction is not used to describe the effects in animals; it is a human condition.

Q: What other members of the group were part of that conversation?

A: I can't recall exactly. There were different rooms in our lab. Dr. DeNoble was taking people into the self-administration lab. I was not in the room with Dr. DeNoble when he gave a demonstration to the group. We were all in different rooms at different times.

Q: After the time that Mr. Pollack visited your lab, did you have any discussions with your supervisors or management involving whether to keep your research going?

A: Yes. Jim Charles was very open with Dr. DeNoble and me about the lab. Dr. Charles said we were good to go and the lab would stay open.

Q: Did you, in fact, continue your research after Mr. Pollack's visit in late 1983?

A: Yes.

Q: In addition to the group that toured your lab with Philip Morris USA President

Shep Pollack, did your lab receive any other visitors around that same time period in 1983?

A: Yes.

Q: Who else visited your lab during this time frame?

A: Philip Morris lawyers from the law firm of Shook, Hardy & Bacon came to visit our lab in the months preceding the closure of the lab.

Q: How many attorneys visited your lab?

A: There were three attorneys. One of them was Rhonda Fawcett, who spent a lot of time in our lab.

Q: What did you observe the attorneys doing when they visited your lab?

A: They copied all of our files. They also talked to us and wanted to know everything about our work. Dr. DeNoble and I openly discussed our work with them.

Q: To your knowledge, was the action taken by the attorneys the same for all of the labs at Philip Morris?

A: I am not sure if the attorneys were in the other labs, but they did spend a lot of time with us.

Q: How long did the attorneys' visit last?

A: I believe it started in the summer of 1983, but I don't know how long they stayed after our lab was closed.

Q: When was your lab closed?

A: April 5, 1984.

Q: Can you please explain how your lab was closed?

A: It was a Thursday, at about 3:00 in afternoon and Dr. DeNoble was taken upstairs to meet with Jim Charles. Dr. DeNoble came downstairs and then I was taken up to see Dr. Charles

separately. Jim Charles told me that Philip Morris doesn't do behavioral pharmacology anymore. He said that our lab was being closed immediately. I was told that we needed to clear our stuff out of the lab and that the rats needed to be killed.

Q: What specific reasons, if any, did Dr. Charles give for Philip Morris's decision to close the lab?

A: He said it was a business decision. I asked Dr. Charles personally what did he do to protect our lab. He said that he did all that he could do.

Q: Were you able to return to your lab after Dr. Charles told you that Philip Morris was closing down the lab?

A: I packed up on Friday. We were told to kill the rats and close down our experiments right away.

Q: What was the status of the research being conducted in your lab at the time the lab was closed?

A: There was one study that we were very close to completing. I asked for one more day to complete it, but that was denied. I cannot remember what study it was exactly; I believe it was a brain sites or brain tolerance study.

Q: After the Friday when you packed your things and closed down the lab, did you return to the lab?

A: No, I never went back. They took our badges from us right away, so we couldn't get back into the Research Center without an escort. I understand Philip Morris's need to protect itself, but I thought that was insulting.

Q: When your lab was closed, did Philip Morris offer any scientific reasons why the work was ceased?

A: No. In fact, they were just beginning to allow us to go out and talk about the work – before the self-administration paper had to be pulled.

Q: Were you told your job performance was deficient in any way?

A: No. I always received positive reviews and I had been promoted.

Q: What options, if any, were you offered by Philip Morris at the time your lab was closed?

A: There were three "options." I was told that Philip Morris would give me six months salary to walk out the door and go away. I could continue to spend about six months at the company to look for a job and Philip Morris would provide the placement resources. Or, I could be placed in another position with the company.

Q: What did you decide to do?

A: I opted to be placed elsewhere in the company, as I thought that would be the easiest thing to do. At the same time they had us working with the placement people. Dr. DeNoble and I were moved to a new set-up in offices that used to be an old warehouse. We did not have any duties except to look for another job.

Q: Did Philip Morris ever offer you another position?

