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) Next scheduled court appearance: Trial (ongoing)

WRITTEN DIRECT TESTIMONY

OF

VICTOR J. DENOBLE, II, Ph.D.

SUBMITTED BY THE UNITED STATES PURSUANT TO ORDER #471

Q: Please state your name for the record.

A: My name is Victor John DeNoble, II.

Q: Where do you live?

A: I live in San Diego, California.

Q: Did you receive a subpoena to testify in this case?

A: Yes.

Q: What is your current occupation?

A: I am a guest lecturer in the field of drug addiction and biological science.

Q: Do you work for an organization?

A: I am self-employed. My business is called Hissho, Inc.

Q: To whom do you speak in your work?

A: I speak to 300,000-400,000 school-age children each year, from elementary schools to colleges and universities. I also speak to health professionals and teachers, and give some lectures that serve as continuing medical education.

Q: Please describe your educational background.

A: I have a Bachelor of Arts degree (1971), a Masters of Science degree in experimental psychology (1974), and a Ph.D. in experimental psychology (1976). I did post-doctoral research at the Downstate Medical Center in Brooklyn, NY, and the University of Minnesota.

Q: Did you focus on a particular area of experimental psychology for your doctoral study?

A: Yes. I focused on how a certain type of brain damage affects the emotional behavior of rats. The technical name for my dissertation was "Response Acceleration and Suppression Produced by Response-Independent Food Presentation in Rats with Septial Lesions."

Q: Did your post-doctoral research concentrate on a particular area of experimental psychology?

A: In both post-doctoral programs, I did research in the area of behavioral pharmacology – basically, studying what drugs do to the brain and behavior of animals. At the Downstate Medical Center, I focused on alcohol addiction, working with rats and monkeys. At Minnesota, I did research on a broader range of drugs, including alcohol, pentobarbitol, and methahexatol.

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

A: I went to work at Philip Morris.

Q: In what city did you work?

A: Richmond, VA.

Q: How long did you work at Philip Morris?

A: I was employed by Philip Morris from April 1, 1980 to April 5, 1984.

Q: Please briefly recount your employment history since leaving Philip Morris.

A: From 1984 to 1987, I worked at Ayerst Laboratories as a Research Associate in central nervous system research in Princeton, New Jersey. From 1987-1991, I held the same position at DuPont deNemours & Co. in Wilmington, Deleware – first when it was just DuPont, then with DuPont Merck when the two companies merged in 1990. From 1991-1992, I was a Manager of Development and Training at DuPont Merck. From 1992-1997, I was a Senior Behavior Analyst with the Delaware State Department of Mental Retardation. I then worked for the Delaware chapter of the American Lung Association for about 10 months, in their Tobacco-Free Delaware project. In 1994, I formed Hissho, Inc., a consulting business, mostly lecturing about drug addiction and brain function, including working with departments of public health and hospitals.

Q: Were you involved in a dispute with DuPont Merck concerning the end of your

employment there?

A: Yes. I was part of a small group of people they let go at the same time, but then provided a reason for terminating my employment that was false. They claimed I had made a biostatistical error in work that I had never performed. I sued for wrongful termination.

Q: What was the outcome of that dispute?

A: They withdrew the basis for the termination, and said that since Delaware is an at-will employment state they did not have to give a reason for letting me go.

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

A: Yes.

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

A: Sackman v. Liggett, Shires v. Celotex, the Reed/Richardson case in Maryland, and the Scott case in New Orleans.

Q: In which, if any, of those cases did you provide trial testimony?

A: Scott is the only case in which I have given trial testimony.

Q: In any of these cases, did you serve as an expert witness?

A: I believe in Scott I was identified as an expert witness for a time, but I ended up testifying only as a fact witness.

Q: Are you testifying today as an expert witness?

A: No.

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

A: No.

Q: Have you provided assistance on tobacco-related issues to any governmental

regulatory or legislative bodies?

A: Yes.

Q: When did you first provide such assistance?

A: I was contacted by FDA investigators in about February 1994. I told them I was bound by a secrecy agreement. Then I met with representatives of Congressman Waxman's staff in March 1994. In early April 1994, I met with Dr. David Kessler and members of his staff as well as a Waxman aide. I then testified before Congressman Waxman's subcommittee on health and welfare on April 28, 1994.

Q: Can you briefly describe assistance to governmental bodies subsequent to your testimony before Congressman Waxman's committee?

A: After that congressional testimony, I gave an affidavit to the FDA in 1994 and worked with Dr. Kessler. I participated in a consultantship to Vice President Gore when the White House was evaluating the first proposed tobacco settlement in 1997. Also, I have provided assistance to numerous state and local health departments working on smoke-free ordinances.

Q: Dr. DeNoble, I will now ask you questions about the four years you worked at Philip Morris. What were the positions you held while at Philip Morris?

A: I joined the company as a Project Leader. On August 1, 1983, I was promoted to Associate Senior Scientist.

Q: Where did that 1983 promotion place you in the hierarchy of the Research & Development Department?

A: Associate Senior Scientist is the level just below Senior Scientist, which at that time was the top rank of non-executive scientists at Philip Morris.

Q: Can you briefly describe how you came to accept a job at Philip Morris?

A: I received a call in Minnesota from Dr. William Dunn. He invited me to establish a behavioral pharmacology laboratory to support the nicotine analogue program at Philip Morris.

Q: Who is William Dunn?

A: Dr. Dunn was the manager of the Psychology Research Group at Philip Morris. The Psychology Research Group consisted of behavioral pharmacology, social psychology, and electrophysiology and a human smoking pattern group.

Q: How did he explain what the nicotine-analogue program was?

A: He said that the purpose of the program was to develop a substitute for nicotine that would retain the physiological and behavioral effects of nicotine on the central nervous system, specifically nicotine's reinforcing qualities, but would not retain nicotine's adverse effects on the cardiovascular system.

Q: Why did you accept the job at Philip Morris?

A: At the time, it was a very exciting opportunity for me, as a scientist, to do work that I thought had the potential to have a direct, positive impact for society. I thought that here was a tobacco company saying that they wanted me to do something to make the product safer.

Q: How many people worked in the Psychology Research Group?

A: About a dozen in all.

Q: Please briefly describe what type of research was done in the sections of the Psychology Research Group other than your behavioral pharmacology work.

A: The electrophysiology project, run by Frank Gullotta, focused on experimental neuropsychology. It studied the effects of cigarette smoke on EEG, electro activity of the brain, in humans. The social psychology project, run by Sandra Dunn, identified how and why people smoked from a social point of view. The human smoking pattern research, run by Frank Ryan

and Jan Jones, examined smoker compensation and why people chose certain brands of cigarettes.

Q: Was there behavioral pharmacology work being done before you arrived to establish the behavioral pharmacology lab?

