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 EXAMINATION

OF

JACK E. HENNINGFIELD, Ph.D.

SUBMITTED BY THE UNITED STATES PURSUANT TO ORDER #471

Q: Please state your full name for the record.

A: Jack Edward Henningfield.

Q: Where do you currently work?

A: I currently work for Pinney Associates in Bethesda, Maryland, as well as The Johns Hopkins University School of Medicine in Baltimore, Maryland.

Q: You have been shown U.S. Ex. 78,534. Do you recognize this to be a copy of your *curriculum vitae* as of December 9, 2003?

A: Yes.

Q: Let's briefly review your educational background. Where did you go to college?

A: I received my undergraduate degree from the University of Minnesota's College of Liberal Arts.

Q: What year did you graduate?

A: I graduated in 1974.

Q: What was your major and degree?

A: I graduated with a Bachelor of Arts degree with a major in psychology and a strong supporting program in biological sciences.

Q: Did you graduate with honors?

A: Yes, *summa cum laude.*

Q: Did you go on to graduate school after graduation?

A: Yes, I did.

Q: Where did you go to graduate school?

A: I attended the University of Minnesota.

Q: Did you receive any type of fellowship?

A: Yes.

Q: What was the nature of the fellowship?

A: I was awarded a United States Public Health Service Predoctoral Fellowship established to train scientists to specialize in drug addiction through the Psychopharmacology Training Program at the University of Minnesota.

Q: What was the focus of your Ph.D. program?

A: It was an Experimental Psychology in the Psychopharmacology Training Program.

Q: What is Experimental Psychology in Psychopharmacology?

A: The training program was a Ph.D.-only program to train scientists specializing in drug addiction. The program combined the departments of Experimental Psychology, or "research psychology," from the Graduate School, with Pharmacology from the Medical School, to provide training for the relatively new field of "psychopharmacology."

Q: What is psychopharmacology?

A: Psychopharmacology is essentially the study of drugs that affect the brain and hence mood and behavior. The major category of these "psychoactive" drugs in which I specialize in my work are the addictive drugs, including nicotine.

Q: Is there any other name for the field of psychopharmacology?

A: Yes, there is. The field is increasingly called "behavioral pharmacology," emphasizing the interaction between drugs and behavior and the behavior-modifying effects of the drugs. Of course, the brain is the physiological target of the drugs, but behavior change, including addictive behavior in some cases, is the main consequence.

Q: What types of training have you received to become a psychopharmacologist?

A: I was trained in psychology, pharmacology, research design and evaluation, drug

formulation and dosing factors, psychiatric diagnosis, and many other aspects relevant to understanding the effects of drugs, including alcohol, amphetamines, cocaine, morphine, nicotine, and sedatives.

Q: Did you perform any research while in this program?

A: Yes, I did.

Q: What type of research did you perform?

A: I performed research on the behavioral and pharmacological factors involved with the self-administration of addictive drugs by rats and monkeys

Q: What do you mean by "self-administration" and "behavioral and pharmacological factors"?

A: Self-administration refers to the behavior of an animal to give itself a dose of drug. For example, in the laboratory, it can be arranged so that pressing a lever will result in an intravenous injection of nicotine or cocaine. Alcohol studies more typically involve pressing levers to provide tiny drinks of alcohol solutions.

Pharmacological factors include the comparison of the physiological effects of different drugs or chemical entities, and the dose, or amount, of the drug administered. Behavioral factors include how the accessibility of the drug – e.g., 1 hour per day versus 3 hours per day versus 24 hours per day – affects the animal's behavior; and how the cost of the drug – e.g., "paying" by pressing a lever ten, one hundred, or a thousand times per dose – influences behavior. Other factors included physiological state such as whether the animals were hungry or had eaten their fill.

Q: Did you focus your research on any particular substances?

A: Yes. It was focused primarily on alcohol and barbiturate sedatives. However, I also

assisted in the conduct of research involving cocaine, amphetamines, morphine-like opioids, marijuana, and other drugs.

Q: When did you complete this Ph.D. program?

A: I completed it in 1977.

Q: What did you do upon completion of your Ph.D. program?

A: I was awarded a fellowship by the National Council on Alcoholism to continue my research on the development and evaluation of animal models of alcoholism.

Q: What is the National Council on Alcoholism?

A: It is a nongovernmental, non-profit organization that supports research, clinical practice, and policy to prevent alcoholism and alcohol abuse, as well as to find more effective treatments for those afflicted.

Q: Did you receive this fellowship after a selective process?

A: Yes. I submitted a research proposal to continue work to develop an animal model of alcoholism involving rhesus monkeys as an extension of my thesis work. I do not know how many proposals were submitted, but I believe I was the only awardee and was told that it had been highly competitive. It was a great honor.

Q: What were duties in that position?

A: I conducted research to extend and validate the monkey model of alcoholism and participated in graduate and postdoctoral seminars on drug addiction and addiction research. I also conducted studies of the importance of the dose of alcohol; the frequency of access; the "cost" of the alcohol to the animals, that is, how hard animals will work to get alcohol; and potentially interactive alterations in diet. I also conducted research on pentobarbital, a barbiturate sedative.

Q: What type of research did you do on pentobarbital?

A: I studied the sedative's potential similarities and differences with alcohol, including the effects of drug dose and cost per dose on self-administration patterns.

Q: What did the studies show about the effects of drug dose and cost per dose on self-administration patterns?

A: Essentially, we found that self-administration of drugs in animals is similar, in key respects, to how humans behave when there are changes in drug dose, as well as the cost to attain the drug. For example, the behavior of self-administration is generally inversely proportional to the amount or dose of the substance given. As alcohol dose or concentration is decreased, the animals take more drinks, and vice versa. This is similar to findings with food studied in other laboratories and reflects the biological effects of drugs and food to modulate the behavior.

Q: Do you mean that the animal or person will maintain a constant intake of drug by compensating for changes in the dose?

A: In actuality, compensation is rarely perfect because as the dose increases, the number of units taken tends to decrease but not in perfect proportion. Therefore, the user generally ends up taking in somewhat more drug, or food if caloric value or meal size is increased. Conversely, as the dose decreases, the number of units taken tends to increase, but compensation is generally not complete and the total intake is less.

Q: Is there a minimum dose required?

A: At very low doses, it may be physically very difficult if not impossible to maintain desired intake or the intake necessary to sustain addiction. For example, in prior studies in which I was involved, when we decreased the alcohol concentration to .5%, the animals were not able to consume enough liquid to sustain reliable behavior and for the observance of the behavioral

effects of alcohol.

Q: Was any of your compensation research published?

A: Yes. My first journal-published paper, which investigated the effects of changing the amounts of alcohol provided to rats by variation of miniature "cups" used to "serve" the alcohol, was accepted with minimal revision by the journal *Pharmacology, Biochemistry and Behavior*. My other studies on the subject were also accepted, published in major international journals and presented at national and international meetings including the College on Problems of Drug Dependence, the International Council on Alcoholism and Addictions, and the International Society Investigating Drugs as Reinforcers.

Q: Have you done any research in humans analogous to your animal studies of alcohol and dose-related changes in behavior?

A: Yes. I have studied whether and how smokers alter their smoking behavior when given cigarettes of varying deliveries of nicotine, by allowing people to take differing numbers of puffs per cigarette, and other manipulations of dose.

Q: What do you call such dose-related changes in smoking behavior?

A: Compensation.

Q: In total, how many research articles have you published that address compensation?

A: The vast majority of my 300-plus research papers and reviews have addressed the issue of responsiveness to changes in the dose of an addictive drug by animals and humans. Many of these studies and review papers have involved either changes in self-administration and/or changes in liking or satisfaction as a function of drug dose. This is because for any addictive drug, the dose level is key to the observed behavior including resulting patterns of behavior. In turn, the importance to people, and even animals, in obtaining their preferred dose, is a major

characteristic of addictive drugs. By contrast, drugs like aspirin or antibiotics are generally taken according to specific instructions and not to adjust any psychoactive mood effect. Thus, it is not surprising that compensation was of such great interest to tobacco researchers or, as we now know, from the previously secret documents of the tobacco industry, how prominent it was to its research and product design efforts.

Q: We will come back to your tobacco compensation research later. When did you complete your National Council on Alcoholism postdoctoral fellowship at the University of Minnesota?

A: I completed it in 1978.

Q: What did you do next?

A: I was recruited to a faculty position at The Johns Hopkins University School of Medicine and Baltimore City Hospital to assist in the development of a research program investigating the behavioral pharmacology of tobacco and nicotine.

Q: Was this generally considered a prestigious position for researchers in the field?

A: Yes. The laboratory was and still is considered one of the nation's lead laboratories on addictive drug research and for evaluating drugs to determine their addictive potential – also called abuse liability, abuse potential, or addiction potential. This laboratory is relied upon by the National Institute on Drug Abuse (NIDA), the Drug Enforcement Administration (DEA), and the Food and Drug Administration (FDA) for its methods development and research findings concerning addictive drugs, and for its work to determine if drugs meet criteria as addictive drugs for the purposes of FDA labeling, and regulation by DEA under the provisions of the Controlled Substances Act. As a result, I saw it as an incredible opportunity and a great honor to be able to join the laboratory where I could learn from the leaders of the field and perhaps even contribute

to their efforts to further the understanding of addiction.

Q: What was the purpose of this research program?

A: To investigate the similarities and differences between tobacco and known addicting substances through studies involving the manipulation of tobacco and nicotine dose, access, cost, and other factors known to affect the intake and effects of prototypic addictive drugs.

Q: What other "addicting substances" did you study as part of this program?

A: My own published studies included those involving alcohol, amphetamine, and barbiturates, and I collaborated on research involving other sedatives, marijuana, methadone, and other drugs.

Q: What, if anything, did you do to help develop this program?

A: I literally helped to build the laboratory test rooms, testing equipment and programming the computer programs to collect the data. I also contributed to assessing how to implement the goals that were described in the grant application, and developing a viable plan for scientific studies. After these activities, I then collaborated in the development, implementation, conduct, analysis, presentation, and publication of research findings.

Q: How would you characterize the work you were doing to develop the tobacco research program?

A: It was challenging, and that was part of the appeal. We were breaking new ground and our work was eagerly received at scientific meetings, with rapid acceptance of papers submitted for publications, and invitations to present our work and publish papers and reviews.

Q: What made the tobacco research program challenging?

A: It was challenging because the measurement and quantification of cigarette smoking behavior and dose intake had not been standardized. As a result, viable objective measures of

intake, such as nicotine absorption, were in their infancy and not readily available, and even the most appropriate technique of manipulating one of the most important pharmacological variables, namely tobacco and/or nicotine dose, was not clear.

Q: How did this lack of established, standardized measures affect the research?

A: This meant that discovering the nature of the relationship between dose and behavior, including potential compensation, one of the fundamental aspects of drug addiction research, was elusive.

Q: How did you study dose manipulation or compensation?

A: We used many techniques to assess the overall pattern and thereby determine the relevance of various factors as well as which techniques were the most valid and relevant to human tobacco use.

Q: What were some of your techniques?

A: One technique involved using cigarettes with different FTC ratings on the assumption that they provided a reasonable correspondence to relative nicotine dosing potential. This was the most common technique by others in the field. We also used ventilated cigarette holders to dilute the smoke to various degrees.

Q: Why did you do this?

A: The most common means of manipulating dose in drug studies is on the basis of the labeled drug doses, so our laboratory, like many others, began their studies of cigarette smoking by selecting cigarettes with different nicotine ratings on the assumption that this was the equivalent of giving drugs of differing doses. By examining the changes in behavior in response to changes in dose, we presumed that we could compare the importance of nicotine in cigarette smoking to drugs in other substance use and abuse. Therefore we used these and other

techniques to adjust the dose of nicotine or smoke and thereby determine the degree to which cigarette smoking resembled a true drug dependency, in which the dose of the substance is one of the factors influencing drug-taking behavior.

Q: What were the other techniques?

A: In addition, we provided research volunteers with opportunities to smoke, and would limit either the number of puffs they could take or the opportunities that they could smoke each day. Finally, we used a series of research cigarettes developed by the National Cancer Institute to attempt to investigate the specific effect of nicotine dose manipulation. However, we were never certain of the integrity of the cigarettes, which had been frozen for many years and needed to be thawed and rehydrated before use.

Q: Did you undertake any other activities related to tobacco use while at Johns Hopkins?

A: I assisted in the review of papers and documents, such as the 1979 Surgeon General's Report.

Q: What was your role there?

A: To assist Dr. Roland R. Griffiths, who had been invited to serve as a reviewer of that Surgeon General's Report.

Q: Did you also conduct research at Johns Hopkins in areas other than tobacco use?

A: Yes. I also led the development of a baboon model of alcohol self-administration which enabled the laboratory to expand its capabilities to investigate the addictive effects of alcohol and other sedative drugs. This laboratory now stands as one of the world's lead laboratories providing data that helps to determine if new medications meet criteria as addictive drugs subject to the legal controls of the Controlled Substances Act.

Q: How long did you stay at Johns Hopkins?

A: I remained in my initial full-time position for 2 years and then became a part-time faculty member in 1980. I have remained in part-time or "adjunct" capacity through the present.

Q: Has your position at Johns Hopkins changed since 1980?

A: Yes, I have been regularly promoted until my present rank of Professor, Adjunct. I have been more involved in the School of Public Health, and I now direct the Robert Wood Johnson Foundation Innovators Awards Program at Johns Hopkins Medical School, which is a program to recognize America's most innovative leaders in efforts to control all forms of substance abuse and addiction, including tobacco. The program also hosts think tanks and other activities involving leading health, science, medical, policy, and regulatory experts in America to address challenges in the control of addiction.

Q: What else did you do when you scaled back to part-time at Johns Hopkins in 1980?

A: I accepted a position at the NIDA Addiction Research Center (which is now called the NIDA Intramural Research Program) on The Johns Hopkins Medical School Campus.

Q: What is NIDA?

A: The National Institute on Drug Abuse, or "NIDA" as it is commonly called, is part of the National Institutes of Health. It is the nation's lead institute dedicated to scientific research on drug addiction and abuse. It works to provide the scientific foundation necessary to reduce addiction-caused death and disease through treatment and advances in national drug control policy. It is one of the three federal agencies that have the official congressionally mandated responsibility for determining if drugs meet the legal criteria as addictive or abusable drugs, and therefore merit what is termed "scheduling" according to the provisions of the Controlled Substances Act.

Q: What is the Addiction Research Center?

A: The Addiction Research Center was established in 1935 in Lexington, Kentucky as the nation's lead laboratory to investigate drug addiction, to develop treatments for drug addiction, and to apply them to evaluate drugs for addiction potential. A major activity was to develop methods to determine whether or not a substance should be treated as addictive, in part to guide the development of less addictive medicines to replace those which were important in medicine but were highly addictive. For example, Addiction Research Center research helped develop buprenorphine to replace morphine for many patients. It also identified delta-9-tetrahydrocannabinol, or THC, as the key psychoactive and addictive chemical in the complex mixture emitted from the marijuana cigarette. Its methods became the backbone, recognized world wide, for assessing addiction potential of drugs, and its methods continue to be relied upon by the World Health Organization, FDA, DEA and other agencies for evaluating drugs for addiction potential – more technically and widely termed "abuse liability." The ARC became the Intramural Research Program of NIDA when NIDA was established in 1972, and moved to the Johns Hopkins Bayview Hospital campus in 1980. Today, it is referred to as the Intramural Research Program (IRP) of NIDA and remains one of the world's lead laboratories investigating drug addiction.

Q: What types of research does the Center perform on drug addiction?

A: The Addiction Research Center conducts a broad range of research, including molecular genetics, animal studies, pharmaceutical development, human studies, clinical drug trials, treatment studies, and brain imaging studies of the effects of drug action and drug withdrawal. It continues to refine methods used to assess the addictiveness of drugs to guide regulatory agencies in decision making regarding known addictive substances and substances for which addiction

risk needs to be determined.

It conducts research on all classes of addictive drugs, including hallucinogens, opioids, stimulants, and sedatives, by routes of administration including injection, oral, smoking, and transdermal.

Q: How did you end up in this position?

A: I was recruited by then-Director Dr. Donald R. Jasinski to take a lead role investigating the possibility that nicotine satisfied the most stringent criteria as an addictive drug. Specifically, he proposed that NIDA apply the same methods and standards to assess nicotine as were used to assess prototypic addictive drugs and new drugs being developed by pharmaceutical companies or found in "street" use.

Q: What was your title?

A: Staff Fellow.

Q: What was the focus of this investigation?

A: It was to apply the methods used in evaluating the addiction potential or "abuse liability" of drugs in humans in my research on nicotine and tobacco.

Q: How many other people did you work with?