A: They never offered either of us a position. We asked the personnel people several times about other positions in the company. At one point, they told us to stop asking or we would be sweeping floors. It was clear that the only option was to get another job.

Q: Dr. Mele, how long did it take you to find another job?

A: Our lab was closed in April 1984 and I was offered the job in Bethesda around October or November. So, that would be about 6-8 months. The job wasn't starting until February 1985, so I asked Philip Morris if I could stay until then. I was allowed to stay until the end of the year and

I actually left in December 1984. For about one month in January 1985, I was technically unemployed.

Q: During your tenure at Philip Morris, did you enter into a Confidentiality Agreement with the company regarding your work?

A: Yes.

Q: After the time when your lab was closed, did you have any meetings or discussions with anyone at Philip Morris regarding your Confidentiality Agreement?

A: I do not recall if the agreement was discussed when I was leaving. There was no formal exit interview or meeting.

Q: Did the terms of the agreement expire a certain period of time after the termination of your employment with Philip Morris?

A: I don't recall.

Q: After leaving Philip Morris, did you renew attempts to publish the research that you and Dr. DeNoble conducted on nicotine?

A: Yes. We attempted to do a series of presentations. We presented a poster for the Federation of American Societies for Experimental Biology in St. Louis in 1986.

Q: In addition to the poster presentation in St. Louis, did you and Dr. DeNoble attempt to have your research on nicotine printed in any scientific journals or publications?

A: Yes. We submitted the self-administration paper. We also submitted the brain sites paper where we mapped out different areas in the brain affected by intraventricularly administered nicotine, which we presented at the APA conference in Washington, D.C. There was also an abstract that we submitted to the Society of Neuroscience on a pharmacological phenomenon called "super-sensitivity." This is where nicotine receptors in the brain are blocked

by a drug that is chronically administered for 30 days. Then nicotine is administered to see if the brain becomes more sensitive to the nicotine.

Q: Did either you or Dr. DeNoble request permission from Philip Morris prior to taking steps to publish your work?

A: Yes. Dr. DeNoble contacted Philip Morris and requested permission to publish one of our studies. We received a reply from Dr. Osdene by mail that Philip Morris denied the request.

Q: When did this occur?

A: In 1985, shortly after we left.

Q: You stated that you and Dr. DeNoble presented a poster for the Federation of American Societies for Experimental Biology in St. Louis in 1986. What data did you present at that meeting?

A: We presented the behavioral tolerance data.

Q: Prior to making the presentation, did you request Philip Morris's permission to present the behavioral tolerance data?

A: No.

Q: Why not?

A: We thought that it was important enough to try to get the data out. In this way the scientific community would make a decision about whether the work was important and if it was useful in any way.

Q: What contact, if any, did you have with Philip Morris after your presentation in St. Louis?

A: I received a letter from one of Philip Morris's attorneys.

Q: You have been shown U.S. Exhibit 22,772. Do you recognize this document?

A: Yes.

Q: What is it?

A: It is the April 23, 1986 letter that I received about our presentation in St. Louis.

Q: Who sent this letter?

A: It's from Eric Taussig, the Assistant General Counsel of Philip Morris Companies.

Q: Was it sent to your address at 3205 Whispering Pines Drive, Apt. 13, Silver Spring, Maryland 20905?

A: Yes. That was an apartment that I was living in when I moved to this area to take the job at Bethesda Naval.

Q: Did you receive it in the mail delivered by the U.S. Postal Service?

A: I remember receiving it by mail.

Q: Beginning with the second sentence of the letter, what does this letter say?

A: "As you are aware, upon your employment at Philip Morris on November 16, 1981, you signed an agreement (a copy of which is enclosed) requiring you to keep confidential, unless expressly permitted otherwise, research developed while an employee of the Company. The disclosure of such information as a result of your employment at Philip Morris without permission constitutes a breach of your agreement with the Company. In the future you are expected to comply with the terms of the agreement."

Q: What was your personal reaction when you read this letter?