A: A little. A short time before I arrived, there was a scientist named Carolyn Levy who had been doing some basic drug screening studies with rats, called drug discrimination and place preference studies, with nicotine analogues. But she was not trained in behavioral pharmacology, and so was not able to do some of the more sophisticated types of drug studies in rats that I had done in my previous research and that I was hired to perform.

Q: Whom did Dr. Dunn report to in 1980 when you joined the Psychology Research Group?

A: Dr. Dunn reported to Tom Osdene, who reported first to Dr. Robert Seligman, who was Vice President for Research, and later to his successor, Dr. Max Hausermann.

Q: Was the reporting chain the same for the entire time you were at Philip Morris?

A: No. In 1981, my group was moved into the biochemistry division and I reported directly to Dr. Jim Charles who was the manager of that division. Dr. Dunn and Dr. Charles reported to Dr. Tom Osdene who was the Director of all research at the Philip Morris Research Center.

Q: What were generally your responsibilities at Philip Morris?

A: As part of my duties at the Philip Morris Research Center, I was responsible for establishing and directing a behavioral pharmacology laboratory. My responsibilities included: ordering the equipment, hiring additional personnel, designing the behavioral experiments, and establishing a fully functioning behavioral pharmacology laboratory.

Q: What was the purpose of the behavioral pharmacology laboratory?

A: The purpose of the laboratory was to study the behavioral and physiological effects of cigarette smoke and components, especially nicotine and nicotine analogues, on the central nervous system, mainly the brain.

Q: What is a nicotine analogue?

A: A nicotine analogue has a chemical structure that has been modified slightly from nicotine so that it may retain some of the properties of the original chemical structure while at the same time adopting new pharmacological properties.

Q: What was the purpose of the nicotine analogue program?

A: The goal of the nicotine analogue program, as defined by the Vice President of Research, Dr. Seligman, and after 1981, by his successor, Dr. Hausermann, and their senior staff, was to develop a nicotine analogue that would retain the effects that nicotine has on the brain, specifically nicotine's reinforcing qualities, but would not retain nicotine's adverse effects on the cardiovascular system.

Q: What are the adverse effects on the cardiovascular system that Philip Morris was aware of at the time and sought to address through the analogue program?

A: During the late 1970's and the early 1980's, there were many scientific discussions that centered on the cardiovascular risk of nicotine. I was told that nicotine increases heart rate, but also constricts blood vessels, a combination that increases blood pressure. One way to think of it is like increasing the flow of water in your garden hose, then putting your finger over part of the opening. Therefore, Philip Morris's goal for the nicotine analogue program was to find a molecule that would not affect the cardiovascular system, but would mimic nicotine's effect on the brain.

Q: Philip Morris knew in 1980 that nicotine had an effect on the brain?

A: Philip Morris knew about nicotine's brain effects well before 1980. I think the Psychology Research Group was formed in the 1960s, so Philip Morris certainly knew by then that nicotine affects the brain.

Q: What are the brain effects of nicotine that Philip Morris wanted an analogue to mimic?

A: Philip Morris wanted an analogue that would, like nicotine, act as a reinforcing agent and that would induce the same rewarding effect on the brain.

Q: Can you describe what you mean by rewarding effect?

A: Basically, causing the brain to say, "I feel good."

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

A: The practical application of this research could enable a company to remove nicotine from tobacco, substitute the synthetic analogue, and produce a "safer" cigarette that still had the reinforcing effects of nicotine.

Q: How many analogues would you estimate you tested while at Philip Morris?

A: Several hundred.

Q: Did you yourself personally create the analogues?

A: No, they were made – actually synthesized – by organic chemists in another part of the Philip Morris R&D Department. They delivered the analogues to us in liquid form in vials, and we would test how they affected rats' brains and behavior.

Q: Did your research result in the identification of any analogues that had the characteristics sought by Philip Morris?

A: During my tenure at Philip Morris, our laboratory did discover a lead series of nicotine analogues which had met the criterion of reduced cardiovascular effects. We were able to

identify at least two nicotine analogues that met the above-mentioned criteria. One dropped out of contention after testing, so there was basically just one.

Q: What was the name of the promising nicotine analogue?

A: 2'-methylnicotine.

Q: Did the nicotine analogue program exist before you got to Philip Morris?

A: Yes.

Q: Did you have access to the records and research that had gone on in the program before you began at Philip Morris?

A: Yes.

Q: Did you review the files to learn the history and prior work of the program?

A: Yes. For the few months, while the research lab was actually being constructed, I read all the research reports for the analogue program, going back to about 1970.

Q: Did you learn why Philip Morris made it a requirement that any analogue keep nicotine's brain effects?

A: Yes. The entire premise of this research, and all nicotine-related research at Philip Morris, was that people smoke primarily because of nicotine's rewarding effects on the brain.

Q: How did you learn this?

A: From the documents I reviewed, and from discussions with Philip Morris scientists and executives in Richmond and New York.

Q: While you were at Philip Morris, did you ever hear anyone seriously challenge this premise?

A: No.

Q: From your experience at Philip Morris, including your review of research that

occurred prior to your coming to Philip Morris, was nicotine's taste the reason why Philip Morris performed research on nicotine?

A: No. I don't think I ever saw a document about nicotine research while I was at Philip Morris that referred to taste.

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

A: Even before I started working for Philip Morris, some analogues had already been synthesized by the company, and there were ongoing animal experiments. I was responsible for designing and implementing the analogue screening procedures, with the exception of the drug discrimination procedure. This procedure was already being used, but had to be expanded to accommodate the analogue synthesis program. I determined the direction of the laboratory in collaboration with the senior management, specifically Drs. Dunn, Charles, and Osdene.

Q: How many other people performed this work with you?

A: About 3 or 4 at any given time.

Q: Will you please identify the main people who worked with you in the lab performing these studies?

A: Over time, the main people were Paul Mele, Lisa Carron, Ann Allen, Karen Barlow, Jennifer Horn, and Yvonne Dragan.

Q: Did you keep your supervisors apprised of the development of your analogue screening work?

A: Yes. As part of my duties I was responsible for keeping my superiors, Drs. Osdene, Charles, and Dunn, informed of the progress of our laboratory. I discussed the work daily with Drs. Dunn and Charles, and had a meeting with Dr. Charles on a weekly basis to discuss research directions and data, and met with Bob Pages and Tom Osdene probably weekly as well. In

addition, our laboratory was required to write progress reports and outlines of the future directions on the research, including quarterly and annual reports.

In addition, as part of the nicotine analogue program, a core team would meet in Richmond approximately once every six weeks with the senior management to provide oral progress updates. These meetings would be attended by research directors, research managers, project leasers, and Philip Morris's outside consultants to the program – Dr. Leo Abood and/or Dr. Gary Bernston.