A: From about 1979 to 1981, three researchers, including myself, were hired to investigate different aspects of the potential addicting effects of nicotine. In addition to me, Dr. Steven R. Goldberg was recruited from Harvard Medical School to further his work on animal models of nicotine addiction, and Dr. Edythe London was recruited from the National Institute on Aging to investigate brain mechanisms by which nicotine might cause addiction. The three of us were thus expected to spend part of our time on nicotine and to collaborate on research, which we did.

Q: What were the components of this program?

A: Dr. Goldberg's research focused on animal self-administration studies to determine the conditions under which animals would take nicotine. He also studied how patterns of nicotine taking compared to prototypic drugs of abuse such as cocaine, how drug taking could be modified by environmental conditions, and any potential models for therapeutic intervention. Dr. London worked with animals to investigate the brain mechanisms of nicotine action as well as to build the knowledge which eventually led to her human imaging studies of how the brain is altered during nicotine administration and withdrawal.

Q: What was the focus of your particular research?

A: My studies initially addressed the effects of intravenous nicotine in human volunteers with histories of drug addiction in order to determine how nicotine compared to prototypic addictive drugs such as morphine and cocaine.

Q: Were there other research projects connected with this program?

A: Yes, there were. The program also investigated whether humans would self-administer pure nicotine when they were not allowed to smoke, and studied the effects of nicotine gum, patches, inhalation, nasal spray, and other drugs on smoking.

Q: Did you conduct any other drug-related research at NIDA?

A: Yes. I studied a broad range of drugs including but not limited to alcohol, amphetamines, antihistamines, atropine, cocaine, marijuana, methylphenidate, morphine, nalmephine, morphine-blocking drugs, and triazlolam.

Q: Were all of these addicting drugs?

A: No, and those that were varied widely in their abuse liability or addiction potential.

Q: What else did you do as one of the researchers at NIDA with special expertise in the area of nicotine?

A: From 1984 until 1992 I took the lead role in developing the nicotine sections of NIDA's Triennial Reports to Congress on Drug Abuse and Drug Abuse Research. I advised the director of the Addiction Research Center and NIDA on the state of the science of tobacco and nicotine addiction research for reports, testimony before Congress, and recommendations of NIDA to other federal agencies. I was given a lead role in NIDA's review of Surgeon General's Reports on cigarette smoking. I was also given the lead role representing NIDA before the Congress, FDA, and other agencies concerning the addictiveness of nicotine relative to other addictive drugs.

Q: What other agencies did you work with at NIDA?

A: These included the Centers for Disease Control's Office on Smoking and Health, the FDA, the Drug Enforcement Administration, the Department of Defense, and the Federal Aviation Administration.

Q: Why was your work relevant to the Department of Defense and FAA?

A: Units of the Army, Navy, and Air Force recognized that nicotine withdrawal could be a serious factor that could impair performance, thinking, and judgment, particularly on complex tasks involving careful attention, rapid decision making, and short term memory. For the military, this had serious implications for impairing pilot functioning and other critical tasks in fighter and reconnaissance jets and marine craft, including battle and surveillance sections of aircraft carriers. As a result, they wanted to address potential withdrawal-related problems in chronic tobacco users. They requested guidance concerning the time course and impact of nicotine withdrawal on task performance.

The Federal Aviation Administration needed scientific input on a report to guide the potential implementation of a smoking ban in the flight deck or cockpit of commercial airlines.

Q: What did you do as NIDA's representative to these agencies?

A: I provided the guidance they were seeking pertaining to the status and implications of nicotine as an addictive drug. With respect to DEA, I assisted in NIDA's determinations regarding whether or not drugs should be subject to the provisions of the Controlled Substances Act as "controlled substances," which is the DEA's legal definition for addictive or abusable drugs.

Q: What did you do in your role as chief scientific advisor to FDA?

A: FDA needed information pertaining to the possible benefits and addictiveness of nicotine containing medicines such as nicotine gum, patches, and nasal spray. From the early 1980s onward, I assisted the director of the Addiction Research Center and NIDA on their advice to FDA concerning the efficacy of medications for treating tobacco dependence as well as their potential addiction potential. I also served as an ad hoc member of FDA advisory panels and worked with FDA staff in their evaluations of nicotine and other drugs.

I also advised the FDA commissioner and senior staff in the late 1980s on the potential risks and benefits of novel tobacco industry products, including the chewable Masterpiece Tobacs (a chewing gum-like product), a nicotine vapor inhaler called "Favor," R.J. Reynolds' cigarette substitute called "Premier," as well as other products. In 1994, I was designated as NIDA's lead scientist to the FDA on its investigation concerning the addictiveness of nicotine and tobacco.

Q: What did you do as NIDA's lead scientist assigned to the FDA for its investigation of tobacco products in the 1990s?

A: I assisted in the review and analysis of the science concerning tobacco products as addicting drugs and in the review of tobacco industry documents to assess the industry's

knowledge of the addictive effects of cigarettes, as well as its application of this knowledge to develop and market products.

Q: In addition to Defendants' documents, did you also review public statements made by Defendants or their representatives?

A: Yes. For example, I reviewed congressional testimony of tobacco company officials in the 1990s as well as earlier testimony of tobacco industry experts and representatives.

Q: For how long did you hold the position of Staff Fellow when you joined NIDA?

A: For approximately two years until 1982, at which time I was converted to a tenured research pharmacologist position in the Clinical Pharmacology Research Branch

Q: What were your duties in that position as a research pharmacologist?

A: As research pharmacologist I was involved in the conduct and analysis of a wide range of studies concerning the abuse liability and mechanisms of addiction of drugs of abuse. One of my key responsibilities was assessing whether or not drugs met criteria as addictive drugs in order to advise NIDA and in turn, the Secretary of Health and Human Services, regarding whether and how various drugs should be regulated if they had addictive effects.

Q: For how long did you hold that position?

A: I held it until my retirement in 1996. However, while my core position remained research pharmacologist, I was promoted to various positions of broader responsibility over the years. For example, in 1984, I became Acting Chief for the Human Performance Laboratory of the NIDA Addiction Research Center.

Q: What is the Human Performance Laboratory?

A: The Human Performance Laboratory was established in 1984 to assist the Department of Defense in understanding the potential behavioral effects of medications that were used and were

under development through the Tri-Services Military Contract to protect troops from potential attack with neurotoxins. They were most concerned with how drug administration or drug withdrawal might impair troop performance. The priority drugs were those affecting what is known as the cholinergic nervous system and the brain. The cholinergic nervous system is a target for many agents used in chemical warfare and cholinergic blockers are among the protective agents that can be given to troops at such risk. Nicotine also happens to be a drug that affects cholinergic system function.

Q: What type of effects were you studying?

A: Although the initial core mission of the laboratory was to assist the Department of Defense in its efforts to protect its troops and minimize performance impairment through potential chemoprotective agents, the laboratory was an extension of the ARC's long history of evaluating behavior and cognitive effects of drugs and drug withdrawal and that was why the Tri-Services task force turned to the ARC for expertise in method development and drug evaluation. With respect to tobacco and nicotine, the laboratory's efforts filled both NIDA's mission of investigating addictive drugs and the military's growing concerns about the potential performance degrading effects of tobacco use and tobacco withdrawal. Therefore, an important series of investigations supported by the military focused on the behavioral and central nervous system effects of nicotine withdrawal. In particular, our characterization of the types of nicotine, withdrawal-induced performance degradation, the time course of the effects of nicotine withdrawal on attention and mental performance, and how to minimize such degradation through treatment was one of the important services that we provided for the military. This was considered especially important to minimize potential threats to optimal troop performance – particularly on tasks demanding attention, rapid decision making, logical reasoning, and short

term memory.

Q: What drugs did you study?

A: Our studies include potential chemoprotective agents such as atropine, the neurotoxin simulator drug physostigmine, antihistamines, tobacco, nicotine gum, and the nicotine patch.

Q: What were your duties with regard to that study?

A: I was the principal investigator, and was thus responsible for ensuring that the program was relevant, appropriate, and supportive of the military's needs. I was the lead contact and served on the Tri-Services Working Group committee that met several times per year to determine priorities and strategies, and to assess methods and findings. At NIDA, I led the team of investigators to design protocols, implement the studies, develop reports, and disseminate the results.

Q: When were the military-related nicotine studies done?

A: They were performed from approximately 1986 to 1992.

Q: What were your main results with respect to tobacco?

A: The research revealed that onset of cognitive performance degradation and changes in brain function began within a few hours of the last cigarette. This degradation included significant deterioration on measures used by the military to assess performance capability.

Q: How long did these effects last?

A: Effects onset within a few hours after the last cigarette, peaked within 1-2 days, and then began to recede. However, wide individual variability existed, with some people showing better and quicker recovery and other people still impaired at 10 days.

Q: Were these effects reversible?

A: These effects could be reversed or prevented using nicotine gum and nicotine patches, or

resumption of cigarette smoking. Although these studies were not intended to determine if nicotine produced physical dependence and withdrawal – that had already been resolved – they added to information that had filled a critical gap identified by the 1964 Surgeon General's Report in its evaluation of nicotine – specifically, that tobacco withdrawal was physiologically based and could be reduced or reversed by administration of pure nicotine and by routes other than cigarettes smoking.

Q: Did the studies reveal an improvement capability for nicotine?

A: Our studies showed no clear evidence that nicotine or smoking actually improved performance in general, but rather supported the conclusion that performance degradation is part of the nicotine withdrawal syndrome and is treatable with nicotine medications.

Q: Were your results used by the military?

A: They were used to develop strategies for sustaining optimal performance in tobacco-using troops when tobacco can not be used. This included addressing the needs of fighter and reconnaissance pilots on extended missions, and performance of personnel on aircraft carriers and other critical environments in which smoking was restricted.

Q: Were your results used by other agencies or organizations?

A: Yes. Our research findings were considered in the development of the criteria and signs of nicotine dependence and withdrawal in the American Psychiatric Association's Diagnostic and Statistic Manual of Mental Disorders, specifically, in the DSM-III-R, published in 1987 and DSM-IV, published in 1994. In addition, one of my lead investigators, Dr. Stephen Heishman – still at NIDA IRP – and I were included in the development of a 1994 CDC report for the Federal Aviation Administration on tobacco and flight performance to guide a potential strategy to eliminate smoking from the flight deck of commercial airlines.

Q: For how long did you hold the position of Principle Investigator on the Tri-Services contract to NIDA?

A: I served in as Principle Investigator position, either in an acting or formal capacity from approximately 1984 to 1988. However, after this time, I did continue to perform follow-up work pursuant to formal requests.

Q: What was your next position at NIDA?

A: I was appointed Chief of the Biology of Dependence and Abuse Potential Assessment Section of the Clinical Pharmacology Branch.

Q: Please describe your job responsibilities in this position.

A: I was responsible for working with the branch chief and the Director of the Addiction Research Center and collaborating with other section and branch chiefs to develop research focused on furthering the understanding of the biological basis of drug addiction and refining the methods for assessing the "abuse liability" or "abuse potential" – also referred to as "addiction potential" – of substances of known or potential abuse, as well as medications in which abuse liability was either unknown or proposed to be lower than those medications for which they were targeted as potential substitutes. In addition, I evaluated substances and medications for abuse potential of interest to FDA and DEA.

Q: What was relationship of this section to the Clinical Pharmacology Research Branch?

A: The section was administratively located within the Clinical Pharmacology Research Branch.

Q: Did you become Chief of the Clinical Pharmacology Branch?

A: Yes, I did. I became acting chief in 1986 when the former chief of the branch, Dr.

Donald R. Jasinski, retired. I was formally appointed to the position in 1989.

Q: What were your duties in that position?

A: I worked with the chiefs of the three branch sections – Chemistry and Drug Metabolism, Clinical Psychopharmacology, and the Biology of Dependence and Abuse Potential Assessment – to develop research priorities, conduct research, and maintain appropriate accountability to the institute. I remained chief of the Biology of Dependence and Abuse Potential Assessment as well.

Q: How long did you stay in that position?

A: I stayed in that position until my retirement in 1996.

Q: Did you hold any other positions with NIDA during this time?

A: In 1990, I assumed the duties of Coordinator for the Addiction Research Center's Minority Recruitment and Training Program, and I served on many committees related to our research, training, and planning.

Q: In your 16 years at NIDA, did you have any contact with the tobacco industry?

A: Not as a research collaborator, although I occasionally met tobacco industry scientists at scientific meetings. NIDA did receive requests for study reprints in the form of standardized mailed request cards, and was also served with several Freedom of Information Act requests from the tobacco industry. These requests sought an incredibly broad range of information related to tobacco and nicotine.

Q: In addition to the positions you described at Johns Hopkins, have you held any other academic positions in your career?

A: Yes. I was an Adjunct Professor in the Program of Toxicology at the University of Maryland at Baltimore, School of Pharmacy from 1990 to 1993. I also served as an Adjunct

Professor for the Department of Psychology at Coppin State College from 1993 to 1994.

Q: What is the nature of your current teaching duties?

A: I lecture in the Medical School on the pharmacology of tobacco/nicotine and the diagnosis and treatment of nicotine dependence and withdrawal. I also lecture at the School of Public Health on the scientific basis for understanding tobacco addition, treatment, public health, and policy. Finally, I give other lectures as called upon by the University.

Q: Are you currently involved in any research?

A: Yes. I am a collaborator or consultant and advisor at a variety of institutions. These institutions include the Robert Wood Johnson Foundation Tobacco Etiology Research Network, NIDA's Teen Tobacco Addiction Treatment Research Unit, The Johns Hopkins Bloomberg School of Public Health Global Tobacco Institute, and the University of Minnesota.

Q: In what areas have you conducted research?

A: Most of my research has been related to addictive drugs and medications for treating drug addiction. I have performed studies on topics ranging from the drug delivery systems themselves, their pharmacology, mechanisms of action, determinants of use, and how they should be regulated and labeled. Tobacco products have been a specialty area and my research there has included the modification of cigarettes, the variation of ventilation characteristics and nicotine delivery characteristics, and the importance of pH in nicotine absorption from oral tobacco formulations, including gum types and smokeless tobacco.

Q: How many papers have you had published?

A: I have over three hundred publications listed on my CV. These include original research papers, invited reviews and chapters, monographs, and several books that I have written or edited.

Q: How many of these publications have been related to tobacco and nicotine?

A: Approximately two-thirds of my publications are related to tobacco and nicotine.

Q: Were these peer-reviewed articles?

A: Most have undergone the peer-review process.

Q: In what journals have your publications appeared?

A: These articles have appeared in a wide range of scientific, medical, and policy journals, including *Addiction, American Journal of Public Health, Behavior Research Methods and Instrumentation, Clinical Pharmacology and Therapeutics, Current Opinion in Psychiatry, Drug and Alcohol Dependence, Epidemiologic Reviews, Journal of the American Medical Association, Journal of Analytical Toxicology, Journal of the National Cancer Institute, Journal of Pharmacology and Experimental Therapeutics, Lancet, New England Journal of Medicine, Nicotine and Tobacco Research, Psychopharmacology, Tobacco Control,* and the *Yale Journal of Health Policy, Law and Ethics.*

Q: Have you contributed to authoritative books on the subject of on tobacco and nicotine?

A: Yes. I have contributed material on this subject for authoritative books including the *Annual Review of Public Health, Encyclopedia Britannica*, the American Society of Addition Medicine's *Principles of Addiction Medicine*, *Psychopharmacology: The Fourth Generation of Progress,* and various text books for college students and younger students**.**

Q: Have you been invited to contribute on tobacco and nicotine to reports by governmental agencies?

A: Yes, I have contributed to many reports, including Canada's Expert Committee Reports on Cigarette Modification, several U.S. Surgeon General's Reports, The Royal College of

Physicians of London Report: Nicotine Addiction in Britain, many reports of the World Health Organization, and several Reports to the U.S. Congress on Drug Abuse and Drug Abuse Research.

Q: In your years as a health researcher and public health professional, have you received any awards for your work?

A: Yes.

Q: Can you briefly identify a few of particular importance to you?

A: Yes. I was awarded the Commemorative Medal from the World Health Organization, for "work having made a highly significant contribution to the understanding of the addictive nature of nicotine and tobacco, and your pioneering research on the treatment of nicotine addiction," in Geneva in 1991.

I received the 1996 annual award from the American Society of Addiction Medicine for my body of work on the addictive nature of nicotine and tobacco, as well as on the methods available to treat nicotine addiction.

I am also honored to have received the Alton Ochsner Award, which is named after an American surgeon who was one of the first health professionals to observe a relationship between lung cancer and smoking. It is awarded annually by the American College of Chest Physicians for distinguished contributions in the area of smoking and health. I shared this award with Dr. Neal Benowitz, from the University of California at San Francisco, and Dr. Michael Russell from the University of London.