A: I knew that what we had done would risk a response from Philip Morris, but I also believed it was important to let our peers in the scientific community judge our science.

Q: Did you have any further contact with Philip Morris after you received this letter?

A: Yes.

Q: When was your next contact?

A: Later – around September 1986.

Q: What was the nature of your contact with Philip Morris?

A: Dr. DeNoble and I gave a poster presentation at the APA meeting related to the brain sites research. Philip Morris had sent someone out to check up on us and take pictures of our poster. After that we received another letter from Mr. Taussig.

Q: You now have before you U.S. Exhibit 21,916. What is this document?

A: This is the second letter I received from Mr. Taussig.

Q: What is the date of this letter?

A: September 10, 1986.

Q: Was this letter sent to your home address at 3205 Whispering Pines Drive in Silver Spring, Maryland?

A: Yes.

Q: Did you receive this letter at your address in Maryland?

A: I was in the process of moving to a new address around this time. I can't remember if I received this letter at this address or not, but I *do* remember receiving this letter.

Q: Do you see at the top of the letter where it states "CERTIFIED MAIL RETURN RECEIPT REQUESTED"?

A: Yes.

Q: Did you receive this letter by certified mail delivered by the U.S. Postal Service?

A: I don't remember specifically signing for certified mail, but I do remember receiving this letter

from Philip Morris.

Q: What is the subject of this second letter from Philip Morris?

A: Philip Morris reminded us again of our responsibilities under the confidentiality agreement and they threatened action against us if we attempted to publish our research again.

Q: Please tell the Court what the last paragraph of this letter says.

A: The last paragraph states: "The Company cannot tolerate this type of conduct. As I stated in my earlier letter, if you wish to publish or otherwise utilize research from Philip Morris, you must request and receive permission from the Company. Any further breach of your agreement will result in action being taken."

Q: What was your personal reaction when you received and read this letter?

A: It was clear that the company was threatening to take legal action against us if we continued to put out our data. Dr. DeNoble and I talked about it. Neither one of us could afford to take on Philip Morris. Financially, we did not have the resources to fight a legal battle with a major corporation. And it is stressful when a major corporation threatens you like that.

Q: What, if anything, did you do after you received the September 10, 1986 letter?

A: We had submitted two papers for publication in scientific journals. One was the brain sites study, for which we had already presented the poster at the APA, and the other was the self-administration study. Dr. DeNoble decided to call Mr. Taussig to discuss those papers. I was not part of the conversation, but I know that the self-administration study was pulled from the journal. This was the second time we sent it out to be published and had to pull it back. I believe the brain sites paper had already been sent to press, so it was published.

Q: To date, has your self-administration study ever been published?

A: The study was published only in the Congressional Record following the testimony Dr.

DeNoble and I gave before Congressman Waxman's committee in 1994.

Q: After September 1986, did you make any further attempts to publish your nicotine research?

A: No.

Q: Dr. Mele, what was your intention in presenting your nicotine research to the scientific community?

A: Science is about peer review of data. As scientists we felt that it was critical to have the scientific community and the public review our research and to allow them to make a decision about the significance of this work.

Q: You mentioned that you and Dr. DeNoble testified before Congress in 1994. From 1986 when you received the letters from Mr. Taussig until the time you testified before Congress in 1994, did you have any contacts with your former employer, Philip Morris?

A: No.

Q: How did you come to testify before Congressman Waxman's subcommittee?

A: My recollection is that in the Spring of 1994, two FDA investigators called me and asked if they could talk to me about my work at Philip Morris. They came to visit me at work. Then, a Waxman staffer, Phil Barnett, called me and informed me that their office had already contacted Victor DeNoble. Dr. DeNoble and I discussed whether we should get involved. I ultimately agreed to talk to them. Dr. DeNoble and I met with Waxman's staff on the Sunday morning before we testified in April 1994.

Q: What was the nature of your testimony before Congress?

A: To describe our work at Philip Morris.

Thank you, Dr. Mele.