Also, as part of a research review held in Philip Morris's New York corporate office during the latter part of 1982, I presented a complete review of the research program to Mr. Millhiser and several other corporate officers.

Q: Who is Mr. Millhiser?

A: To the best of my knowledge, he was either the President or the CEO of Philip Morris USA at that time.

Q: When you say "senior management," to whom are you referring?

A: I'm referring to my supervisors and the senior people in the R&D Department – Drs. Osdene, Dunn, Charles, Seligman, and Hausermann.

Q: Did you also report on your findings to your colleagues in the Research & Development Department?

A: During the first 2 years of the laboratory's existence, we were not allowed to discuss the details of the work being done at the lab. Of course, people knew we were doing research with rats in the building, but we didn't talk about it and people didn't ask. The animals would be brought in at night or in very early morning. And we weren't permitted to discuss our research at any of the research meetings for the first 2 years or so. After that, we did give annual

presentations like the rest of the research department did, but the content of those presentations was restricted to certain subjects.

Q: Were you told not to discuss your animal research with colleagues outside your project?

A: Absolutely.

Q: By whom?

A: Dr. Dunn and Dr. Osdene.

Q: How many people at Philip Morris were aware of the purpose and nature of your animal research?

A: I'm not sure of the exact number. Our reports were restricted access, meaning that only our superiors – people at the Director level and above, and some corporate management in New York – could get copies.

Q: Please take a look at U.S. Ex. 36,135. Have you seen this document before?

A: Yes.

Q: Did you see it while you were at Philip Morris?

A: Yes.

Q: What is it?

A: It is a March 1, 1983 memorandum from Dr. Charles to Dr. Osdene with the subject "Promotion of Dr. Victor J. DeNoble to Associate Senior Scientist."

Q: Does this memorandum accurately describe your work in the behavioral pharmacology lab?

A: Yes.

Q: Turning to the postscript note on the second page, can you please read the first

sentence of that note?

A: It says, "Because of the sensitive nature of Vic's assignment, documentation of much of his work has been restricted to the Director and Vice President level."

Q: Is that consistent with your recollection of the restrictions that were placed on distribution of written reports of your work?

A: Yes.

Q: When your research showed that one of the analogues had promise, what was done with it next?

A: Tests were done to determine whether the analogue was likely to cause the unwanted adverse effects on cardiac activity.

Q: What was this test for cardiac activity?

A: The drug was tested to see if it produced contractions of the guinea pig ileum. This procedure is used to determine if a drug will have cardiovascular effects. At that point, the data would be sent back to my laboratory in Richmond. We would review the data with the nicotine analogue program chemists and if an analogue met the criteria of having nicotine binding effects in the brain but having lower or no cardiovascular liability, we would screen it in animal behavioral tests to determine whether it duplicated nicotine's reinforcing effects in the brain.

Q: Did you personally perform these tests using the guinea pig ileum?

A: No, that was done by Leo Abood.

Q: Who is Leo Abood?

A: Dr. Abood was a scientist at the University of Rochester in New York. He was a consultant to Philip Morris.

Q: What was his role in the Psychology Research Group?

A: Dr. Abood was a biochemist outside the company who was an integral part of the nicotine analogue program. He had discovered that if you placed nicotine directly into a rat's brain, the animal has a particular behavioral response which he called a "prostration syndrome." His research showed that this response was only produced with nicotine-like drugs. He also sat on the committee that worked on the Surgeon General's Reports, so he served as a conduit of information for Philip Morris to keep abreast of the outside scientific world.

Q: Why was Dr. Abood's discovery of the prostration syndrome important to your work?

A: His discovery of the prostration effect gave us an easy way to test whether a compound, like a nicotine analogue, had nicotine-like drug effects in the brain.

Q: Did you and your colleagues in the behavioral pharmacology lab at Philip Morris expand upon Dr. Abood's research on the prostration syndrome?

A: Yes. We located the area in the brain that is primarily responsible for some of nicotine's major effects in the prostration syndrome. This area in the brain is called the vestibular nucleus. This was a significant finding because it allowed us to isolate at least one brain site where nicotine was producing a specific response in the brain.

Q: Was Philip Morris the first to discover nicotine's effects on the vestibular nucleus part of the brain?

A: Yes.

Q: Why was this finding significant?

A: It showed that, like other drugs that make you dizzy, nicotine affected the area of the brain that affects balance and coordination. When people start smoking, they often experience dizziness, a side effect of smoking until they get used to it.

Q: Did you attempt to publish this work while at Philip Morris?

A: Yes.

Q: Were you successful?

A: We published one paper in 1981 describing generally the prostration syndrome in rats injected with nicotine. We then prepared a second paper on our discovery about the particular brain sites responsible for the prostration syndrome in rats. Philip Morris did not allow this research to be submitted for publication.

Q: Dr. DeNoble, I now want to get back to the steps taken in analyzing different analogues at Philip Morris. Who were the chemists with whom you reviewed the data when you received it from Dr. Abood's lab?

A: The chemists who were involved in synthesizing the analogues – Dr. Ted Sanders, Jeff Seeman, Chuck Chavadarin, Henry Seccore – as well as senior management.

Q: In addition to expanding the drug discrimination tests, including testing for prostration syndrome, what else did your lab do for the program?

A: In addition to increasing the capacity of the drug discrimination test and the prostration screen, our laboratory needed to develop a variety of tests that could be used in the characterization of the behavioral effects of nicotine in rats.

Q: How if at all was this work related to the nicotine analogue research you were doing in the behavioral pharmacology lab at Philip Morris?

A: It was the very heart of our behavioral pharmacology work, because these were the tests that would allow us to evaluate how a particular compound, like a nicotine analogue, compared to nicotine in how it affected rats.

Q: Did you develop such procedures?

A: Yes. We eventually developed and used a few different procedures.

Q: We will discuss each of the tests in greater detail, but can you first identify the generic names by which you referred to the different tests?

A: In addition to the drug discrimination and prostration syndrome screens, we developed at least four additional tests. One was a self-administration test, one was a tolerance test, one was a cross-tolerance test, and the last we called a "frustration" test.

Q: We will discuss each of these in turn. Which is the one you developed first?

A: One of the earlier test procedures that we developed was a self-administration test.

Q: How does this test work?

A: Most generally, this tested whether a rat will continue to press a lever to obtain a particular compound, like nicotine, alcohol, or food. If the rat does press the lever, the compound is considered a "reinforcer." In the procedure we developed, an animal can press a lever and deliver a drug solution into its vein. After surgery to give the rat the capacity to receive drug solutions intravenously, the animal is placed inside an experimental chamber and hooked up to an infusion pump. The chamber is equipped with two levers allowing the animal to choose which lever it will press. Pressing one lever has no consequence, but pressing the other lever would activate the infusion pump and deliver a drug solution into the vein. When the rat pressed the levers, programming circuitry would record the response. If a drug solution is a reinforcing agent, then the pressing of the lever which results in the drug being infused into the vein will increase and be maintained by the rat.