Also, in 2000, I was one of five recipients of a Robert W. Johnson Foundation Innovators Award. This is a monetary award that was modeled in part after the MacArthur Foundation awards, in an effort to bring a comparable level of prestige to the field of substance abuse and

addiction control. I was honored to be nominated for this award by my peers.

I am also especially proud to have received Outstanding Service Awards from the Surgeon General for my work on the 1986 and 1988 Surgeon General's Reports concerning Smokeless Tobacco and Nicotine Addiction, respectively.

Q: Have you ever been invited to consult with any medical authorities on the issues of tobacco and nicotine and addiction?

A: Yes.

Q: With whom have you been invited to consult?

A: Some of the organizations that I have consulted to and or been asked to provide briefings on tobacco science, tobacco product, and tobacco policy issues include the following: the Centers for Disease Control's Office on Smoking and Health, the United States Surgeon General's Office, the Food and Drug Administration, American Lung Association, American Cancer Society, European Union, United Nations, World Heath Organization, Canada's Expert Committee on Cigarette Modification, the National Academy of Sciences Institute of Medicine, as well as members of the U.S. House of Representatives and U.S. Senate.

Q: What has been your involvement with the Centers for Disease Control?

A: I have worked primarily with the Office on Smoking and Health since approximately 1982. I advise it on addiction science issues, develop communications with the agency, review its materials, and serve on advisory panels organized by the CDC.

Q: Please describe your involvement with the Surgeon General's Office.

A: I have worked with several Surgeon General's offices evaluating science and communications. Most of my work has involved assisting on the preparation of the Surgeon General's Reports as a reviewer, contributor, and editor.

Q: What did you do as a contributor to the 1986 Surgeon General's Report on smokeless tobacco?

A: I worked with colleagues at NIDA to draft the section summarizing the evidence that nicotine met criteria as an addictive drug and that smokeless tobacco was appropriately characterized as addictive.

Q: How were you selected as contributor?

A: The Surgeon General's advisory committee's made recommendations as to who should contribute. NIDA was given lead responsibility for the addiction related topic sections. The NIDA director and senior staff then chose several other scientists and me to take the lead on that section.

Q: What was your role in the 1988 Surgeon General's Report titled, "The Health Consequences of Smoking: Nicotine Addiction?"

A: I was one of four scientific editors and a contributor.

Q: Who else served as scientific editors?

A: I shared overall scientific editorial responsibilities with three other scientific editors, Dr. Neal Benowitz, Dr. Neil Grunberg, and Dr. Harry Lando, as well as the general editor, Dr. Ronald Davis, and managing editors Dr. Thomas Novotny and Mr. William Lynn.

Q: Was NIDA involved in the preparation of the 1988 Report?

A: Yes. NIDA was involved in this process.

Q: Why was NIDA involved in this process?

A: It was critical for NIDA to be engaged to assure the highest level of science and credibility from the perspective of an Institute that was not focused on tobacco and nicotine but rather had the nation's highest level of expertise in drug abuse and addiction in general.

Q: How did NIDA participate in the preparation of this Report?

A: NIDA committed the time and resources to support me and other investigators who were eventually called upon to assist in preparation of the Report, as well as to review the report to ensure that it met the highest standards in the field of drug addiction.

Q: What specifically did you do as a scientific editor of the 1988 Report?

A: I worked with the other editors to outline the approach, to select contributors and potential section reviewers, and to develop a process for what we understood would be a massive undertaking spanning many disciplines related to addiction in general and tobacco in particular. We divided subtopics into chapters and chapter sections, each taking a lead responsibility for areas in which we were most expert and could work with other leaders in the field to develop. This involved face-to-face meetings, many telephone calls, and remarkably, no email capacity.

Q: Did the editors such as yourself review every draft section?

A: The subsections and chapters were thoroughly reviewed, condensed, and re-reviewed, looking for gaps, reducing redundancy, and obtaining additional opinions on topics such as the natural history of spontaneous cessation – that is, quitting on one's own – to see how tobacco use compared to alcoholism and heroin addiction. All of the editors reviewed all of the sections, and since we each had differing areas of specialty but all were expert in addiction, this enabled us to check, cross-check, and find omissions that any one of us might have missed.

Q: What was your specialty?

A: Animal and clinical studies of addiction across drugs. Indeed, nicotine and tobacco were only part of my training and experience. In addition, my training and Addiction Research Center experience gave me broad experience in the scientific methods for determining whether or not a given substance meets criteria for an addictive drug or controlled substance.

Q: I will ask you more about how the 1988 Report was prepared later in your testimony. Have you performed any other work for the Surgeon General?

A: I contributed sections to the 1994 Report, titled "Preventing Tobacco Use Among Young People." I have also served as a reviewer for every Report issued subsequent to the 1988 Report. Finally, I have advised the Office of the Surgeon General on potential topics and contributors for other Reports.

Q: Let's discuss your consulting work with Pinney Associates. What type of consulting does Pinney Associates provide?

A: We consult to pharmaceutical companies, health care providers, non-profit organizations, and federal agencies on a broad range of health-related issues. However, our specialty issues involve those issues where science, public health, and policy converge. A major area is that now termed "risk management" by FDA and it is focused on the development, regulation, labeling, control, and marketing of drugs and drug delivery systems so as to maximize public health benefits while minimizing unintended consequences.

Q: What are the issues relating to the development of medications?

A: Pinney Associates works to devise strategies to detect, deter, and respond to inappropriate use of medications, as well as the addiction and diversion potential of those medications.

Q: What is involved in this process?

A: This process includes the evaluation of the drug delivery systems – more specifically, how they are labeled, marketed, and regulated, and what studies are needed to assess their risks and benefits.

Q: What kinds of drugs undergo this process?

A: The process involves a broad range of drugs including analgesics, antibiotics, and

sedatives. It also involves drugs relating to the treatment of Attention Deficit Hyperactivity Disorder (ADHD), drug addiction – especially tobacco – and high cholesterol.

Q: How much of this work is tobacco-related?

A: Approximately one half of Pinney Associates' paid consulting is related to tobacco treatment. Less than one half of my paid consulting time pertains to tobacco.

Q: What percentage of the consultative services relates to medication development?

A: Approximately one quarter of Pinney Associates' efforts, and perhaps a somewhat higher percentage of my time, pertains to medications that are in various stages of development and not yet on the market; however, this varies from month to month and year to year.

Q: You testified that Pinney Associates also provides consultative services relating to cigarette smoking. Please describe this aspect of your work.

A: Pinney Associates advises GlaxoSmithKline Consumer Healthcare on the development of new treatments for tobacco dependence and withdrawal, that is "smoking cessation" and improved labeling and medication product use in order to improve the benefits and further reduce the risks of these products. Pinney Associates works to ensure that product marketing and use is consistent with and supportive of public health efforts intended to reduce tobacco use and tobacco-caused disease, and ultimately to reduce the need for these medications themselves so that they will not be used by anyone who is not in need, and will be used no longer than needed for medically appropriate reasons.

Q: You have testified that Pinney Associates also provides consultative services relating to public health policy. What are the issues relating to public health policy on which Pinney Associates consults?

A: These issues include the appropriate regulation and control of medications for treating

addiction, how to deal with medications possessing addiction potential and other risks, and how medications should be labeled and marketed in order to minimize risks and maximize public health benefits.

Q: Have you ever testified in litigation as an expert with regard to issues dealing with smoking and health and nicotine?

A: Yes.

Q: Please identify the cases in which you were asked to serve as an expert witness in litigation related to smoking and health.

A: I was asked to be an expert on behalf of several States in their litigation against the tobacco companies, including the four initial states that settled with the tobacco companies in 1997 and 1998: Mississippi, Oklahoma, Texas, and Florida. I also served as an expert on nicotine for several other states that never went to trial, including Massachusetts, Wisconsin, Connecticut, and Missouri. Finally, I testified in the State of Washington case that was settled in the middle of trial by the Master Settlement Agreement.

I have also been involved in approximately 20 cases in which individual smokers or groups of smokers have sued one or more of the tobacco companies.

Q: Has the subject of your expert testimony been essentially the same in all of these cases?

A: Yes. Most generally, my testimony has addressed tobacco and nicotine addiction and how the tobacco companies' design of the cigarette contributes to a smoker's nicotine addiction.

Q: In all of the cases in which you have been proffered as an expert, has any Court ever found you not qualified to serve as an expert in the particular subject matters for which you have been proffered?

A: No.

Q: At what rate are you being compensated for your work in this case by the United States?

A: Pinney Associates charges $350 per hour for my work on this case. This is not paid directly to me and does not add to my income.

Q: Dr. Henningfield, I now want to ask you some questions about drug delivery systems. Can the delivery system of a drug influence its potential for addiction?

A: Yes.

Q: In what way?

A: The drug delivery system contributes to the liability of the drug for abuse, addiction, and harmful effects because the method of delivery affects the dose that is delivered, where it is delivered, and the speed with which it is delivered to the body.

Q: So how do people in the drug delivery field, like yourself, take account of this when designing delivery systems for potentially addictive drugs?

A: A major goal of drug delivery system development is to minimize the risks of abuse, addiction, diversion, and attractiveness to young people or people with histories of addiction, as well as to minimize the risk of persons who use the drugs for any reason will become addicted. When the medication is used to treat a medical disorder, addiction to that medication is called "iatrogenic addiction."

Q: What are examples of steps you have used in designing drugs and drug delivery systems to minimize the potential for addiction?

A: In my work, I have advised on the use of physical and chemical measures to slow the speed of initial onset of effects; to extend the duration so the person is not on roller coaster cycles

of onset and offset of effects; to reduce the flexibility of the drug to deliver doses other than those indicated in labeling; and, if the drug is to be taken by mouth, nose or inhalation, to find a balance of sensory characteristics that enable compliance but do not make the drug attractive in its own right. This work also includes advising on labeling and instructions for use, because how a drug is used can often be as important as the drug itself as a determinant of desired and unintended effects.

Q: Have you personally contributed to the development of drugs or medical devices that use aerosol delivery systems to deliver medication?

A: Yes, I have consulted on such systems through Pinney Associates, and several such systems covering more than one drug class are or have been in various stages of development.

Q: What is the goal of drug makers when they design their products for inhalation?

A: The goal is to ensure delivery of the desired dose of the medication to the desired location, such as the nasal passage, throat, upper airway or lung, at the desired speed of delivery, with sensory characteristics to enable compliance, but not contribute to abuse or addiction.

Q: Can you explain the importance of each of these factors you have identified – dose, location, and speed?

A: The dose is the amount of drug that is to be delivered and absorbed. The location of absorption can be determined by how the product is used – for example, nasally, orally, by deep or shallow inhalation – as well as by the size of the particles of the aerosol and the aerodynamic characteristics of the particles. The speed of absorption is critical and can be influenced by where the drug is targeted, the pH, and the concentration of drug in the aerosol.

Q: Why is speed of absorption so important?

A: More rapid drug absorption is generally associated with more addictive effects, more

likely to lead to addiction, and can be more harmful. A major effort of my own laboratory at NIDA in the 1990s was to explore speed of drug delivery because of the apparent implications for understanding the importance of the drug delivery system to addiction to various forms of nicotine, cocaine, and heroin.

Q: Please provide real-world examples that illustrate how speed of absorption affect the addictive potential.

A: In the opioid area, OxyContin is an example of a controlled released pain reliever that was designed to provide effective pain relief for 12 hours or more. Unfortunately, drug abusers discovered that by crushing the tablet and then swallowing it or sniffing it in their nose, also called "snorting" or more technically, "nasal insufflation," they could subvert the slow release mechanism and obtain a rapid dose and thus provide a highly addictive effect. In response to this misuse, the maker of OxyContin has agreed to strong remedial actions to minimize such risks while the company is developing less readily abusable forms of the medicine.

With respect to illicit drugs of abuse, one of the best known examples is cocaine in which the smokable crack form of cocaine greatly contributed to the spread of cocaine addiction by providing a means to self-administer cocaine that provided the drug effect much more rapidly than sniffing and more conveniently than by injection.

I am also co-developer and have co-patented a drug delivery system which we have initially used for nicotine in which control over the speed, amount, and flexibility of nicotine delivery is the core feature of the patent and the physical effects of the product. In brief, by controlling nicotine release and absorption by buffers and other substances in a chewing gum-type of product, we are able to provide substantially more rapid craving relief than the currently marketed nicotine gum but without such rapid speed as to produce addictive effects. Of course,

in our product we are also careful to limit the speed and amount of nicotine delivery so that it will be unlikely to be addictive in its own right or a gateway to addiction in persons not already addicted. The ceiling level of nicotine delivery will be no more than that which will be specified in labeling and advertising and is targeted to minimize addiction risk.

Q: How do the cigarette design efforts of Defendants compare to the efforts of designers of drug delivery systems, like yourself?

A: They use many of the same types of techniques to control the nicotine dose and speed of absorption to the blood stream. However, they use these techniques to increase the ability to obtain more drug than advertised and to increase addictive potential.

Q: From your review of the documents, do the Defendant tobacco companies understand the importance of the different dimensions of drug delivery you have identified – dosage form, location, speed of delivery, and dose – to addiction potential?

A: Yes. The tobacco companies understand the techniques and their effects, have studied nicotine dose control for many decades, and employ many such techniques in their marketed products.

Q: How in your view do cigarettes designed and sold by Defendants reflect that understanding?

A: Cigarettes sold by Defendants facilitate addiction development and maintenance by enabling rapid and readily controlled nicotine delivery. In comparison to cigars, which have mildly alkaline smoke that is not necessary to inhale to provide nicotine absorption, cigarettes have smoke that is easier to inhale, and indeed reinforce inhalation with their high speed of nicotine absorption. In contrast, the nicotine patch is not an attractive dosage form for causing or sustaining addiction, but it is acceptable to people to use for smoking cessation.

I have already discussed the importance of speed of delivery as a determinant of the effects of addictive drugs. With respect to nicotine, absorption of one milligram of nicotine from a cigarette or intravenous injection can produce distinct effects on heart rate and mood. In contrast, the approximately one milligram of nicotine delivered per hour by a nicotine patch produces little discernable effect on mood or heart rate, although it will relieve tobacco withdrawal symptoms. Indeed, Defendants recognized long ago that the cigarette is an optimal vehicle for delivering nicotine.

The dose of drug absorbed is another major determinant of its effects. The approach of the tobacco industry, in light of their understanding that cigarette smokers differ both in the levels of nicotine they self-administer and in their needs for different levels of nicotine to sustain addiction, is to ensure that virtually any major cigarette brand can readily provide any desired dose. The maximum dosages that can be obtained are several times greater than those advertised. Moreover, while smokers in general have become increasingly concerned about the health effects of tar and nicotine, and have increasingly sought brands delivering lower levels over the years, the response of the tobacco industry has been to ensure that virtually any cigarette on the market is capable of providing the nicotine doses needed by smokers to sustain their addictions.

Q: You have been shown U.S. Ex. 46,420 for review. Please describe this document for the Court.

A: This document is a September 30, 1966 report from BATCo titled "Further Work on 'Extractable' Nicotine."

Q: Please identify any portions that you believe support your conclusions about Defendants' understanding of the importance of the rate of delivery.

A: This 1966 document illustrates a sophisticated understanding the importance of

controlling the dose and speed of delivery in the addictive effects of nicotine. For example, in the paragraph headed "Summary and Conclusions" on Bates page 00039306, the document states that "at the present time, it would appear that increased smoker response is associated with nicotine reaching the brain more quickly." Then, on page 00039310, the report states:

> It is generally thought that the physiological response to nicotine in smoke follows the sequence
>
> (i) absorption of nicotine in the various regions of the respiratory system;
>
> (ii) transport of the nicotine by the blood-stream to the brain where it exhibits its physiological effect.
>
> On this basis, it appears reasonable to assume that the increased response of a smoker to the smoke with a higher amount of extractable nicotine may be either because the nicotine reaches the brain in a different chemical form or because it reaches the brain more quickly.

The document then goes on to discuss the issue and to indicate that more research is needed to even more thoroughly understand the factors controlling nicotine delivery.

Q: What is the significance of this document?

A: This document, like many others I have reviewed, clearly reveals that the tobacco industry understood the concept that rate of drug delivery was an important determinant of the effects of nicotine on the brain, and it reveals a sophisticated understanding of this concept that substantially predates NIDA's research efforts on the topic. These efforts on rate of nicotine delivery as a determinant of physiological effects has little, if anything to do with using nicotine for flavoring of the cigarette.

Q: Dr. Henningfield, you have been provided U.S. Ex. 22,967. Please describe this document for the Court.

A: This is a report titled "Motives and Incentives in Cigarette Smoking," prepared by Philip Morris nicotine researcher William Dunn, about a 1972 industry-sponsored conference about nicotine.

Q: Please identify the portions of this document that bear on your conclusions about Defendants' understanding of the cigarette as a delivery device.