Q: What does that mean, the pressing will "increase and be maintained?"

A: It means that the rat will press the lever more frequently to obtain the drug and will keep doing it over time.

Q: Did you invent this type of test?

A: No. Self-administration testing was invented by James Weeks in 1962. Our laboratory at Philip Morris used the same basic procedures that NIDA used to test whether a drug had abuse liability potential.

Q: Had other researchers previously done self-administration testing with nicotine in rats?

A: Yes, there were at least three other publications dealing with nicotine self-administration in rats.

Q: Was there anything different about the self-administration testing you and your colleagues developed compared to previous work?

A: Yes, in two ways. First, prior studies by other investigators outside the company used food inducement conditions which made the analysis of nicotine's reinforcing effects difficult to assess. For example, it was difficult to determine whether nicotine was a true reinforcing agent, or whether it was coupled to another factor in the animal's life such as obtaining food. However, we were able to do the test without food by giving the rat each dose of nicotine in a shorter period. If the rat pressed the lever, instead of getting a dose of nicotine over 11-13 seconds, the rat got that entire dose over 3-4 seconds.

Q: What was the second way in which your rat self-administration testing differed from previous work?

A: We showed that it was the brain effects of nicotine that were responsible for the rats' self-administration by lever pressing.

Q: How did you do that?

A: We did the same self-administration tests, but also gave rats two different kinds of drugs.

One drug, called mecamylamine, blocks the effects of nicotine in the brain. The rats given mecamylamine did not self-administer nicotine. The other type of drug we gave rats, hexamethonium, blocks the peripheral effects of nicotine, but doesn't affect the central nervous system, including the brain. Rats given this drug continued to self-administer nicotine, which showed us that it was nicotine's effects on the brain, not on the peripheral nervous system, that triggered self-administration.

Q: What were the results of these self-administration tests for nicotine that you reported?

A: We found that in the absence of any inducement conditions, nicotine functioned as an weak reinforcer in rats when delivered intravenously. When a nicotine solution was delivered to rats, the pressing of the lever would increase and be maintained until the nicotine was no longer available. We also found that the amount of lever-pressing varied with dose: if we reduced the dose of nicotine dispensed with each press, the rat would press the lever more frequently. We showed clearly that the animal was pressing the lever to obtain nicotine. And we showed that this behavior was caused by the effects on the rats' brains.

Q: What do you mean by a "weak reinforcer"?

A: It means that compared to some other drugs that are self-administered, such as cocaine and amphetamine, rats will not work as hard to get a dose of nicotine.

Q: Does the level of reinforcement as demonstrated by rat intravenous self-administration of a substance automatically predict the strength of that substance as a reinforcer in humans?

A: Not necessarily. In most cases yes, but there are exceptions. Just because something is a weak reinforcer in rats does not necessarily predict what will happen in humans.

Q From your own research, are you familiar with any such exceptions?

A: Yes. Alcohol is a weak reinforcer in rats.

Q: How many rats did you use in this self-administration study?

A: I believe we used a total of 18 rats but not all went through the same manipulation.

Q: In your work and experience in the area of animal research, is that a large number of animals in one experiment?

A: Yes.

Q: At Philip Morris, did you conduct some of the research experiments using fewer rats?

A: Yes. In some studies, we used as few as 4 rats.

Q: Is it considered scientifically valid to use relatively few test animals in an experiment?

A: Yes. The most scientifically rigorous study design is to use the same animal as its own control, where you are comparing the same rat in phases of the research under different conditions. We had some rats involved in the same experiment for six months to a year. In fact, there are reports in the peer-reviewed literature that have used only one animal.

Q: So that the scope of your work is clear, was this self-administration testing intended to test whether nicotine is addictive?

A: No. It was intended to develop a cleaner rat self-administration test to use in testing other nicotinic compounds and other constituents in cigarette smoke, and to figure out whether the self-administration was caused by nicotine's effects on the brain.

Q: Did your results have any relevance to the issue of whether nicotine is addictive?

A: Yes. Self-administration is one of the hallmarks of a drug that has abuse potential. Self-

administration is not alone sufficient to determine whether a drug is addictive, but it is one indicator that the drug is having rewarding brain effects.

Q: While you were at Philip Morris, did you write memoranda that discussed your research in the context of whether smoking or nicotine is addictive?

A: Yes, I wrote memos with other scientists to clarify the nature of some of our research for senior management who were not trained in my area, to explain that because you show that something is a reinforcer as measured by self-administration does not mean that it is addictive.

Q: Did you also write memoranda that reviewed articles and statements by independent public health bodies that concluded that smoking and nicotine were addictive?

A: Yes I did. I was asked to write these reviews by Drs. Osdene, Dunn, and Charles.

Q: What did they ask you to do?

A: They asked me to review the various documents as if I were an outsider in the academic world, and not to review them as a person inside the tobacco industry with additional information.

Q: Were you told why you were asked to write these reviews?

A: Yes. They wanted to have a response ready so that they could prepare somebody if they ever had to respond publicly and they wanted a response that did not include any information obtained from the Philip Morris Research Center.

Q: Getting back to the nicotine self-administration research you conducted at Philip Morris, in what form did you report these results and conclusions?

A: In a variety of forms – including oral presentations, and monthly, quarterly, and annual written reports.

Q: To whom did you report these results and conclusions?

A: I reported them to my immediate supervisors – Drs. Dunn, Charles, and Osdene. Via annual reports, I reported these results to other Directors and Managers in the R&D Department, and to New York management.

Q: You have been shown U.S. Ex. 20,100. Please review the document and tell the Court what it is.

A: It is the Annual Report covering the Behavioral Pharmacology Lab work for 1983.

Q: Did you prepare this document?

A: Yes.

Q: What is the date of the document?

A: June 1, 1983.

Q: Is the standard form in which you and other Philip Morris researchers prepared official reports of your work?

A: Yes.

Q: The last entry in the distribution list indicates 2 copies went to "Central Files." What is Central Files?

A: In my understanding, Central Files was a central storage repository for documents.

Q: To your knowledge, did copies of all of these types of formal reports like annual reports go to Central Files?

A: Yes.

Q: Were scientists required by Philip Morris to send copies of formal reports to Central Files?

A: Yes.

Q: Turning to page Bates number ending in 3891, do you see the title, "Nicotine Self-

Administration Summary?"

A: Yes.

Q: Is this a report on the self-administration research that was contained in the manuscript that you prepared in the fall of 1982?

A: Yes.

Q: And now looking at Section II, on page 11 of the report, Bates number ending in 3899. This section is titled "Effects of Mecamylamine, Hexamethonium and Naloxone on Nicotine Self-Administration." Is this a scientific write-up of the research you just described that involved giving the rats drugs to test whether self-administration was the result of brain effects, as opposed to peripheral nerve system effects?

A: Yes.

Q: Did you seek to publish this research while at Philip Morris?

A: Yes. In the fall of 1982, I submitted a manuscript to Philip Morris on self-administration studies, seeking permission to publish the paper.

Q: What was the review process for your manuscript?

A: It was reviewed by my immediate management, Dr. Charles or Dr. Dunn. Then is was sent to the director of research, Dr. Osdene. I think it also went to other Directors, to the Vice President of R&D, and then to the legal department in New York.

Q: What was the decision on your self-administration paper?

A: In January 1983, I was granted approval to submit it to the journal Psychopharmacology, as well as to present a poster at the American Psychological Association meeting in Anaheim in 1983.

Q: Was the manuscript subsequently peer-reviewed and accepted for publication by

Psychopharmacology at that time?

A: Yes.

Q: Was the manuscript then published after this peer review?

A: No. It was scheduled to be published in September 1983. In July 1983, I was told by Philip Morris management that I would have to withdraw it.

Q: Who told you to withdraw it?

A: Jim Charles and Tom Osdene.

Q: What reason were you given for why you had to withdraw the self-administration paper?

A: I don't recall the particular reason. I think Dr. Charles told me that they felt the work was sensitive, and that New York management was concerned that the timing wasn't right, and that they would try to publish it later.

Q: Did you withdraw the paper in response to the instruction from management?

A: Yes.

Q: Did you proceed to make the presentation to the APA in Anaheim in 1983?

A: No, the presentation never occurred.

Q: Why did your presentation to the scientific meeting not proceed?

A: I was told by management I couldn't present the poster.

Q: Did you ever send the draft manuscript outside of Philip Morris?

A: Yes.

Q: Is that a usual thing for a scientist to do, in your experience?

A: Absolutely. Typically you send the paper to a colleague for a critical review before submitting it to a journal.

Q: To whom did you send the draft manuscript?

A: I sent it to Jack Henningfield.

Q: How did you know Dr. Henningfield?

A: We did overlapping postdoctoral fellowships at the University of Minnesota.

Q: After you were told to withdraw the self-administration paper, did you contact Dr. Henningfield?

A: I can't remember.

Q: Did you ever report the results to people at Philip Morris outside the R&D Department?

A: Yes. I first discussed it at a Richmond meeting in January 1982, and there were people from New York at that meeting. Also, in mid-to-late 1982, I believe, we were notified by our senior management that we were going to go to New York corporate headquarters to give a presentation on the activities of the behavioral pharmacology lab. We were flown to New York, and we gave a presentation to corporate staff.

Q: Which, if any, of your superiors in the Research & Development Department in Richmond went with you to New York?

A: My recollection is that Dr. Osdene, Dr. Charles, Dr. Dunn, and Dr. Pages went.

Q: Were you asked questions about your presentation?

A: I was only asked one question.

Q: What was that question?

A: The question was, "Why should I risk a billion dollar industry on rats pressing a lever to get nicotine?"

Q: Do you remember who asked that question?

A: Ross Millhiser.

Q: What happened at the behavioral pharmacology lab in the period following that meeting?

A: We went back to our work, and in early 1983 several lawyers showed up and started reviewing and copying all of our documents.

Q: Were you told why they were there?

A: Yes.

Q: What reason were you given?

A: We were told that the tobacco industry was under threat of litigation and they were reviewing the research.

Q: Who told you this?

A: Jim Charles and Tom Osdene together.

Q: How long did they stay in your research area?

A: About six months.

Q: Did you ever test the promising nicotine analogue you identified earlier, 2'-methylnicotine, in the self-administration test that you and your colleagues in the behavioral pharmacology lab developed?

A: I have been asked that question before. I thought that we did, but not a lot, although since leaving Philip Morris I have not been able to find it in any of my old research reports that I have seen.

Q: You have been provided U.S. Ex. 35,632 for review. Have you seen this document before?

A: Yes.

Q: What is it?

A: The first page is a cover memo for a progress report on the work of the behavioral pharmacology lab that I wrote to Dr. Dunn in August 1981.

Q: Did you also prepare the attached report?

A: Yes.

Q: **Please turn to page 17 of the attached report, Bates number 1002973603. Under the heading "Nicotine Analogue Self-Administration," the report states:**

> **At present, two experiments are in progress. One is an attempt at direct substitution of 2'-methylnicotine for nicotine in rats for which nicotine serves as a positive reinforcer. . . . Direct substitution of 2'-methylnicotine for nicotine will provide information about the ability of the analogue to substitute for nicotine in a reinforcement system. However, 2'methylnicotine may also be a positive reinforcer that does not directly substitute for nicotine. For that reason, we will also attempt to establish 2'methylnicotine as a positive reinforcer using naive animals.**

Dr. DeNoble, does this report support your testimony that you used some 2'-methylnicotine in self-administration testing?

A: Yes.

Q: What were the results of those studies, if you recall?

A: My recollection is that the animals self-administered the analogue as if it was nicotine.

Q: To whom did you report these results?

A: The same group of supervisors – Drs. Charles, Dunn, and Osdene.

Q: Looking back at U.S. Ex. 20,100, the 1983 Behavioral Pharmacology Annual Report. Please turn to Section V, beginning on page 31, Bates number ending in 3919. This section of the report is titled "Tolerance to Chronic Nicotine Administration: Behavioral v. Metabolic Factors (Written by Paul C. Mele)." Did you participate in this research?

A: Yes, Dr. Mele and I worked together on all projects in the behavioral pharmacology lab. This was an experiment he designed.

Q: Can you please describe what this research was?

A: Dr. Mele designed a study where we would repeatedly inject rats with nicotine over several days and then we would determine how rats responded to the disruptive effects of nicotine.

Q: Did this work have a stated objective?

A: Yes, the stated objective was to try to evaluate the development of nicotine tolerance.

Q: What do you mean by disruptive effects of nicotine?

A: When an animal was injected with nicotine while working on a lever for food, the performance of the animal became impaired.

Q: What were the results of this research?

A: We found that performance impairment decreased over time with the animal's exposure to a given amount of nicotine. That is, after a while, the same amount of nicotine did not affect the rat as much. Also, as time went on, higher doses of nicotine were required to produce the effects that were both quantitatively and qualitatively similar to those effects that were observed earlier in the experiment.

Q: Did the research have a stated conclusion?

A: Yes. We concluded that we demonstrated in the experiments that rats would develop

tolerance after repeated injections of nicotine, and this tolerance was in part behavioral, and in part physiological.

Q: In what form did you record these results and conclusions?

A: In addition to the annual reports, like the one you just showed me, we recorded and reported these results in quarterly reports and oral presentations.

Q: To whom did you present these results and conclusions?