A: The report stated, beginning on page 3 of the document, Bates number 2023193288:

> Most of the conferees would agree with this proposition: the primary incentive to cigarette smoking is the immediate salutary effect of inhaled smoke upon body function. . . .
>
> The majority of the conferees would go even further and accept the proposition that nicotine is the active constituent of cigarette smoke. Without nicotine, the argument goes, there would be no smoking. Some strong evidence can be marshalled to support this argument:
>
> 1) No one has ever become a cigarette smoker by smoking cigarettes without nicotine.
> 2) Most of the physiological responses to inhaled smoke have been shown to be nicotine-related.
>
> * * * *
>
> The cigarette should be conceived not as a product but as a package. The product is nicotine. The cigarette is but one of many package layers. There is the carton, which contains the pack, which contains the cigarette,

which contains the smoke. The smoker must strip off all these package layers to get to that which he seeks. . . .

Think of the cigarette pack as a storage container for a day's supply of nicotine. . .

Think of the cigarette as a dispenser for a dose unit of nicotine:

1) It is readily prepped for dispensing nicotine

2) Its rate of combustion meters the dispensing rate, setting an upper safe limit for a substance that can be toxic in large doses . . . .

Think of a puff of smoke as the vehicle of nicotine.

1) A convenient 35 cc mouthful contains approximately the right amount of nicotine.

2) The smoker has wide latitude in further calibration: puff volume, puff interval, depth and duration of inhalation. We have recorded wide variability in intake among smokers. . . .

3) Highly absorbable: 97% nicotine retention.

4) Rapid transfer: nicotine delivered to blood stream in 1 to 3 minutes. . .

5) Non-noxious administration.

Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.

Q: You have been shown U.S. Ex.* 75,975, a compilation of papers from a June 1984 internal BATCo conference. Have you seen this document before?

A: Yes.

Q: Please direct your attention toward the end of the document, Bates page 400993320,

a memorandum written by C.C. Greig, entitled "Structured Marketing Group, Marketing Scenario." What, if anything, in this document bears on your conclusions about the cigarette as a drug delivery vehicle?

A: The first paragraph states:

> Before starting on any future scenario, let us look at what we are currently selling and where and how it has developed.
>
> A cigarette as a "drug" administration system for public use has very very significant advantages:
>
> > 1) Speed – Within 10 seconds of starting to smoke, nicotine is available in the brain. Before this, impact is available giving an instantaneous catch or hit, signifying to the user that the cigarette is "active". Flavour, also, is immediately perceivable to add to the sensation.
>
> Other "drugs" such as marijuanha, amphetamines, and alcohol are slower and may be mood dependant.

Q: What is the significance of these last two documents?

A: These documents show recognition of nicotine as the most important pharmacological component of cigarette smoke, and show extraordinary understanding that the cigarette acts as an effective drug delivery device on many of the key dimensions I identified earlier – dose, form and ease of drug delivery, rate of delivery, absorption, and location.

Q: Turning to a related subject, Dr. Henningfield, have you actually examined the design of cigarettes in the course of your training or professional work?

A: Yes.

Q: In what capacity?

A: In my early research it was due to the interest of our laboratories at Johns Hopkins Medical School and then NIDA to use the cigarette as a means of studying nicotine pharmacology by selecting cigarettes with differing ratings of nicotine delivery. We also attempted to control nicotine and/or tobacco dose by cutting cigarettes in to smaller segments, adding ventilated holders, comparing different brands, and using research cigarettes such as those developed by the National Cancer Institute in the 1970s and those developed by the University of Kentucky Tobacco Research Program. Of course, my colleagues and I also learned and exchanged knowledge at professional meetings where drug addiction research, including research on tobacco and nicotine, was disseminated.

Q: Why is the design of cigarettes important to your research?

A: At the beginning it was primarily due to our interest in controlling nicotine dose in order to indirectly assess the importance and role of nicotine in cigarette smoking. In addition, as it became evident that many factors are important in determining smoking patterns, including cigarette deprivation, tobacco smoke concentration, and puffing at the beginning versus the end of the cigarette, we became more interested in what design features might influence cigarette smoking.

Q: What is your overall conclusion about the role that cigarette design plays in the product?

A: My overall conclusion is that conventional cigarettes are designed to dispense nicotine in addicting doses on the premise that cigarette smoke is a palatable and effective vehicle for nicotine delivery, albeit a highly toxic vehicle.

Q: On what do you base that conclusion?

A: Documents show that nicotine dosing characteristics have been extensively studied and controlled by the tobacco industry. Furthermore, laboratory and real world studies confirm that despite the possibility of substantially altering nicotine delivery from cigarettes, actual nicotine intake varies remarkably little across a wide range of advertised yields. My own extensive reviews of the scientific literature confirm that wide variations in presumed nicotine dose, as suggested by the FTC rating, produce remarkably small changes in actual nicotine intake.

Q: Dr. Henningfield, do you know exactly the relative contribution of different design features to the ultimate delivery of nicotine?

A: No.

Q: Why not?

A: The tobacco companies have a multitude of tools for manipulating nicotine dose and designing the cigarette to enable users to readily obtain addictive doses. These tools appear to be used to different degrees across cigarette brands. Furthermore, for any given brand, the tobacco manufacturers have given the cigarette smoker a multitude of ways to obtain addicting doses of nicotine through the design of the cigarette. Precisely how each design feature affects the ultimate delivery of nicotine and tar to the smoker is very difficult to figure out.

Moreover, I have never worked for a tobacco company, and so do not have a full enough understanding of the roles that all the components and additives play in commercially marketed cigarettes.

Q: In the course of your research, have you studied cigarette filters?

A: Yes.

Q: What do you mean by "study"?

A: I have physically examined filters, learned through published works, expert meetings, and

in my work with the FDA in their investigation of cigarettes to determine if they met criteria as drug delivery devices. I have learned still more in recent years through tobacco industry document analysis.

Q: How would you characterize your understanding of filter design?

A: While I have learned a great deal from my research, there remain significant gaps in my knowledge about filter design.

Q: What are the key gaps?

A: Mainly in that it is not clear what types of filter manipulation techniques are present in specific brands of commercially marketed cigarettes. Furthermore, it is not clear how the many types of variation of filter design features and ingredients interact with the rest of the cigarette to control the relative dosing of nicotine and other substances.

Q: Do these gaps impair your ability to accurately predict the effects of different filter design features on nicotine intake?

A: Yes.

Q: What in your view is the role of cigarette filters, as used by the tobacco company Defendants, in the delivery of nicotine?

A: The cigarette filter is only one aspect of the cigarette that is used to control tar and nicotine dose as well as the relative delivery of tar and nicotine. It is my opinion that tobacco manufacturers have engineered filters to allow smokers to increase or decrease the amount of nicotine that comes out of the cigarette and into the lungs.

Q: What forms the basis for your conclusion?

A: This has been described in tobacco industry documents, both previously secret and public.

Q: Are there different characteristics of a filter that influence its effectiveness?

A: Yes.

Q: What are they?

A: As a function of the nature of the materials, the physical design of the filters, the density of the filter packing, the length of the filter, the porosity of the filter wrapper, ventilation holes and channels, and various potential ingredients, the nicotine yield, and features affecting the palatability and absorbability of the nicotine can be manipulated. For example, the nicotine concentration of the puffs, the ratio of free base nicotine to bound nicotine, and the size of the smoke particles can all be influenced by the design of the filter.

Q: How does each of these parameters affect the delivery of nicotine and other chemical compounds?

A: There are some general findings, but the chemical cocktail can be manipulated in so many ways that it is difficult for someone outside of the tobacco industry like me to understand all of the specific influences of each design variable.

Q: Looking at one factor you identified, particle size, how have Defendants sought to use filters to control the particle size of nicotine in cigarette smoke?

A: The filter density, length, and ventilation can alter the ability of the smoke particles to coagulate and form particles in the brief transit from the tobacco column of the cigarette to the mouth of the smoker. Think of how snowflakes can be very small or very large depending upon the many environmental determinants of coagulation of water vapor particles, and you will understand the basic concept.

Q: Why is particle size important?

A: Physiologically, if the particles are too big they cannot efficiently get into smokers' lungs. If they are too small they may not be transferred across membranes before exhalation. In fact,

large particles cannot efficiently get into the deep alveoli of the lung regardless of how hard you attempt to inhale smoke.

Q: How long have Defendants been aware of the importance of particle size to inhalation and absorption?

A: Documents written as early as the 1950s show that Defendants were aware that particles that were too big would not be readily deposited in the lung.

Q: What is the importance to the Defendant tobacco companies of getting particles into the lungs?

A: The importance of particles getting deep into the lungs is that, as with most addictive drugs in general, the faster the particles are delivered, the stronger their effect. The fastest way to get the drug to the brain is through the lung. It is as fast as or even faster than an intravenous injection.

Q: What are other ways that the Defendant manufacturers have devised to control particle size?

A: In principle, the size is determined by an interaction of the filter factors I have described, in addition to the moisture content of the cigarette, glycerin compounds which readily form absorbable particles when heated appropriately, air ventilation, and the physical and chemical make-up of the filters.

Q: On what do you base this conclusion about Defendants' efforts to control particle size?

A: Their own documents, some of which I have cited in my expert report, and the testimony of one of their own particle experts, Dr. Bradley Ingebrethsen of R.J. Reynolds.

Q: What is another set of design features that you have studied for its capacity to affect

the delivery of nicotine?

A: Three others that are closely intertwined are perforations for increased ventilation, the physical placement of ventilation holes, and paper porosity and composition.

Q: What do you mean by perforation and placement of ventilation holes?

A: These two factors are related and refer to the tobacco companies' use of tiny holes in the filter paper. The holes are created by a perforation process that can be done with lasers, mechanically, or electrostatically, and result in what are known as ventilation holes.

Q: Where on the filter do the tobacco companies place the ventilation holes?

A: Generally on the filter beyond the point where they would be covered by the orifice of the FTC smoking machine.

Q: What do the ventilation holes do?

A: If you view the cigarette as a tube that allows some leakage of air through the paper, but mostly through the tip – that is the end away from the smoker's mouth – then you can see that it is a relatively closed system in which the packing of the tobacco and the nature of the filter determine how hard you must draw or puff on the cigarette to get smoke into your mouth. Placing holes in the filter provides fresh air vents which have several effects: they can make it easier to puff; the smoke becomes more dilute and more cool and therefore easier to inhale; and the chemistry of the smoke is altered because the environment has been altered. Interestingly, diluting the smoke with fresh air reduces the tar and nicotine concentration and hence the level that is measured by smoking machines, but can increase the free nicotine in the smoke by a process called "off-gassing." Thus, the ventilation can also affect the tar-to-nicotine ratio in complex ways that I do not fully understand.

Q: What is the specific effect of ventilation for the smoker?

A: Again, it is difficult for me to link a particular design tool to a particular effect in smokers. In principle, ventilation could contribute to the well documented phenomenon whereby the actual nicotine blood levels of cigarette smoker shows very little relation to machine ratings, except in the most highly ventilated cigarettes that may have 80-90% air ventilation. Smokers of less ventilated cigarettes, such as regular Marlboro, sometimes describe smoking these highly ventilated cigarettes as "sucking on a straw."

Q: Do the ventilation holes affect tar and nicotine levels?

A: They lower the tar and nicotine levels delivered to machines, but not necessarily to people. In fact, they are one of the main techniques of the tobacco companies to achieve lower tar and nicotine levels by the FTC standardized smoking method.

Q: What is the FTC testing method?

A: Since 1967, cigarettes sold in this country have been tested for tar and nicotine yields using a test commonly known as the FTC Cigarette Test Method. The FTC method was adopted by the FTC in the 1960s from a tobacco industry test to provide a relative ranking of nicotine, tar, and carbon monoxide yields from various cigarettes.

Q: How was the FTC method developed?

A: The method was a slight variation on a test first described by the American Tobacco Company in 1936 for the purpose of enabling comparisons of delivery of nicotine and other substances across cigarettes with different blends and types of tobacco in which the design of the cigarettes was similar. Compared to modern cigarettes, cigarettes of the 1930s were relatively simple devices – few employed filters, and perforated filter ventilation was not in production.

Q: What was the original purpose of this test?

A: It was intended to provide specific estimates of tar and nicotine intake, in order to provide

a basis for consumers to select brands of cigarettes that would expose them to lower levels of tar and nicotine.

Q: Were Defendants aware that people smoke cigarettes differently from the machine?

A: Yes. No single test method can accurately replicate individual smoker's behavior.

Q: Did Defendants inform the FTC of this at the time the FTC method was implemented?

A: Yes. In fact, the tobacco companies initially resisted imposition of the testing method and claimed that it would not be accurate. They did tell the FTC that the machine yields would not accurately predict the intake of different smokers, all of whom smoke differently – and even that individuals smoke differently at different times.

However, the FTC was determined to provide what it believed to be useful guidance for consumers who could not quit smoking that would enable them to achieve the goals of less tar and nicotine exposure, as encouraged by the Surgeon General.

Q: At this time, were Defendants aware of the role of nicotine in influencing and maintaining smoking behavior?

A: Yes.

Q: At the time the FTC method was implemented, did Defendants inform the FTC of their view of the role that nicotine plays in smoking behavior?

A: I am not aware of any evidence that the industry informed the FTC that a major reason that the method could yield misleading data was that nicotine addiction would drive smokers to achieve relatively stable nicotine intakes. Without this understanding, I believe that it was not unreasonable for the FTC to conclude that the method would provide meaningful comparative data across cigarette brands.

Q: At the time of the adoption of the FTC test, did Defendants inform smokers directly about the limitations of the FTC ratings?

A: Not that I am aware of.

Q: At the time the FTC adopted the standardized machine test method, or any time since, have Defendants informed smokers directly that their physiological need to obtain nicotine substantially lessens the accuracy of the FTC ratings?

A: Not that I am aware of.

Q: What is the basis for your conclusion that Defendants understand that smokers' need for nicotine contributes to the inaccuracy of the FTC test ratings?

A: There are many documents that show that the companies are aware of compensation, and that smoker compensation is driven by a smoker's need to obtain nicotine. Of course other factors, including palatability of the smoke and tar level, also influence intake so it is not exclusively nicotine, but nicotine is the powerful biological driving force. Some documents make the link directly to the impact of compensation on the accuracy of the FTC machine ratings. For example, U.S. Ex. 34,799 is a June 27, 1978 BATCo memorandum, entitled "Compensation for Changed Delivery," which stated:

> Numerous experiments have been carried out in Hamburg, Montreal, and Southampton within the company as well as many other experiments by research workers in independent organizations, that show that generally smokers do change their smoking patterns in response to changes in the machine smoked deliveries of cigarettes. . . . In general, a majority of habitual smokers compensate for changed delivery, if they change to a lower delivery brand than their usual brand. If they choose a lower

> delivery brand which has a higher tar to nicotine ratio than their usual brand (which is often the case with lower delivery products) the smokers will in fact increase the amounts of tar and gas phase that they take in, in order to take the same amount of nicotine.

Likewise, Joint Ex. 53,394 is a January 30, 1976 BATCo report from the Group Research and Development Center, also entitled "Compensation for Changed Delivery," authored by D.E. Creighton, which stated, at pages 8-11 of the document: "There are may ways in which a smoker can compensate for changes in the design and delivery of a cigarette" including "puff volume, puff number, puff distribution, butt length, puff interval, puff profile, inhalation pattern, and number of cigarettes smoked." Other documents discussed later in my testimony show the Defendants' sophisticated understanding of compensation and its effect on actual dose received by the smoker.

Q: Dr. Henningfield, please review U.S. Ex. 35,744, and identify it for the Court.

A: It is part of a report titled "Human Smoking Habits" and says "PME Research Laboratory, June, 1974.

Q: Do you recognize any of the names handwritten on the top right part of the first page?

A: Yes, I recognize "Dr. Dunn," "F. Ryan," and "HWake" as Philip Morris scientists William Dunn, Frank Ryan, and Helmut Wakeham, respectively.

Q: Please identify any important part of this document for the Court.

A: In the second paragraph on the first page, the document refers to

> A controlled experiment with a group of some 150 smokers who were given at random high and low nicotine delivery cigarettes (0.8 mg/cig and

1.6 mg/cig.) showed the existence of a definite compensation mechanism in the smoke which operates on a per cigarette based (preferred delivery fairly independent of standard delivery) and not a "cigarettes smoker per day basis (5). . . .

Being involved in new product research and being confronted with the fact of the public's awareness of league tables for nicotine and tar deliveries, the problem becomes acute to check objectively if standard analytical smoke yields have anything to do with the preferred smoke yield of the smoker. The experiments which are reported have shown that the answer is an absolute NO.

Q: Please explain the importance of the second paragraph you identified.