A: Drs. Dunn, Charles, and Osdene, most directly.

Q: Did you and Dr. Mele consider the tolerance study worthy of publication?

A: Absolutely. Previous research had demonstrated nicotine tolerance, but Dr. Mele's experiment was very strong.

Q: Did you ever attempt to publish the results of this research with Dr. Mele while you were at Philip Morris?

A: We requested permission, but were told we could not do that.

Q: Did you ever perform experiments to see whether rats who had received nicotine regularly would change their behavior if the nicotine was taken away?

A: Yes. We performed a few such experiments.

Q: What were your results?

A: We did not observe any changes in behavior once the nicotine was taken away.

Q: Please look again at U.S. Ex. 36,135, the 1983 memo from Dr. Charles to Dr. Osdene recommending your promotion. In the last paragraph on the first page, please look at the sentence that says:

> **Most important for PM and the industry, Vic's studies have shown that abrupt withdrawal of chronic high doses of nicotine will not**

disrupt ongoing schedule controlled performance in rats (i.e., nicotine does not have properties attributed to drugs which produce physical dependence).

Is it your understanding that Dr. Charles is referring to the work you just described, where rats' behavior didn't change when nicotine was taken away?

A: Yes.

Q: Other than in this promotion memo, did Dr. Charles ever tell you that this particular research was important to PM and the tobacco industry?

A: I don't recall him saying that specifically. But it was the only study they encouraged me to publish while I was at Philip Morris.

Q: From your work at Philip Morris, why do you think Dr. Charles would have considered this aspect of your work, quote, "[m]ost important for PM and the industry?"

A: At that time, Philip Morris wanted evidence that nicotine is not addictive. Physical dependence, as indicated by withdrawal symptoms, was considered a classic characteristic of drug dependence.

Q: You testified earlier that the purpose of the behavioral pharmacology laboratory was to study the behavioral and physiological effects of cigarette smoke and components. While you were at Philip Morris, did you ever conduct research on smoke components other than nicotine or nicotine analogues?

A: Yes. In late 1981 and early 1982, we began to investigate the behavioral effects of other smoke components. In our search to discover molecules in cigarette smoke other than nicotine that may have reinforcing properties, we identified a molecule called acetaldehyde.

Q: Was your nicotine analogue testing work still going on then?

A: It was still going on, but not as intensely. After a while, it became hard for us to get sufficient quantity of the analogues to test.

Q: Did Philip Morris already know that acetaldehyde was delivered in cigarette smoke when you identified it as something to look at from a behavioral pharmacology perspective?

A: Yes.

Q: Why did acetaldehyde catch your attention?

A: For a few reasons. First, we noticed there is a lot of acetaldehyde in smoke, almost as much as nicotine. The second reason for my interest was that acetaldehyde is a major metabolite of alcohol. In the 1970s, there were some theories that this metabolite would react in the brain with catecholamines and that the result of this reaction may be a biochemical basis for alcohol addiction.

Q: How did you know about these theories?

A: Since my post-doctoral work involved alcohol research, I learned of it during that time.

Q: Were the theories about acetaldehyde's role in alcoholism ever verified?

A: No.

Q: So what interested you about acetaldehyde in smoke?

A: Unlike in alcohol, where the acetaldehyde is ingested and metabolized to acetic acid by the liver, and thus does not reach the brain quickly, acetaldehyde in inhaled smoke goes from the lungs to the heart and then to the brain, so it reaches the brain more quickly than if ingested.

Q: What sorts of tests did you perform using acetaldehyde?

A: We used a lot of the same tests we did with nicotine and nicotine analogues. Discrimination tests, prostration, interaction tests. Biochemical research was done at the

University of Rochester. And we ran self-administration procedures.

Q: What were the results of this research?

A: None of the discrimination tests or prostration tests gave positive results. However, in the self-administration tests, we found that acetaldehyde was a reinforcer for rats – that is, it caused rats to maintain lever-pressing behavior to obtain it. We also found that when nicotine and acetaldehyde were tested together, they interacted so that the combination yielded stronger results than just the sum of the two compounds when tested separately.

Q: What do you mean by that?

A: Our conclusion from the nicotine/acetaldehyde combination studies showed that nicotine and acetaldehyde acted synergistically. Specifically, access to low doses of nicotine produced positive results, but not particularly strong results; however, the combination of nicotine with low doses of acetaldehyde caused more powerful results than either one of the drugs acting alone.

Q: Did you report the results of your research?

A: Yes.

Q: You have been provided U.S. Ex. 87,091 for review. What is this document?

A: This is a report for the Behavioral Pharmacology lab from 1982.

Q: How do you know that?

A: It says on the first full page of text that "The following are our accomplishments for the period of March 1, 1981 to March 1, 1982."

Q: What is the heading number 3 on page 18?

A: It says "Nicotine-Acetaldehyde Self-Administration."

Q: In that section, on page 19 of the document, ending in Bates number 0464, please read from the fourth sentence in the center paragraph to the end of that paragraph.

A: It says,

> The combinations maintained responding above either compound when presented alone. In addition, the level of lever pressing maintained by (-)-nicotine or acetaldehyde does not exceed vehicle levels. This suggests that a combination of a dose of acetaldehyde and a dose of nicotine that alone would not be reinforcing, is reinforcing when presented together. Further, the joint effect of the combination is greater than an additive effect, suggesting a synergistic relationship.

Q: Now looking again at U.S. Ex. 20,100, the 1983 Annual Report for the Behavioral Pharmacology Laboratory, please read the last two sentences of the first paragraph under the headings "III. Nicotine Acetaldehyde Interactions. A. Self-Administration Studies."

A: It says, "It was shown that the joint effects could not be predicted from a simple additive model, which adds the effect of the first component to that of the second. The effect of the combination deviated from the prediction of the additive model, suggesting a behavioral supraadditive interaction."

Q: Did you give any oral presentations on acetaldehyde and nicotine to any Philip Morris people outside of R&D?

A: In January of 1982, I discussed our research findings on nicotine and acetaldehyde at a meeting held in Richmond. This meeting was attended by Philip Morris corporate officers from New York, including but not limited to Clifford Goldsmith, Shep Pollack, Frank Resnik, and Hugh Cullman. After we presented the nicotine/acetaldehyde combination data, the discussion revolved around whether the data establishing the optimally reinforcing ratios of nicotine to acetaldehyde could be used to develop a product that would initially be marketed in South

America.

Q: Do you know whether Philip Morris ever pursued research or product development to take advantage of your findings about nicotine and acetylaldehyde?

A: I have no knowledge of whether Philip Morris ever used any of our research to change the acetaldehyde or nicotine content in any commercial cigarette.

Q: As with your other research, did you also report the acetaldehyde work in written reports?

A: Yes. In quarterly reports and annual reports.

Q: How did Philip Morris respond to your reports of this nicotine and acetaldehyde research?