A: This is another document among many I have seen showing that the industry understood well that nicotine yields to smokers are not meaningfully related to machine-based estimates, which are based on the FTC method.

Q: You have been shown U.S. Ex. 35,731. What is this document?

A: It is a September 8, 1975 letter from Philip Morris's William Dunn to Stanley Schachter at Columbia University.

Q: Please identify what, if anything, in this document is significant to your opinions.

A: This document indicates significant awareness of compensation and the various specific mechanisms of compensation; further, it suggests that commonly used measures in the field at the time, namely cigarettes consumed, as estimates of nicotine intake were poor measures. Further, the focus on nicotine in the bloodstream contradicts public statements that cigarettes were not smoked for the central nervous system effects of nicotine and rather that nicotine was mainly important for its sensory effects.

The letter states:

> My own prejudice is that the smoker is oblivious at the conscious level to major changes in the composition of his smoke, but not wholly unresponsive. I am more of the belief that we have many ways in which to accommodate to a variable smoke, and perhaps the least of these is to smoke more cigarettes. For too long investigators have relied on measures relatable to the cigarette (number of cigarettes, number of puffs, butt length) as consumption rate indices. True enough, the number smoked is an infallible index of cigarette consumption, but we should be thinking more in terms of <u>smoke</u> consumption. Cumulated puff volume tells us more, but even this is but a measure of smoke taken into the mouth. The ultimate index is how much passes over into the bloodstream, a not so readily monitored phenomenon. We're now looking at the fate of the smoke entering the mouth; how much goes down, how much comes back out, and related behavioral events that we anticipate finding to be dose-regulating mechanisms of remarkable precision and sensitivity.
>
> Thus to accommodate to the 15% reduction in available Marlboro nicotine, the smoker who was getting 50% of the available nicotine over into his blood from the Marlboro delivering 1.3 mg of nicotine into a smoking machine and now must get 59% of what the current Marlboro offers him. He can take bigger puffs, or inhale more from the supply drawn into the mouth (we have varying quantities of residual smoke in the mouth at the end of an inhalation) or for more efficient extraction of the

goodies, he can draw it in deeper or hold it in longer.

Q: From the document, what do you interpret to be the "goodies" that Dr. Dunn refers to as the reason that smokers alter their smoking behavior?

A: The "goodies" seems quite obviously to refer to nicotine, and more specifically, to the nicotine that would enter the bloodstream and be transported to the brain.

Q: You have been shown U.S. Ex. 49,198 for review. What is this document?

A: It is a July 25, 1983 internal Reynolds memorandum from J.H. Robinson to Alan Rodgman, titled "Critique of 'Smokers of Low-Yield Cigarettes Do Not Consume Less Nicotine.'"

Q: Do you know who wrote the article discussed in this memorandum?

A: Yes, Dr. Benowitz.

Q: Was this considered an important article by the independent research community when it was published?

A: Yes.

Q: Why?

A: It was considered very strong evidence that FTC ratings are virtually meaningless predictors of how much nicotine people actually get from smoking cigarettes.

Q: What about this document is significant to your conclusions about Defendants' understanding of compensation?

A: The Benowitz study confirmed what the industry already understood. In fact, as noted in U.S. Ex. 49,198, the writer states that "The paper itself expresses what we in Biobehavioral have 'felt' for quite some time. That is, smokers smoke differently than the FTC machine and may very well smoke to obtain a certain level of nicotine in their bloodstream." Further down the

page, the document states that "the data reported in this paper remind us of the HMSM experiment done with the German Camel and Marlboro cigarettes. While there were certain imperfections in this experiment, you may recall that the smokers apparently obtained almost exactly the same amount of nicotine no matter which of the four cigarettes they smoked. This was one of the first indications that smokers may in fact smoke to obtain a certain level of nicotine in their bloodstream."

Q: How did the Defendant tobacco companies respond to the adoption of the FTC test?

A: Rather than work with the FTC toward procedures that would provide meaningful data, and provide data regarding the actual intake of nicotine from different cigarettes, the tobacco industry began to modify their cigarette designs so as to exploit the particular features of the standardized machine in a way that rendered the tar and nicotine ratings obtained from the machine unrealistically low and thereby defeat the testing method. In their own words, they designed their cigarettes to be more "flexible" dosing systems so that they could advertise that the cigarettes were lower in tar and nicotine delivery, but still deliver tar and nicotine at levels equal to those of "full flavor" products.

Q: Dr. Henningfield, you have been shown U.S. Ex. 21,707 for review. Please describe this document for the Court.

A: This document is a 1984 memo from the research and development group of BATCo that recommended the following course:

> Irrespective of the ethics involved, we should develop alternative designs (that do not invite obvious criticism) which allow the smoker to obtain significant enhanced deliveries should he so wish.

This course was followed despite the fact that an alternative course was possible –

namely, to design cigarettes that would make it more difficult to obtain tar and nicotine levels above the FTC test levels. For example, another BAT memo, U.S. Ex. 21,579, is a May 19, 1981 document that stated: "It was agreed that efforts should not be spent on designing a cigarette which, through its construction, denied the smoker the opportunity to compensate or over smoke to any significant degree."

Q: Has the FTC test been modified at all since its introduction in 1967?

A: No, not beyond minor details of how the protocol is carried out. Of course, the tobacco companies themselves have done the testing since the 1980s, but in principle this is according to the 1960s FTC protocol. Since the test was implemented in 1967, the major companies have strongly resisted efforts to modify the test so as to provide more accurate data, as evidenced by their comments in the NCI Monograph #7, and in 1996 in response to the FDA Proposed Tobacco Rule.

Q: Do lower FTC ratings mean lower tar and nicotine intake for smokers?

A: Not necessarily, but the basis of comparison is important. So-called light cigarettes may deliver several times their rated tar and nicotine level to smokers, while "ultra light" brands may deliver more than 5 times their rated levels. In some studies, the lower rated cigarettes produced lower intake than the more highly rated cigarettes, though all of them produce several times more intake than their advertised levels. In general, the FTC ratings are a very poor measure of actual tar and nicotine intake because the FTC ratings significantly understate the amount of tar and nicotine received by human smokers for the vast majority of cigarettes on the market.

That is one of the problems with the claims of tobacco companies that their cigarettes are "light," "reduced," or "lower" in tar and nicotine. The various compensation mechanisms used by smokers to ensure they get enough nicotine – including smoking more intensively, smoking

more cigarettes, and blocking ventilation holes – (1) result in substantially higher levels of tar and nicotine for the smoker compared to the FTC ratings; (2) often reduce the difference between cigarettes advertised as "light" and those advertised as "full flavor"; and (3) cause actual tar and nicotine delivery to smokers of most cigarettes advertised as "light" to be well within the range of the cigarettes advertised as full flavor. These conclusions are supported by individual government-supported investigators as well as in tests supported by or required by health agencies in Massachusetts, Canada, and England, and by the World Health Organization.

Q: Does the FTC have any control over which cigarettes Defendants advertise as "light" or "ultra light"?

A: No. The FTC does not impose, regulate, or require such terms. How those terms are applied, and on which brands, is entirely up to the tobacco companies.

Q: From your work in pharmaceutical and drug delivery development, have you personally been involved in deciding what information to provide to consumers along with the product in drug labeling?

A: Yes.

Q: Please describe that involvement.

A: I work with companies and I have worked with the FDA on developing communications about how to label and advertise drugs with respect to their drug dosing characteristics as well as how to inform consumers how to use, or not use, products in ways that could increase exposure to the drug and increase the risk of drug abuse.

Q: Drawing on your background and experience in drug labeling and providing information to consumers, have you reviewed how smokers understand information they are given about cigarettes?

A: Yes.

Q: Does that study include how smokers understand the FTC ratings?

A: Yes.

Q: How do smokers understand the FTC ratings?

A: I have examined and relied upon surveys done of smokers about their awareness of the difference between the ratings and what they actually get when they smoke a cigarette. What I have found, not surprisingly, is that (1) smokers are not always familiar with the FTC rating; (2) smokers are aware of whether their cigarettes are "light" cigarettes or regular cigarettes; (3) people believe that "light" cigarettes deliver less tar and nicotine than regular cigarettes; and (4) people believe that regular cigarettes are more hazardous than "light" cigarettes.

Q: How, if at all, do ventilation holes contribute to the discrepancy between the FTC machine and human smoker intake levels?

A The FTC machine smoking test never blocks the vent holes, because the cigarette is not inserted in the machine far enough to be blocked. Human smokers, however, can block the vent holes with their lips or fingers, lowering the ventilation levels. The FTC test registers tar and nicotine yields lower than those that occur if the vent holes are partially or completely blocked. Whatever theoretical reduction in tar and nicotine obtained in machine tests will be negated by the extent to which vent hole blocking occurs during human smoking.

Q: Does ventilation hole blocking happen with actual smokers?

A: Yes.

Q: To what extent does such ventilation hole blocking occur?

A: It varies widely across studies with some studies showing some degree of vent blocking in the majority of smokers and other studies suggesting that fewer than 50% of smokers blocked

ventilation holes.

Q: Why is there such variation?

A: Different studies use different criteria for determining if vent hole blocking occurred, and most studies appear more likely to under-report blocking than to over-measure it. For example, some studies measure lipstick marks or saliva, but do not detect finger blocking. Also, vent hole blocking appears to increase with increased ventilation. There are probably many other factors that alter its frequency and whether it is detected in a particular study. The point is that it happens and can happen without the smoker being aware of doing it or aware of the dire health consequence.

Q: What is the dire health consequence?

A: The well-documented exposure to substantially higher levels of tar and nicotine than advertised.

Q: Why do people block the holes?

A: For various reasons, including nicotine addiction, product design, and failure of the tobacco companies to provide smokers with information that would at least give them a choice. Addiction is the biological force driving smokers to sustain addictive levels of nicotine intake and thereby avoid withdrawal. Product design makes it easy for the smokers to inadvertently cover some or all of the holes some or all of the time.

Q: Do smokers know the ventilation holes exist?

A: Smokers are not informed by the companies, the holes are generally not marked and in fact are concealed on most brands, so while I do not know how many smokers know of their existence and function, I do not believe that smokers generally know of and understand ventilation holes.

Q: Can smokers see the holes?

A: On most cigarettes they are basically invisible to smokers.

Q: Why does it matter that the vent holes are not known or visible to smokers?

A: From a health standpoint, it matters because it means that smokers who don't know about or see the vent holes will cover at least some of the holes at least some of the time, and end up getting more tar and nicotine. Failure to inform smokers about the existence, placement, and role of the ventilation holes is also important because smokers may not realize they are there, and if even if they are aware of the holes they would have no basis for understanding the impact of partial or full coverage of the holes on their tar and nicotine intake.

Nevertheless, the industry blames smokers for compensating and for covering the ventilation holes. There are several ways cigarette manufacturers could have designed their products to avoid ventilation problems, thereby preventing excess particles from getting to the smokers' lungs. Such options range from very simple to very sophisticated.

Q: Is ventilation hole blocking a significant part of compensation?

A: It is for some smokers.

Q: What is the basis for your conclusion about the phenomenon of vent hole-based compensation?

A: Most simply, if ventilation holes exist for the purpose of reducing the delivery of tar and nicotine into the body, as tobacco manufacturers claim, then the ventilation holes should be visible so smokers can see them. This could be easily done by placing stripes on the tobacco rod to indicate where the ventilation holes are placed. Indeed, many cigarette brands have stripes on the filter already, but those stripes do not highlight the vent holes.

A second way that smokers could be informed about how to avoid reducing or blocking

ventilation holes is to provide instructions with the cigarette pack. When it has suited their interests, cigarette manufacturers have provided instructions on products. These have ranged from the small insert provided by R.J. Reynolds for Eclipse to the approximately 40-page instructional booklet provided by Philip Morris for Accord, and informational materials that have accompanied other recent cigarette brands. These examples demonstrate the tobacco companies' capacity to provide information and even usage instructions, beyond package warnings, when it is in their interest.

The instructions that could help smokers avoid covering the vent holes and avoid compensatory smoking in this way, and thereby reduce the likelihood that smokers would obtain higher levels of tar and nicotine than advertised, could probably be much simpler and briefer than these examples. At the most fundamental level, the instructions could state that the cigarette has ventilation holes that give smokers fresh air, and as a result, smokers should not block the holes with their mouth or fingers since this will yield more tar and nicotine than is reflected in the cigarette rating. The smokers would probably also need motivation in the form of a clear warnings that blocking vent holes will lead to higher levels of exposure to tar and nicotine and that this can increase risk.

A third way would be for tobacco manufacturers to place the ventilation holes where the lips and hands are less likely to cover them accidentally. If smokers do not block the holes, they will inhale less tar and nicotine into their lungs from that cigarette.

Of course these are not mutually exclusive options, and "actual use" studies could be done to make sure that the design and instructions are having the intended effect of reducing vent blocking and reducing tar and nicotine exposure, just as such actual use or "field" studies are done with other products with potential safety hazards.

Q: Are Defendant cigarette companies aware that the ventilation holes can accentuate the difference between the FTC and human tar and nicotine deliveries, because the smoker, but not the machine, can block the ventilation holes?

A: Yes.

Q: What is the basis for your conclusion that the companies are aware of this?

A: Internal company documents show they are aware of this. One such document is U.S. Ex. 34,286, a July 19, 1977 Lorillard document titled "By-Pass Filter for Low Tar Cigarettes." The second page of the document states that "Since filters can be designed to deliver more tar (taste) to the smoker than tests indicate, the current tar and nicotine procedure is vulnerable to abuse." Then, on the first page, the memorandum states: "A potentially useful idea would be to develop a filter that delivers a higher tar and nicotine level to the consumer than indicated by a standard tar and nicotine analysis. A practical approach to such a filter might take advantage of the five to ten mm width of the human lip which holds the cigarette versus the two mm width of the dental dam used in the Cambridge filter holder." It goes on to propose using a method of ventilation that "dilutes the smoke" in the machine: "[H]owever, since the air diluting surfaces are covered by the smoker's lips, the consumer would receive a higher level of cigarette taste and smoke impact than expected."

Q: Do you know whether Lorillard ever sold a product using such a design?

A: No.

Q: Did any cigarette maker?

A: Yes.

Q: Which one?

A: Brown & Williamson designed and sold the Barclay brand, which utilized ventilation

channels.

Q: What is the significance of U.S. Ex. 34,286 to your conclusions?

A: It shows both that Lorillard already knew that filters could be designed to exploit the FTC test, and that filter ventilation was one such way to do so. Indeed, while the design described in the Lorillard document was the result of a "brainstorming session," the method of exploiting the FTC test is similar to what vent holes on marketed cigarettes do.

Q: Would smokers be able to block the ventilation holes on a cigarette, wherever they might be placed?

A: Yes, and that is why instructions and actual use studies are needed with any cigarette brand employing ventilation technology to achieve lower yields.

Q: Can you tell manufacturers the best place to put ventilation holes?

A: No.

Q: Why not?

A: First, because I am not a cigarette designer, and second, because wherever the holes are placed they could be blocked deliberately or inadvertently if the smoker is not given the guidance to enable them to avoid blockage and motivation to comply with the guidance. Therefore, I would not represent that the solution to the problem is simply placing the holes in a different place. The solution requires testing the cigarettes so that they are rated according to their maximal possible yields, and/or providing guidance to consumers to instruct them how not to obtain excessive yields, as well as post-marketing monitoring to find out what is happening in actual use to enable correcting any emerging problems.

Q: Let's go back to other cigarette design features that influence nicotine delivery. You also identified cigarette paper porosity and composition as important. What do you mean

by "porosity"?

A: By that I mean the permeability of the paper to allow air to pass through it to fuel the burning and smoldering tobacco.

Q: What effect does porosity have on the smoke?

A: Controlling the porosity is another means of controlling the composition and amount of smoke that is collected by smoking machines by altering the mix of gases, temperature of the burning tobacco, and the speed at which the cigarette is burned.

Q: Does the effect of paper porosity on smoke composition include nicotine levels and particle size?

A: Yes, but I cannot predict exactly how or the magnitude of the effect because I have not done that kind of testing and it is a very complex process.

Q: How do you know that paper porosity can affect the smoke composition?

A: This is basic physics and chemistry. It is not completely unlike the difference between smoldering charcoal in a Weber barbeque kettle with the vents closed versus open. More air provides more oxygen, hotter burning, potentially faster burning, and an altered ratio of chemicals interacting. I can't tell you exactly what difference that specific changes in porosity will make in the nature of the chemical cocktail coming out of the smoke, but I can tell you that it will alter the chemistry of the smoke in ways that could be beneficial, harmful, or both.

Q: What is it about the nature of the cigarette paper composition, other than porosity, that influences nicotine delivery?