A: Philip Morris was very interested and supportive of our research in this area.

Q: Did you try to publish this research?

A: No, Philip Morris considered this very confidential. In fact, in the early phases of our work on acetaldehyde, we were not allowed to call it acetaldehyde, it had a code name, E-44.

Q: To your knowledge, had this research on nicotine-acetaldehyde interaction ever been published in the scientific literature?

A: No.

Q: As a results of your research showing the interaction between nicotine and acetaldehyde, were you asked to do any more research into this interaction?

A: Yes. After the Richmond meeting, Dr. Osdene told me that executives from corporate headquarters in New York wanted to know whether there is an optimal ratio that was the most reinforcing in rats.

Q: Did you subsequently undertake such research in response to the request from New

York?

A: Yes, we also studied which ratios of nicotine to acetaldehyde had the greatest effects. Our data, though preliminary, suggested that an acetaldehyde-to-nicotine ratio of one-to-one had the greatest effects.

Q: Did you report the results of this research to your superiors?

A: During a meeting that I attended in mid-1982, I discussed with Jim Charles and Frank Ryan, who was another member of the psychology smoking group, the data on the reinforcing effects of combining nicotine and acetaldehyde in different ratios. The discussion focused on whether nicotine/acetaldehyde ratios of current cigarettes on the market could be used by the company to predict cigarette sales. Frank ran a computer correlation and was able to predict the best selling cigarettes by looking at the concentration of nicotine and acetaldehyde. Based on the combination of the nicotine and acetaldehyde delivery, Frank was able to predict cigarette sales at above an 80 percent level of accuracy.

Q: Please review U.S. Ex. 35,826. What is this document?

A: It appears to be notes from the June 28, 1982 meeting about nicotine and acetaldehyde that I just mentioned.

Q: About mid-way down the first page, it states that "Data for A + N predict sales at 96% accuracy." Do you agree that is what the document appears to say?

A: Yes.

Q: From your attendance at the meeting, what does "A + N" refer to?

A: Acetaldehyde and nicotine.

Q: Is this statement consistent with your recollection of Frank Ryan's statistical analysis?

A: Yes.

Q: How did Frank Ryan's statistical analysis affect your view of the research?

A: We felt it lent anecdotal credibility to our lab research.

Q: Did anyone at Philip Morris conceive of how to design a cigarette that might be able to exploit the results of any of your findings about nicotine, analogues, or acetaldehyde?

A: In January 1982, I drew what I thought would be a design that would allow for the application and manipulation of analogues of nicotine, acetaldehyde, and flavorings, etc., and would filter out some gas phase compounds.

Q: Did you show your design concept to anyone?

A: Yes, I showed it to Jim Charles.

Q: Please review U.S. Ex. 89,160. Have you seen this document before?

A: Yes.

Q: What is it?

A: It is a handwritten note I wrote, dated January 8, 1982, to Jim Charles, with the drawing for a cigarette filter design I prepared the day after a January 7 meeting.

Q: Did anyone other than Jim Charles ever see the drawing?

A: Yes. I know it was given to Dr. Farone, to Dr. Osdene, Dr. Dunn, and Bob Pages for review. Ian Uydess, another Philip Morris scientist, also saw it, and thought it might be a way to reduce delivery of carcinogens in smoke.

Q: Do you know whether Philip Morris ever pursued your idea to see whether commercial development was possible?

A: I have no idea.

Q: After you reported your research on nicotine and acetaldehyde to your superiors in

New York in mid-1983, did Philip Morris want you to continue doing further research in this area?

A: Yes.

Q: Did they tell you they wanted to keep doing the research in your behavioral pharmacology laboratory in Richmond?

A: In September 1983, they told us about a few different options for how to structure the work. First, they considered having us go to Lausanne, in Switzerland, where there was a Philip Morris research facility, to do the research. They considered trying to set us up at a university, where we could work with Philip Morris from the outside. They proposed firing us and having us establish an independent laboratory in Richmond and contract with Philip Morris, so we would do the work but not as Philip Morris employees.

Q: How did you learn about these possibilities?

A: From discussions I had with Drs. Charles and Osdene.

Q: Did anyone at Philip Morris ever explain to you why they were proposing that the work not occur in Philip Morris's own Richmond research facilities?

A: I was told that the acetaldehyde work was very sensitive and that Philip Morris did not want it to be misinterpreted if it got out, so they wanted to move it out of Philip Morris's Richmond labs.

Q: Did any of these possibilities come to fruition?

A: No.

Q: You have testified that you went to New York around late 1982 to brief corporate management on your work. Did any Philip Morris executives ever come to Richmond to see your research firsthand?

A: Yes. In November 1983, Shep Pollack and Fred Newman came down and toured the lab.

Q: Who are Shep Pollack and Fred Newman?

A: I think that Shep Pollack at that time was the President of Philip Morris USA, and Fred Newman was a top attorney in Philip Morris.

Q: Who else, if anyone, do you recall being present during the tour in Richmond?

A: Paul Mele.

Q: What did Mr. Pollack and Mr. Newman see on their tour?

A: We set up a demonstration for Mr. Pollack, so that he could actually see the animals pressing the lever for nicotine.

Q: Had either Pollack or Newman been present for your presentation in New York?

A: I think that Mr. Pollack may have been present.

Q: Did they ask you any questions about what they saw at the lab during the tour?

A: Shep Pollack asked, "Does this mean that it's addicting?"

Q: What did you tell him?

A: Before I could answer, Mr. Newman told me, "Don't answer that question."

Q: Did Mr. Newman ask any questions?

A: Yes. Mr. Newman asked if the test procedure we were using was the same test procedure that a government agency would use to demonstrate addiction.

Q: What did you tell him in response?

A: I said that it's the exact procedure that NIDA would use to demonstrate abuse liability.

Q: What was his response, if you recall?

A: He said, "Dammit, you've made us into a pharmaceutical company!" and almost literally pulled Shep Pollack out of the lab.

Q: What happened to your research after that visit?

A: We just kept doing experiments. In fact, in January 1984, we were told to expand the labs.

Q: You testified earlier that you left Philip Morris in April 1984. What happened that caused you to leave a few months after being told to expand the labs?

A: They shut down the lab. On April 5, 1984, at three in the afternoon, Dr. Charles 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. Then he said that Philip Morris was discontinuing animal research beginning now. He told me to shut the equipment off; terminate the experiments, even if they were ongoing – which they were; and to kill all the animals. Our passes were deactivated so we couldn't get back into the lab the next day.

Q: Were you told why the lab was being shut down?

A: The response that we got was that the work we were doing was inconsistent with the industry's position in litigation.

Q: Did you kill all the rats?

A: Yes.

Q: After shutting down the lab, did you leave Philip Morris immediately?