A: The companies have a range of choices for what type and composition of paper to use to wrap the filler materials in the cigarette rod. Cigarette paper used on manufactured cigarettes is treated both with chemicals that can affect nicotine delivery and with burn accelerant chemicals

that make the cigarettes burn hotter and faster so as to deliver less tar and nicotine to FTC smoking machines – which puff much less frequently than most people – than they do to people. They are also treated with substances to modify the appearance of smoke and ash, as well as how neatly and evenly the cigarette burns down.

Q: What relevance do smoke and ash appearance have in addiction?

A: It makes the addictive substance more attractive and use of the substance less unattractive, and therefore can contribute to the overall prevalence of tobacco addiction.

Q: What types of chemicals in cigarette paper can affect nicotine delivery?

A: Buffering compounds including alkaline compounds, which make the paper white and keep the ashes a relatively attractive light grey color, and burn accelerants.

Q: What types of chemicals used in cigarette paper are burn accelerants?

A: Sodium and potassium citrates are examples.

Q: On what do you base your understanding of burn accelerants?

A: One source is a book titled "The Design of Cigarettes" by Colin Browne of Hoecsht-Celanese, a company that is one of the primary suppliers of filters to the tobacco companies. The book discusses all aspects of cigarette design, including chemicals like burn accelerants, and their impact on FTC tar and nicotine yields. I have also learned from reports that have addressed the problem of cigarette-caused fires.

Q: Are there any other features of cigarette paper that are relevant to your conclusions about how cigarette design affects the accuracy of the FTC ratings?

A: Yes. Filter overwrap.

Q: What is the filter overwrap?

A: The filter is wrapped with a tough layer of material that resists decomposition when held

in the lips. This material typically extends beyond the filter from a few millimeters to nearly one centimeter and covers the tobacco column, thus attaching the filter segment of the cigarette to the tobacco-filled segment.

Q: What difference does that make in tar and nicotine levels?

A: By convention, the FTC smoking machine stops smoking at a point that is 3 mm beyond the overwrap; that is so the cigarette butt is longer than it would be if the machine smoked all the way to the beginning of the overwrap or all the way to the beginning of the filter.

Q: What does that mean?

A: It means that the smoking machine does not burn all of the tobacco in the cigarette even though cigarette smokers can smoke all of the tobacco.

Q: How much tobacco is this?

A: It varies widely across brands but can easily provide the equivalent of a few extra puffs for the smoker and may account for why studies of smoking show that smokers typically take more puffs than machines take.

Q: Do these puffs differ in any way from the puffs that consume the tobacco farther away from the filter down the cigarette rod?

A: Yes in two basic ways. First, these last puffs provide the smoker with more tar and nicotine laden puffs because with each successive puff on a cigarette, the remaining tobacco and the filter collect tar and nicotine which can, in turn, be released by continued puffing. Second, because the smoke becomes more concentrated in tar and nicotine with each successive puff, just a few extra puffs can mean a disproportionately large increase in tar and nicotine exposure.

Q: Does the amount of tobacco material in the cigarette influence the nicotine delivery?

A: Yes, although the actual amount of tobacco, the blend of the tobacco materials that make

up the filler, the nicotine content, and the smoke-producing potential of a "light" cigarette and its corresponding "regular" or "full flavor" version are not necessarily any different across some brands that differ widely in their machine-rated tar and nicotine deliveries. Thus, although tar and nicotine delivery can be controlled by variation of the amount and blend of tobacco, in practice, a major means by which the differences are achieved is through the use of physical design characteristics and ingredients that can be used to manipulate the amount of smoke delivered to a machine, while leaving the human smoker free to easily obtain substantially higher levels of tar and nicotine than advertised.

Q: On what do you base your testimony that the primary means for achieving differences in tar and nicotine ratings are physical design characteristics?

A: Many of these techniques are now well known, some can be revealed by physical dissection of cigarettes, and some are acknowledged by the tobacco industry trade journal, *Tobacco Reporter*, and by monographs such as Colin Browne's "The Design of Cigarettes."

Q: Dr. Henningfield, have Defendants employed these design features you have mentioned – including filters, ventilation, burn accelerants, and paper porosity – to facilitate nicotine delivery?

A: That is where it gets tricky for a researcher like me. I can see some differences among different types of cigarettes, and I know that the companies have all these design tools at their disposal, including the ones in your question and others like tobacco blending and moisture content. However, I cannot always tell whether or how each of these is used in a particular brand, or whether or how much the variation in a particular tool makes a difference in what happens when a smoker uses that cigarette.

However, it is clear to me that the companies have a wide range of choices in how they

design cigarettes and the different component parts. Since the internal documents make clear that the companies have the ability to reduce or even eliminate all tar or nicotine from a cigarette, and that the Defendants' research showed that the cigarettes they designed had great elasticity of yield, I conclude that the tar and nicotine yields are the result of choices made by the companies. And what other researchers and I have noted is that a result of the cigarette design choices is that smokers of cigarettes from a wide range of FTC tar and nicotine ratings show very similar blood nicotine levels as a result of smoking their cigarettes.

Q: So what conclusion do you draw from that last observation about blood nicotine levels?

A: What I conclude is that virtually all cigarettes – and certainly the brands and styles of cigarettes that comprise well over 90% of the market – are capable of delivering levels of nicotine to the smoker that can create and sustain addiction.

Q: Dr. Henningfield, I have provided you U.S. Ex. 35,250. Please describe this document.

A: This is a March 1976 Philip Morris research report by Barbara Jones titled "Manipulating Smoke Impact in Very Low (Less than 8 mg Tar) Delivery Cigarettes."

Q: What about this document bears on your conclusions?

A: This document generally describes Philip Morris research to increase the "smoke impact" in very low delivery cigarettes by various means. Page 8 of the document, Bates number 1000360948, includes the phrase "as our targeted tar and nicotine deliveries continue to decrease . . . ." This phrase indicates that Philip Morris sets FTC tar and nicotine deliveries for its products, then uses all of the design tools in a way that results in cigarettes that have those "targeted tar and nicotine deliveries."

Q: Dr. Henningfield, what do you conclude is the effect of Defendants' design choices with respect to the FTC ratings?

A: Some of the design choices, like the length of the filter overwrap and ventilation, increase the discrepancy between the FTC machine ratings and yields received by human smokers.

Q: What else can affect the delivery and absorption of nicotine from cigarettes?

A: Chemicals in the tobacco, the paper, and the filter can affect what is called the bioavailability of the nicotine.

Q: What does bioavailability mean?

A: Bioavailability is a measure of how much nicotine is actually absorbed into the blood stream. The way a smoker smokes a cigarette controls how much nicotine is delivered.

Q: What else besides how a smoker smokes affect the bioavailability of nicotine?

A: Other factors include the concentration of nicotine in these particles, how they burn, the burning temperature, the porous nature of the paper, and the level of moisture inside.

Q: Are you familiar with the role of pH on nicotine form and delivery?

A: Yes.

Q: The Court has previously received testimony describing the pH scale, so I will not ask you to repeat that. However, to assist the Court in understanding your testimony, can you please tell the Court the magnitude of the difference between pH units, such as the difference between a pH of 7 and a pH of 8?

A: The pH scale is logarithmic, like the Richter scale, so a solution with a pH of 8 is ten times more basic than a solution with a pH of 7.

Q: What does that mean in terms of the significance of differences in pH?

A: It can mean that a small difference in pH can be very significant in terms of its chemical

and biological effects.

Q: What is your view of whether pH level affects nicotine form and delivery?

A: My view is that pH does affect nicotine form and delivery. It has been well scientifically established that the pH – which is a measure of the acidity or alkalinity – of tobacco smoke affects the rate and amount of delivery and absorption of nicotine over time. It is also well established scientifically that the pH influences the percentage of nicotine that is in the "free" form in smoke – that is, the nicotine molecules that are not electrically charged, are therefore more rapidly transferable across cell membranes and are thus more rapidly absorbed in the oral cavity.

Q: What is the relationship between pH and nicotine?

A: The higher the pH – that is, the more basic or alkaline the smoke – the greater the percentage of nicotine will be in its "free" form.

Q: How can Defendants raise the pH to cause these chemical phenomena to occur?

A: The companies found that adding basic substances – like ammonia compounds, urea, or even other substances to bleach the tobacco paper and keep the cigarette ash a more attractive silvery grey color – might raise the pH and the percentage of uncharged nicotine in the smoke. This can be done by adding substances as ingredients to the tobacco in the cigarette as well as in the processing of the tobacco to make reconstituted tobacco material.

Q: What is the basis for your conclusion about Defendants' knowledge of pH and nicotine in cigarettes?

A: Both tobacco industry and non-tobacco industry research documents show that the pH level affects the amount of nicotine that can be readily released from the tobacco rod of a cigarette and, in turn, readily absorbed into the body of the cigarette smoker. For example, it is

based on clearly described scientific research of the tobacco industry – much of it revealed relatively recently – and its own documents concerning manufacturing practices.

Internal research studies conducted by the tobacco manufacturers reflect that there have been studies where the pH of cigarettes has been manipulated. I have seen the data tables that the tobacco industry presented that showed the increased fraction of free nicotine as a function of the pH of those cigarettes. These documents show a variety of ways of affecting pH by altering the pH of the tobacco material, the paper, wrapping material, the additives, and the filter material. All of these methods of manipulating pH were tested. Apparently, and not surprisingly, the pH of cigarette smoke has been researched not only for its affect on nicotine delivery, but also on how it affects acceptability to smokers. This is sometimes called flavor or sensory characteristics, but acceptability appears to be related to many factors including flavor, smell, throat bite, temperature, and overall mouth feel.

For example, in one case, one of the tobacco companies had developed cigarettes that had a higher fraction of free nicotine by means of the pH manipulation, but the cigarettes were disliked, in part because high levels of nicotine can add harshness and throat discomfort which are considerably masked in modern cigarettes.

Q: What is that example?

A: U.S. Ex. 66,272. This is a June 30, 1980 memorandum from an N.L. Bodenhamer to a Dr. Glock at American Tobacco. The document states that when different levels of "alkaline metal salts" were sprayed on a tobacco blend, the sprayed cigarettes had a "harshness and biting" taste compared to the unsprayed blend. The author stated that this harshness "suggested that more nicotine had transferred to the smoke, with the 5% being more harsh than the 2%."

Q: What do you interpret this document to mean?

A: It indicates that the companies confirmed that adding bases to tobacco blends increased the amount of nicotine transferred to the smoke, and that too much nicotine makes a cigarette harsh. Also, their own study showed that while quantitatively it is a very small amount, the relative increase from 2% to 5% produced a harsh biting taste.

Q: Is this harsh nicotine effect unique to cigarettes?

A: No.

Q: Please give the Court an example involving nicotine.

A: The Nicotrol vapor inhaler approved by the FDA for smoking cessation.

Q: What is the basis of your knowledge concerning that product?

A: I was one of the consultants to its developer, Pharmacia, in Sweden in the 1980s and early 1990s, and I have done my own tests with the product, as well as an early prototype that was briefly marketed as a tobacco substitute called Favor.

Q: What happens when people use this product?

A: They obtain very low concentrations of nicotine vapor per "puff," typically less than one-tenth the amount of nicotine per puff from a cigarette. But even these very low levels of nicotine produce a side effect that limits compliance with product use – namely throat burn – because the harsh sensory effects of nicotine are not masked by tar and the cocktail of substances present in modern cigarette smoke.

Q: You stated just above that the harshness of nicotine is "masked" in modern cigarettes. How is that done?

A: By control over humidity, and by ingredients such as glycerol, chocolate, menthol, and other substances added to the cigarette.

Q: Dr. Henningfield, you have been provided U.S. Ex. 59,993, a December 16, 1971

Liggett memo titled "Development of a Cigarette with Increased Smoke pH." Have you seen this document before?

A: Yes.

Q: What part of this document bears on your conclusions about Defendants' research to use pH to manipulate nicotine?

A: The last paragraph on the first page states:

> Increasing the pH of a medium in which nicotine is delivered increases the physiological effect of the nicotine by increasing the ratio of free base to acid salt form, the free base form being more readily transported across physiological membranes. We are pursuing this project with the eventual goal of lowering the total nicotine present in smoke while increasing the physiological effect of the nicotine which is present, so that no physiological effect is lost on nicotine reduction.

Q: What is the significance of this passage?

A: This document provides a strong indication, in the context of other documents I have reviewed, that Defendants were attempting to deceive smokers by developing cigarettes that would test lower in machine tests, which is what should happen if they lowered the total nicotine present in the smoke, while increasing the amount or impact of the nicotine which is actually absorbed by the smoker.

Q: You have been shown U.S. Ex. 22,077. What is this document?

A: It is a document titled "Handbook of Ammonia Technology" from Brown & Williamson.

Q: Please identify the passages, if any, that support your testimony as to B&W's understanding of the chemical capabilities of ammonia.

A: The document describes different types of ammonia technology in use at BAT companies, and states:

> Within the blend, AT [ammonia technology] can be applied to any component. However, it has been shown that the ammonia will migrate to other blend components. Also, the component with the ammonia applied will tend to scavenge nicotine from other blend components. It is best to apply the AT to a component low in alkaloids, such as stems or reconstituted tobacco. This will set up an exchange where the ammonia will transfer to leaf blend components, and nicotine will transfer to the low alkaloid component. Without going into detail, this is a desirable occurrence, and increases smoke nicotine transfer efficiency.

Q: What does "smoke nicotine transfer efficiency" mean?

A: It can mean several things, but here I believe it refers to the transfer of nicotine from the tobacco into the smoke which would make it available for inhalation.

Q: What does this document tell you about B&W's understanding of ammonia's effect on nicotine?

A: It shows that they understood the effect from the physical chemistry level, as well as the potential effect to enhance the addictive effect on the smoker.

Q: Let me return your attention to U.S. Ex. 21,707, the 1984 memo from BATCo titled "R&D Views on Potential Marketing Opportunities" that you discussed earlier. What about this document bears on your conclusions about cigarette design and nicotine?

A: On the first page, the document states that "Nicotine is the key pharmacological component of cigarette smoke." Then, at the top of the second page, the memo states: "Another

area of importance is the exploitation of physical and chemical means to increase nicotine transfer, ie to increase the effective utilisation of nicotine."

Q: A handwritten notation on the first page states "NOT FOR CIRCULATION." If it wasn't circulated, why do you consider the document important?

A: This is another of the many, many documents I have seen across the companies which illustrate that they understood the critical importance of nicotine in cigarette smoking, that the importance was not nicotine in the mouth but nicotine that can be absorbed into the bloodstream, and that they understood that these were means of manipulating the addictive effects of nicotine.

It is also a reminder to me that while the leading independent nicotine addiction researchers and research centers in the 1970s and early 1980s were conducting research to determine if nicotine was critical to smoking and addictive, the tobacco industry already was conducting its research and product design predicated on the conclusion that nicotine was the critical pharmacologically addicting component of cigarette smoke. The tobacco companies had advanced to questions concerning the practical application of that knowledge, to develop cigarettes that they could advertise as lower yielding without reducing their actual nicotine delivery or addictive effects to smokers.

Q: Dr. Henningfield, you have been provided U.S. Ex. 20,807 for review. What is this document?

A: This B&W document is titled "Ammonia Technology Conference Minutes, Louisville, Kentucky, May 18-19, 1989."

Q: Why is this document is important to your conclusions?

A: Its frank and detailed understanding of how ammonia can be used to manipulate the dosing capability of cigarettes and contribute to attracting and retaining cigarette smokers

indicates the focus of the industry on keeping smokers smoking, attracting and retaining smokers, as well as using sophisticated techniques of dose manipulation to achieve these ends.

It also indicates an effort to comprehensively understand the use of ammonia compounds in cigarette manufacturing as tools to increase nicotine transfer from the tobacco to the smoker, as well as to sensory characteristics and palatability of the smoke.

Q: Are these chemical concepts associated with pH limited only to cigarettes?

A: No. These concepts are not unique to tobacco-delivered nicotine. They are understood and employed by pharmaceutical companies to control the bioavailability of many drugs, including nicotine in nicotine-delivering medications. It is a well established, scientifically effective means of dose control for certain substances, in particular substances in which variation of pH within physiologically tolerable parameters affects the fraction of drug transferred across membranes of the mouth and throat. Therefore, it is not surprising that a company seeking to increase nicotine impact would employ such techniques.

What is remarkable is that the tobacco industry would now deny that such a technology could affect nicotine bioavailability, and instead assert that it only employs these chemical additives to produce better tasting cigarettes. Frankly, even if the effects were eventually shown to be of lesser magnitude than they expected in the 1970s, it does not change the fact that the companies were operating on the understanding, drawn from their own experience and internal research, that the central nervous system effects of nicotine were critical to smoking and that nicotine was addictive, and that they employed sophisticated pharmacological techniques to manipulate nicotine with the intent of increasing its "impact" or "kick," to use their terms.

Q: Can you please identify some of the documents on which you rely for your conclusion that Defendants understood the effect of pH on nicotine delivery, and identify

what in the documents supports that conclusion?

A: Yes. There are many documents from Defendants that show they researched and understood this relationship between pH and nicotine, including many such documents from Lorillard from the 1970s and 1980s. These include:

- U.S. Ex. 34,194 – This is a May 4, 1976 Lorillard internal memorandum titled "Nicotine Augmentation Project (NAP)." This is a summary of the project, and there are many documents about different types of research undertaken as part of this project. This document confirms on page 4 that "[i]t has been reported in the literature, and verified by experiments here that air dilution of cigarette smoke results in up to 40% higher nicotine delivery than might be expected by conventional construction." The next page, under heading number 4, states: "it is known that the higher the pH of the smoke is (i.e., the more basic), the more nicotine exists in the free form. Free nicotine has a greater physiological effect, and it is this effect we want to achieve without sacrificing taste. We know many successful competitive products have higher smoke pH than Lorillard products."
- U.S. Ex. 56,759 – This is a June 30, 1977 document titled "RL Enrichment Project." It discusses adding nicotine to Lorillard's reconstituted leaf, or RL. It states: "If by increasing the pH of the slurry to just short of producing a harsh smoke, one would increase the pure nicotine content for a given nicotine concentration; hence, by changing the pH from low to high one can use less nicotine to achieve the same impact. . . . I think it is an important and worthwhile product because it gives us precise control over nicotine contents in all our products."
- Joint Ex. 34,191 – This is a June 16, 1976 memorandum to Dr. A.W. Spears, who was

Lorillard's Research Director, concerning Lorillard's "Nicotine Augmentation Project." In the last paragraph on the second page, the document discusses research on "altering smoke pH to deliver more free nicotine without an adverse taste effect." It also states, on the middle of the third page, "It is known that air dilution increases the pH of smoke and increases the nicotine/tar ratio." This is important because it shows that Lorillard was aware of different ways to alter pH to produce more free nicotine – not just by adding chemical bases like ammonium compounds.

- U.S. Ex.* 56,265 – This is another research document indicating Lorillard's work on ways to elevate free nicotine levels by increasing pH. In this December 6, 1983 document, a researcher reported adding a basic substance, an "aryl alkyl amine," to the filter of a cigarette. The reported result was "increased smoke pH and a six-fold increase in free nicotine while mainstream nicotine . . . remained almost unchanged." The researcher noted that the patent for such a filter "claimed increased smoke pH, free nicotine concentration and physiological impact."
- Similar discussions and conclusions within Lorillard about the greater relative physiological impact of free nicotine in the throat and chest, the role of increased pH in increasing the amount of free nicotine, and various design methods for influencing smoke pH, can be found in U.S. Ex. 34,200, 34,217, 34,220, and U.S. Ex. 34,203.

Q: Dr. Henningfield, in U.S. Ex. 34,203, let me direct your attention to page 11, Bates number 00044933. The two-column table at the bottom of the page "compares various cigarette brands in terms of their pH's." What is the pH listed for Marlboro cigarettes?

A: The listed pH is 6.98.

Q: Do pH determinations for cigarettes depend on the measurement technique used?

A: Yes, to a significant degree.

Q: You have been shown U.S. Ex. 50,608, for review. Please describe this document, and identify any passage that bears on your conclusions.

A: This is a December 16, 1971 R.J. Reynolds memorandum titled "VANTAGE Cigarettes – Attempted Flavor Improvement Through Increasing the Free Nicotine Content of the Smoke." On the first page, the document states, "Under Project 2820, an attempt was made to increase the free nicotine content of the VANTAGE smoke by adding selected salts to the VANTAGE blend." It goes on to list several different salts that were added during the tests.

Q: Let me ask a follow-up question about this document. On the next page, the document states: "It is recommended that additions of salts added to tobacco investigated in this work not be continued." If the research recommended that the work be abandoned, why do you consider this document important?

A: This document struck me as being parallel to the type of research my colleagues and I have done to improve the nicotine gum we have developed. We tried many different chemical buffers and additives to find the right combination that would allow us to provide our targeted dose delivery in a way that allowed rapid absorption in a controlled way.

Q: Are there other documents you want to identify on this topic?

A: Yes.

- U.S. Ex. 20,820 is an undated RJR memo discussing "ammoniation" technology. It defined "ammoniation" as "the rea[c]tion of ammonia with tobacco to produce ammoniated tobacco which smoke differently and produce a milder smoother flavored smoke." It goes on to state:

> Philip Morris began using an ammoniated sheet material in 1965 and

increased use of the sheet periodically from 1965-1974. This time period corresponds to the dramatic sales increase Philip Morris made from 1965-1974. . . . RJR introduced ammoniated sheet material in the Camel filter product in 1974. Better market performance was indicated in the subsequent years. . . . Ammoniated sheet was introduced into the Winston KS product in 1979. Market tests indicated significant product improvement. . . .

Product Characteristics:

- Milder smoother taste
- Higher smoke pH . . .
- Cleaner taste with more free nicotine
- Stronger physiological impact with less harshness . . .

This document shows that the tobacco companies actually used ammonia to change the characteristics of their marketed brands, and understood both the chemistry and that one of the positive attributes was more free nicotine and greater physiological impact.

- A document from RJR is U.S. Ex. 23,051, a December 4, 1973 document from Frank Colby, an RJR scientist, to the Director of Marketing Planning. In discussing an idea for a new cigarette, Colby stated that older higher delivery cigarettes "delivered more 'enjoyment' for 'kicks' (nicotine)," and added that for the proposed new cigarette, "any desired additional nicotine 'kick' could be easily obtained through pH regulation."
- A September 21, 1976 Reynolds document, U.S. Ex. 85,467, titled "Product Characterization Definitions and Implications," states on the second-to-last page that "[t]he pH also relates to the immediacy of the nicotine impact. As the pH increases, the

nicotine changes its chemical form so that it is more rapidly absorbed by the body and more quickly gives a 'kick' to the smoker."

- U.S. Ex. 35,106 is an October 1974 report from T.R. Schori in Philip Morris's Behavioral Research Laboratory titled "Smoke Impact from a Psychologist's Vantage Point." This document contains extensive discussion about smoke pH and nicotine. It states on page 2, Bates number 1000048538, that, when assessing "smoke impact" of nicotine, "The important factor . . . is not the amount of nicotine in the smoke per se but rather it is the amount of free nicotine in the smoke, which determines degree of smoke impact." On the next page, under the section headed "Importance of pH," the researcher states:

> The way in which nicotine is typically reported can be misleading. This is due to the manner in which nicotine determinations are made. For instance, cigarettes X and Y may both be reported to deliver (based on the standard smoking machine tests) 2 mg nicotine/cigt. However, a given smoker may actually inhale much more free nicotine from cigarette X than from cigarette Y. . . . The amount of free nicotine available to the smoker is determined by the degree of alkalinity (or pH) of the smoke as well as own degree of alkalinity . . . . As pH increases, there is a corresponding increase in the proportion (of the total possible free nicotine) that is actually liberated.

Q: Referring your attention to page 4 of U.S. Ex. 35,106, Bates number 1000048540, the first paragraph states:

> **As pH increases, there is a corresponding increase in the proportion (of the total possible free nicotine) that is actually liberated (Handy**

> **1971). This relationship is depicted in Figure 1. From this figure, it can be seen that as pH increases from 5½ to 9 there is a very sharp increase in the proportion of nicotine that is freed. Thus, it should be possible to increase smoke impact by artificially increasing pH.**

Is the statement that "there is a very sharp increase" in the percentage of free nicotine as pH increases from 5½ to 9 consistent with your understanding?

A: Yes.

Q: Now looking at the next page, Bates number 1000048541, there is the chart referred to in the sentence quoted in the last question. It describes the percentage of free nicotine for a given pH of the main two types of tobacco, bright and burley. What does this chart say about the relationship between pH and percentage of free nicotine?

A: It shows that percent of free nicotine goes up sharply as pH rises.

Q: Does the rate of increase in free nicotine percentage show a "very sharp increase" as pH rises for actual cigarettes?

A: Yes.

Q: Dr. Henningfield, the discussion of pH and free nicotine in this document, U.S. Ex. 35,106, is concerned with "impact," what the writer defines as "the individual's awareness of the presence of smoke in the back of the throat." How if at all does this affect your conclusions about the role of free nicotine?

A: It is consistent with my opinions. First, it confirms Philip Morris's sophisticated understanding of the relationship between pH, nicotine, and the greater physiological effect of free nicotine. Second, smoking addiction is a complex behavior, and there is certainly a sensory component to it as well. This document focuses on that sensory component. Moreover, if there

is more free nicotine in the smoke, there will be more free nicotine being inhaled into the lungs as well as hitting the back of the throat. As has been shown in human and animal studies, including studies in which I have been directly involved, the reinforcing properties of nicotine are mediated in the brain, not in the peripheral nervous system.

Q: Dr. Henningfield, what impact would the industry documents and information you have identified about cigarette design, and the effects of different design features, have had on your work as an addiction researcher had you seen them during your tenure at NIDA?

A: If I had seen the tobacco industry documents prior to the time when I did, it would have made a tremendous difference to me as a scientist and public health professional. Specifically, I, like many other scientists, conducted research with the assumption that tar and nicotine intake at least generally corresponded in dosing characteristics to FTC ratings.

Q: Does the public health community still hold that assumption?

A: No. However, it was not until the studies of Dr. Benowitz and others in the early 1980s that it became apparent that the main determinant of nicotine intake was not the FTC machine yield, but rather, how many cigarettes were smoked regardless of the FTC ratings.

Q: What was Defendants' position after the Benowitz study?

A: At least through 1996, in its comments on the FDA's proposed tobacco rule and in the 1995 NCI Expert Committee meeting on this topic, the tobacco industry continued to maintain that there was a meaningful relationship between FTC rating and tar and nicotine exposure.

Q: Why was the issue of the FTC rating's accuracy important to independent researchers like yourself?

A: It is important to understand that the drug dosage level that gets into the body is one of the basic determinants of the effects of the drug, and is a basic tool in studies of the

pharmacology of a given drug. We were familiar with the work of Armitage and others that described "fingertip dosage control" over cigarette dose. However, scientists such as myself used cigarettes with different FTC ratings as a means of attempting to manipulate nicotine dosing in our research. Although we were aware that this system was not perfect, we did not understand that it was fundamentally flawed and offered little useful information about actual dose.

Q: What was the impact of these flaws in the FTC rating system on public health policymakers?

A: Perhaps the most critical problem to public health stemming from the FTC method was that the FTC and the Surgeon General believed that the FTC rating system was giving consumers a way to pick between cigarette brands that was actually related to their expected tar and nicotine exposure levels. Of course, the FTC and Surgeon General also understood that the system was not perfect, but they, like researchers, believed that the system was providing consumers with information as to differences that would be meaningful in terms of biological effects and health.

Q: Dr. Henningfield, have you ever heard Defendants suggest that a good analogy for the FTC tar and nicotine ratings is the gas mileage ratings given for cars?

A: Yes.

Q: Do you consider that analogy to be an appropriate one?

A: No.

Q: Please explain why not.

A: First, if you have two cars with significantly different mileage ratings, for both of them, it shows a city driving range and a highway. So first, the mileage rating is not giving a single number and it's definitely not giving you a best-case number. It's giving you a range. And then people understand that riding the gas and driving a lot faster is going to give you poorer gas

mileage. And we know through that rating system that if you buy a car with a better gas mileage rating, virtually no matter how you drive it, you're going to get better mileage than a car with a worse rating. But in cigarettes, by just subtle changes in the way you smoke and things that most people don't even know about, the ventilation and the channels and the burn accelerants and all these different tricks, makes those two cigarettes look the same. Thus, for example, when humans smoke Marlboro cigarettes or when machines are programmed to smoke more intensively than in the FTC tests, Marlboro Lights can yield approximately twice as much nicotine as the Regulars are claimed to deliver by the standard FTC method. Marlboro Ultra Lights can deliver three times their advertised rating and most of the Carlton brands can deliver seven or more times their advertised rating.

Q: How does the FTC ratings for cigarettes compare to the nutritional information on labels for packaged foods or the labels for pharmaceutical products?

A: They are totally different because food labels, such as that for cheese sold by Altria's Kraft subsidiary, or Low Fat Oreos, accurately explain to the consumer what they will receive if they consume the serving size identified on the label. The labeling tells you what a serving size is, such as how many slices of cheese or cookies, so you know the amount upon which the nutritional information is based. If you eat the listed serving size of Kraft cheese, you will receive the amount of fat, protein, calories, etc., listed on the label. The only way to get more than the labeled amount is to consume more than the serving size. This is the same as with dose information provided with drugs approved by the FDA – the label typically tells you the maximum dose of drug you can obtain if you consume the labeled amount.

By contrast, as I have explained, the advertised FTC tar and nicotine ratings for cigarettes bear very little relation to the actual dose a smoker can and, in most instances, does receive from

smoking that cigarette. The inaccuracy in the FTC ratings is especially pronounced for cigarettes sold as "light" or "low tar" by the tobacco companies. This discrepancy is especially serious because it is in the direction of more toxins than advertised.

Q: What impact did the poor understanding of the meaning of the FTC ratings, and the flexibility inherent in cigarette design features have on addiction and smoking researchers?

A: Effectively, this sent researchers on wild goose chases, even to the point of questioning the role of nicotine in smoking, because researchers' attempts to manipulate nicotine dose – by switching brands of cigarettes – often had erratic or smaller than anticipated effects.

Q: Are you aware of the public statements about pH, ammonia, and nicotine that Defendants have made more recently?

A: Yes.

Q: What is your understanding of what Defendants say in their current public statements about this subject?

A: Essentially, that ammonia compounds do not significantly increase free nicotine, nicotine delivery by the cigarette, or nicotine levels likely to be produced in the bloodstream of smokers.

Q: How do you respond scientifically to these more recent statements by Defendants about pH, ammonia, and free nicotine?

A: The statements are inconsistent with their own research and conclusions, their use of massive quantities of ammonia in cigarette making, and the conclusions of the FDA and CDC investigations. The statements are not rejected by recent tobacco industry studies on this topic since those studies are of uncertain validity and relevance to real world cigarette smoking of actually marketed cigarettes.

Q: Can you give the Court an example, outside the context of cigarettes, tobacco, and

nicotine, in which manipulation of pH occurs intentionally to affect the bioavailability of a drug?

A: Reacting cocaine salts with alkaline compounds such as sodium bicarbonate can produce the more addictive free-base form.

Q: Returning to tobacco and nicotine, is free nicotine more addictive than bound nicotine?

A: Molecule for molecule, the addictiveness of nicotine is not changed; rather, the pH of the tobacco or cigarette smoke is an important determinant of how many molecules reach the bloodstream and over how much time. Therefore, the addictiveness of the chemical entity, nicotine itself, is not necessarily changed; however, the overall addictiveness of a formulation of nicotine, or by analogy, cocaine, can be increased. This is because small increases in pH can provide more molecules in the smoke, more molecules in the mouth and lung, and more molecules being absorbed in the mouth rather than being exhaled or swallowed into the gastrointestinal tract, where they will be rendered ineffective.

Q: Are you able to tell exactly how and which design features Defendants have actually incorporated into marketed products?

A: No.

Q: Why not?

A: As I said earlier, I do not and have never worked for a cigarette manufacturer, and there are so many different brands of cigarettes, so it is difficult to know – especially for some types of design features – exactly what mix of components have been utilized.

As to the chemical additives, the companies are required to disclose some categories of the chemical ingredients used in cigarettes, but until the mid 1990s potential ingredient lists were

not disclosed to consumers, and still are only done on an industry-wide basis, rather than on brand-by-brand basis. Some companies provide partial listings of ingredients of their brands on their websites; however, these lists appear to leave out ingredients used in processing, those added to the paper, and perhaps other ingredients that are not considered by the industry to be "additives." Thus, a cigarette with burn accelerants and flavors which may prove toxic upon combustion may be included in cigarettes advertised as "natural" or without additives. Providing incomplete ingredient disclosures on a brand-by-brand basis and additional information as to what might be used in a given brand by a long list of approximately 600 potential ingredients has very limited usefulness to research scientists like myself who study nicotine pharmacology.

Q: Turning to the subject of Defendants' conduct and knowledge in the area of smoking, nicotine, and addiction, Dr. Henningfield, based on your review and understanding of Defendants' scientific documents, please describe Defendants' internal view about the whether smoking is addictive and about nicotine's role in smoking.

A: Defendants have long understood that nicotine is the addictive agent in cigarette smoke, and that nicotine is essential to the sustaining pleasure and satisfaction that smokers report that they derive from smoking, as well as the compelling need to keep smoking.