A: No. They told me that I could stay with the company, but in a position that was of a much lesser caliber – Jim Charles told me I would basically be a janitor. I was also given the option of leaving the company immediately and receiving a cash settlement. The third option that I was given was that I could remain employed by Philip Morris while I looked for new employment. Based on the options that I was given, I decided to remain on the payroll while I found another job. We were provided offices in a building across the river separate from the lab

facilities. We may have been the only people in the building. And we were provided funds to look for other jobs.

Q: Did you ever reenter the lab again?

A: Yes. The next week, they couldn't open the safe in the lab that contained controlled substances, so I was called back to the research center to open it because I had the combination.

Q: What did you find when you went back into the lab?

A: The lab was gone, everything was gone except for some tables. The equipment was gone, the cages were gone, the animals were gone, all the data was gone. There were sliced wires sticking out of the ceiling where they had been cut.

Q: How long did it take you to find another job?

A: I think I had a job within a week or two, but I did not start that job until September 1984.

Q: Dr. DeNoble, I now want to ask you about some events that occurred after you left Philip Morris. After you left Philip Morris, did you renew attempts to publish any of your research that you had not been permitted to publish while at Philip Morris?

A: Yes. I first sent a note to Dr. Osdene in March 1985, asking for Philip Morris's permission to submit for publication research that we had performed while at Philip Morris. After I sent the note, I called him to discuss the issue.

Q: Why did you seek permission?

A: Because we had signed a confidentiality agreement when we first started at Philip Morris.

Q: Did the confidentiality agreement specify the types of activities to which it applied?

A: Yes.

Q: Did the agreement by its terms expire a certain period of time after the termination of your employment?

A: No.

Q: Have you ever signed a confidentiality agreement from a company other than Philip Morris?

A: Yes.

Q: How did the Philip Morris agreement compare in scope to others that you have signed?

A: It was life long, as opposed to a non-compete clause that expires after a period of time.

Q: Getting back to your request to Philip Morris in 1985, did Philip Morris grant you that permission?

A: No. I got a note from Dr. Osdene in May 1985 saying that Philip Morris had decided not to grant me permission to submit my research.

Q: You have been shown U.S. Ex. 89,144 for review. Is this the May 1985 note you just referred to?

A: Yes.

Q: Did you receive this via the U.S. mails at the Ayerst Laboratories address listed below your name?

A: Yes.

Q: What if anything did you do regarding that research after Philip Morris denied permission to submit it for publication?

A: In early 1986, we sent two papers – the brain sites paper and the self-administration paper – to the journal Psychopharmacology.

Q: Did you get Philip Morris's permission to submit the papers?

A: No.

Q: Why at that time did you submit them without Philip Morris's permission?

A: It's one thing for industry to hold back scientific 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. 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 these kinds of research. So we took the risk.

Q: Did you and Dr. Mele undertake efforts to publish your research about rats' diminished response to nicotine over time after you left Philip Morris?

A: Yes. In 1986 we presented the data on behavioral tolerance development to nicotine in rats before the Federation of American Societies for Experimental Biology in St. Louis.

Q: Did you seek Philip Morris's consent before going?

A: No.

Q: What happened after you gave the presentation?

A: They sent us a letter saying it was a violation of our confidentiality agreement and that they would not tolerate that kind of conduct in the future.

Q: You have been shown U.S. Ex. 44,603. Have you seen this document before?

A: Yes.

Q: What is this document?

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

Q: Who is it from?

A: It is from Eric Taussig, Assistant General Counsel of Philip Morris Companies Inc.

Q: Was it sent to you at your work address at Ayerst?

A: Yes.

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

A: To the best of my knowledge.

Q: The letter states in part:

> **It has come to our attention that you presented a paper at the Federation of American Societies for Experimental Biology in St. Louis on "The Development of Behavioral Tolerance Following Chronic Nicotine Administration." As you are aware, upon your employment at Philip Morris on April 21, 1980, 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.**

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

A: Fear.

Q: Why were you afraid?

A: I knew Philip Morris was desperate to keep this information confidential and I wasn't sure how far they would go in retribution.

Q: After April 1986, did you have any further contact with anyone from Philip Morris or Philip Morris Companies?

A: Yes.

Q: When was your next contact with someone from a Philip Morris company?

A: Later in 1986.

Q: Where did that occur?

A: In August of 1986, Dr. Mele and I spoke at a convention of the American Psychological Association in Washington, DC, about another aspect of our work for Philip Morris. We saw Frank Ryan of Philip Morris there.

Q: If you were afraid after receiving the April 23 letter, why did you speak at the APA convention?

A: We were fearful, but nothing had happened, so we tested the waters again because we thought it was important to get the information out.

Q: Did you have any interaction with Frank Ryan at the APA conference?

A: Yes.

Q: Did you hear again from Philip Morris after that meeting?

A: Yes, I received another letter.

Q: Who sent the letter?

A: Mr. Taussig again.

Q: You have been shown U.S. Ex. 21,916. Is this the second letter you received from Mr. Taussig?

A: Yes.

Q: Is it dated September 10, 1986?

A: Yes.

Q: And it is again from Eric Taussig, Assistant General Counsel at Philip Morris Companies Inc.?

A: Yes.

Q: Did you receive this letter at the New Jersey address written below your name?

A: Yes.

Q: Do you see that the letter states at the top, "CERTIFIED MAIL RETURN RECEIPT REQUESTED?"

A: Yes.

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

A: Yes.

Q: The letter reminds you about Mr. Taussig's earlier letter, informs you that they were aware that you discussed your brain sites work at the APA meeting in Washington, and 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." Do you see that?

A: Yes.

Q: What did you do when you received this letter?

A: I called Mr. Taussig to let him know that we had already sent out two more publications by the time I received this letter.

Q: Did you speak to him on the phone?

A: Yes.

Q: How did he respond to your call?

A: With anger, and lots of it.

Q: What was your reaction, if any, to what Mr. Taussig said?

A: Fear, and lots of it.

Q: What did you do after that call with Mr. Taussig?

A: I called Herb Barry at the journal and asked him what the status of the two papers were. He told me that the first paper, which was the brain sites paper, had already gone to press. It was out, there was nothing we could do. The self-administration paper was in press but it had not gone to proof, so we were able to again, for the second time in three years, unfortunately, tell Herb that he had to pull the paper back.

Q: To this day, has your paper on nicotine self-administration in rats ever been published in a scientific or medical journal?

A: No.

Q: In the end, Dr. DeNoble, after your experience at Philip Morris, do you still feel that during the time you were at Philip Morris the company was committed to making and selling a product that reduced or eliminated the adverse cardiovascular effects of nicotine?

A: Absolutely not.

Q: Why do you say that?

A: I say that because I saw the company choose not to continue research or go further to support research that was making progress toward something they could implement or use to make the product safer.

Q: Thank you, Dr. DeNoble.