Q: When, in your view, did Defendants reach this scientific understanding?

A: The tobacco manufacturers knew that nicotine was addictive by the 1960s.

Q: How does what the industry knew about nicotine in the 1960s compare with what the public health community knew at that time?

A: The truth is that compared to the independent scientific community, the tobacco industry had additional knowledge that led it to conclude at a far earlier point in time that the primary reason that people kept smoking cigarettes was to obtain nicotine and that smoking produced

addictive drug effects.

Q: On what were Defendants' internal conclusions based?

A: The tobacco industry has conducted, in its own laboratories and through outside-funded contracts and grants, extensive research to characterize nicotine's drug effects on the brain, peripheral nervous system, hormonal systems, and behavior. Therefore, the industry itself has documented many of the attributes of nicotine that lead to the conclusion that nicotine is appropriately categorized as a dependence-producing drug. Furthermore, it was the effects of nicotine on the brain and hormonal system, and not its irritating sensory effects in the nose throat and mouth, that were prominent in much of its nicotine research.

Defendants' internal documents show that they invested enormous resources – human and financial – into understanding and researching methods to exploit the effects of nicotine on the nervous system. In addition, many aspects of the effects of nicotine relevant to its importance as an addictive agent were explored by the tobacco industry. Defendants' documents show that the constant, essential objective of product development and design efforts was to ensure that smokers could obtain adequate levels of nicotine from cigarettes to sustain their addiction. For example, internal documents of the tobacco industry reveal that it was studying the threshold levels of nicotine for delivery in a cigarette that were necessary to keep people smoking. The "threshold" is the amount of drug that it takes to produce an effect. One of the things that the industry studied was how much nicotine a cigarette must have to be able to easily give consumers enough nicotine to develop and satisfy the physical addiction to nicotine.

Q: You have been shown U.S. Ex. 20,112. What is this document?

A: This is a June 1959 BATCO internal document.

Q: What information in this document do you consider significant with respect to the

issue of Defendants' knowledge of the addictiveness of nicotine?

A: This 1959 document on page 3 indicates that one approach to cigarette development would be to "[k]eep up the nicotine content of cigarettes to maintain the, as yet, firmly entrenched nicotine habit developed by the majority of smokers." Just below that, it states that "to lower nicotine too much might end up destroying the nicotine habit in a large number of consumers and prevent it from ever being acquired by new smokers."

Q: Why are these statements significant?

A: It shows recognition within the industry in 1959 that smoking was not simply a habitual behavior, but one caused by nicotine, and that reduction of nicotine to a point that could not sustain or induce addiction would threaten the industry's viability.

Q: You have been shown U.S. Exhibit 20,577. Please describe it for the Court.

A: It is a BATCO internal document from 1961 written by Sir Charles Ellis.

Q: What information in this document do you consider significant with respect to the issue of Defendants' knowledge of the addictiveness of nicotine?

A: The following passage from page 2, Bates number 301083863, is significant: "If the competition is to be met successfully, it must be important to know how the tranquillising and stimulating effects of nicotine are produced and the relation of addiction to the daily nicotine intake."

Q: Why is this statement significant to your conclusions?

A: This is another illustration of how far ahead of the public health community the tobacco industry was in its understanding of the role of nicotine in cigarette smoking. Until the 1980s, public health researchers such as at NIDA were trying to determine whether or not nicotine was critical to smoking. This document shows that by 1961 the industry recognized that nicotine was

essential, and that industry research was motivated, at least in part, to find out how to sustain addiction by providing adequate doses of nicotine to produce its critical pharmacological effects.

Furthermore, this document indicates to me that the tobacco industry understood that its products did produce powerful pharmacological effects important in the addiction process and that understanding the mechanisms of actions could enable a company to compete more effectively with other companies. This industry analysis is also similar in certain respects to that of a pharmaceutical company that attempts to explore the mechanisms of action of medicines in order to maximize desired effects.

Q: You have been shown U.S. Ex. 21,530. What is this document?

A: An August 28, 1979 BATCo memorandum, entitled "Key Areas Product Innovation Over Next 10 Years for Long-Term Development."

Q: What information in this document do you consider significant with respect to the issue of Defendants' knowledge of the addictiveness of nicotine?

A: The document explicitly recognizes in several places that smokers are dependent on nicotine, and, in addressing potential development of products other than cigarettes, favorably states the view that "high profits additionally associated with the tobacco industry are directly related to the fact that the customer is dependent upon the product. Looked at another way, it does not follow that future alternative "Product X" would sustain a profit level above most other product/business activities unless, like tobacco, it was associated with dependence."

Q: Why is this statement significant?

A: This industry document is a very clear way of stating what I think is now obvious: people will keep buying tobacco products even though most of them know tobacco products are harmful. This document very clearly states the fact that smokers are dependent upon the tobacco

industry's products not just for some flavor and satisfaction but because their bodies literally depend on nicotine to feel and function well.

Q: Are there other documents you consider significant to your conclusion that Defendants have long considered smoking to be addictive primarily because tobacco-delivered nicotine is an addictive agent?

A: Yes.

Q: Dr. Henningfield, to assist the Court, please identify, in chronological order, some of these other significant documents, and the passages in them that bear on your conclusions. First, what documents, in addition to the ones you have already discussed, do you consider significant in terms of Defendants' knowledge of the addictiveness of smoking and nicotine from the 1960s?

A: Some of the relevant documents from the 1960s include:

- Joint Ex. 53,468 – This is a 1962 report titled "Smoking and Health – Policy on Research" from a BATCo conference in Southampton, England, in which Sir Charles Ellis states, "Smoking is a habit of addiction that is pleasurable."
- U.S. Ex. 53,152 – A report for British-American Tobacco by C. Haselbach and O. Libert entitled "A Tentative Hypothesis on Nicotine Addiction" from 1963. This early document offered a physiological theory attempting to explain "the addiction of the individual to nicotine," including concepts of withdrawal and tolerance.
- U.S. Ex. 34,695 – A letter from R.B. Griffith of Brown & Williamson to John Kirwan of BATCo dated September 1963, in which Griffith states: "Nicotine is by far the most characteristic single constituent in tobacco and the known physiological effects are positively correlated with smoker response. . . . just as we can control nicotine and sugar

levels we will some day achieve the goal of precision manufacture."

- U.S. Ex. 47,767 – This July 14, 1967 B&W "File Note" reporting on a visit to the BAT Research and Development Center in Southampton by R.R. Johnson. On the first page, the author notes that "The supposed paramount importance of nicotine is evident in almost all of this research." Then, in a section titled "Comments on Nicotine" on page 10, the document states that "the Southampton group is going to be doing a large amount of work on nicotine, and for some good reasons." A few of the listed projects concern "extractable nicotine," including one that discusses analysis of the "pH of whole smoke" for its effect on "extractable nicotine," and another concerning "alkaline filter additives which selectively increase nicotine delivery."
- U.S. Ex. 21,433 – A draft "Proposal for a New, Consumer-Oriented Business Strategy for RJR Tobacco Company" authored by Edward A. Vassallo and Dr. Murray Senkus and dated September 19, 1969, that includes in its calculation a variable for "the physiological habituation factor, assumed to be nicotine."
- U.S. Ex. 35,590 – A Philip Morris interoffice memorandum to Al Udow from Jay Faberman dated November 11, 1969, which in answer to the question, "Why People Smoke," Mr. Faberman writes, "Basically people smoke because they feel that a cigarette helps them function better physically and psychologically in a number of different situations."
- U.S. Ex. 60,664 – This is a presentation titled "Smoker Psychology Research" given to the PM Board of Directors by Helmut Wakeham on November 26, 1969. On page 6, Bates number 1000273747, the presentation discusses Philip Morris's research to learn the "mean daily intake of smoke" for the smoker "by analyzing the nicotine in the filter

when the smoker has finished." On page 11, Bates number 1000273752, Wakeham told the Board that "We are of the conviction . . . that the ultimate explanation for the perpetuated cigaret habit resides in the pharmacological effect of smoke upon the body of the smoker."

- U.S. Ex. 20,167 – In a 1969 Philip Morris document, William Dunn wrote to Helmut Wakeham, Director of R&D, "I would be more cautious in using the pharmic-medical model. Do we really want to tout cigarette smoke as a drug? It is, of course, but there are dangerous FDA implications to having such conceptualization go beyond these walls."

Q: Dr. Henningfield, you have been shown U.S. Ex. 58,756 for review. Please explain what this document is.

A: This is a May 14, 1969 internal memorandum from the American Tobacco Company marked "confidential" and titled "Compound W."

Q: The document states:

> **In the future, our use of nicotine should be referred to as "Compound W" in our experimental work, reports, and memorandums, either for distribution with the Department or for outside distribution. In the event the nicotine is used in the form of a salt, such as nicotine dimalate, it should be referred to as "Compound WM", if used as citrate salt, refer to it as "Compound WS", etc.**

What in your view was American's purpose in setting a policy that nicotine used by American should be referred to as Compound W?

A: The only explanation that makes sense to me is that American was trying to hide the fact that it was using nicotine in its scientific research.

Q: Have you seen other documents from American that show that the policy was implemented and followed?

A: Yes. For example, U.S. Ex. 64,785, a document from about 5 years later, in April 1974, is titled "Compound W" and discusses research in which "Compound W" was added to tobacco and its effects on nicotine blends and yields.

Q: What documents, in addition to the ones you have already discussed, do you consider significant in terms of Defendants' knowledge and understanding of the addictiveness of nicotine from the 1970s?

A: Important documents from the 1970s include the following:

- U.S. Ex. 20,176 – A November 1971 Philip Morris U.S.A. Research Center Special Report entitled "Tar, Nicotine and Smoking Behavior" which contains the following conclusion: "these findings support the hypothesis that the smoker does have daily intake quotas for tar and/or nicotine; and that he titrates his smoke intake to meet his quotas."
- U.S. Ex. 39,723 – A January 1, 1972 document, prepared by T.R. Schori and W.L. Dunn of the Philip Morris Research Center called "Tar, Nicotine, and Cigarette Consumption," states that:

> This finding supports the notion that smokers develop a daily nicotine intake quota and that when smoking cigarettes differing in nicotine delivery from that to which they are accustomed they tend to modify their consumption rate in order to maintain their normal quota. No support was found for the analogous notion of a daily tar intake quota, however.

- U.S. Ex. 20,659 – A March 14, 1972 R.J. Reynolds document, entitled "Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of

Nicotine Therein," states:

> In a sense, the tobacco industry may be thought of as being a specialized, highly ritualized and stylized segment of the pharmaceutical industry. Tobacco products, uniquely, contain and deliver nicotine, a potent drug with a variety of physiological effects. . . . A tobacco product is, in essence, a vehicle for delivery of nicotine. . . . If nicotine [as proposed above] is the sine qua non of tobacco products and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our products and where possible, our advertising around nicotine delivery rather than 'tar' delivery or flavor.

- U.S. Ex. 20,660 – A March 28, 1972 RJR report, stamped "CONFIDENTIAL" by E.A. Vassallo and Dr. Murray Senkus, entitled "A Gap in Present Cigarette Product Lines and An Opportunity to Market a New Type of Product," stated:

> T/N Ratio is simply a way of expressing the number of milligrams of "tar" a smoker must receive per milligram of smoke nicotine. In today's market, it is fair to assume that the smoker will choose the product which delivers the desired amount of nicotine with the least amount of "tar", provided flavor and other qualities are good. That is, at the desired nicotine delivery, calculated to be 1.3 mg., the smoker will choose the cigarette offering the lowest T/N Ratio, if all other qualities are satisfactory.

- U.S. Ex. 36,829 – A May 24, 1972 Philip Morris inter-office memorandum from Al Udow to Chris Bolton with the subject line, "The chemistry of Kool and a

recommendation," has the following appearing as the first paragraph:

> A widely held theory holds that most people smoke for the narcotic effect (relaxing, sedative) that seems to come from the nicotine. The "taste" comes from the "tar" (particulate matter) delivery. Although more people talk about "taste", it is likely that greater numbers smoke for the narcotic value that comes from the nicotine."

- U.S. Ex. 20,170 – An October 1, 1972 Philip Morris research memorandum, called "Smoke Impact, Part I: Cigarette Smoking and Heart Rate," stated that " . . . there is an optimal dose of nicotine, too little or too much is rejected by tobacco smokers."
- U.S. Ex. 48,378 – An August 22, 1975 memorandum by Reynolds' Claude E. Teague proposed an approach to calculate "Aggregate Annual Nicotine Consumption" by an approach that "is based on the simplistic hypothesis that a given smoker has a relatively fixed annual nicotine requirement and, if his cigarette is made to gradually deliver less nicotine, he will compensate by gradually increasing the number of cigarettes he consumes (or change to a higher nicotine brand)." This shows awareness of the concept of nicotine-driven smoker compensation.
- U.S. Ex. 56,775 – A July 1976 Lorillard document regarding a research proposal to develop assays, or scientific tests, for free nicotine stated:

> Cigarette sales are made for one reason. The customer is satisfied with the product either from the taste or the physiological satisfaction derived from the smoke. The consensus of opinion derived from a review of the literature on the subjects indicates that the most probable reason for the addictive properties of the smoke is the nicotine. Indications are that the

smoker adjusts his smoking habits to satisfy the desire for nicotine either by frequent or large puffs on the cigarette, or smoking a large number of cigarettes. . . .

It is generally agreed at this time that a "small" amount of free nicotine is more desirable than a "large" amount of bound nicotine.

- U.S. Ex. 34,210 – A December 10, 1976 report generated at Lorillard Research Center in Greensboro, authored by Drs. H.J. Minnemeyer, F.J. Schultz, and Mrs. A. Anthony entitled "The Pharmacology of Smoke-Dose Nicotine: A Review of the Current Literature," made the following statement in the abstract: "A review has been made of the literature on the pharmacology of smoke-dose nicotine with the goal of discovering some indications of threshold dose and optimum doses of nicotine in the average cigarette smoker."
- U.S. Ex. 20,268 – This is a March 1976 BATCO document, entitled "The Project in the Early 1980s," that stated:

Taking a long-term view, there is a danger in the current trend of lower and lower cigarette deliveries i.e. the smoker will be weaned away from the habit. . . . Nicotine is an important aspect of satisfaction and if the nicotine delivery is reduced below a threshold satisfaction level, then surely smokers will question more readily why they are indulging in an expensive habit.

Q: What is the significance of this document to your conclusions about Defendants' understanding of nicotine's role in smoking?

A: This document expresses concern that the trend toward cigarettes with lower FTC tar and

nicotine ratings could mean that the market would extinguish because people would get to the point that smoking really would be a matter of taste and pleasure and not nicotine receptors in the brain; at that point, people would find it easier to quit.

Q: Please continue identifying for the Court documents that are important to your conclusions concerning Defendants understanding of nicotine's role in smoking, and their approach toward nicotine-related research.

A: Some additional documents are:

- U.S. Ex. 26,074 – This is an October 1977 internal memorandum from Philip Morris's William Dunn to Tom Osdene titled "Smoker Psychology Program Review." It states Philip Morris's legal concern about "any industry-endorsed reference to the pharmacological effects of smoke." This document also shows Philip Morris's sophisticated understanding of many of the different pharmacological and behavioral dimensions that contribute to addiction. On page 5, Bates number 1000046542, Dunn stated that Philip Morris attributed "a primary role to the active chemical compound. Without the chemical compound, the cigarette market would collapse, P.M. would collapse, and we'd all lose our jobs and consulting fees."
- U.S. Ex. 87,160 – This is another memorandum from Philip Morris's Dunn to Osdene, dated November 1977, titled "Proposed Study by Levy." Dunn stated: "If she is able to demonstrate, as she anticipates, no withdrawal effects of nicotine, we will want to pursue this with some vigor. If, however, the results with nicotine are similar to those gotten with morphine and caffeine, we will want to bury it. Accordingly, there are only two copies of this memo, the one attached and the original which I have." This shows Philip Morris's desire to keep secret any scientific evidence that showed nicotine was like other

known addictive drugs.

Q: Dr. Henningfield, you have been given U.S. Ex. 34,423. What is this document?

A: This document is a 1978 internal Philip Morris memorandum from three scientists to Dr. Tom Osdene.

Q: What about this document is significant to your conclusions?

A: In the last paragraph on the first page, the authors state: "The state of the art and the position in which the nicotine program at Philip Morris rests with respect to this state of the art, can best be appreciated by considering the fact that Dr. Avram Goldstein (one of the central figures in endorphin and opiate receptor research) is just initiating a research program on nicotine delivery. . . . The Behavioral Research Group has been testing R-(+)-nicotine (prepared by Drs. R. McCuen and W. Edwards) for some time . . . ."

Q: Why is this significant?

A: It shows that Philip Morris knew that its nicotine program, which was conducted by its Behavioral Research Group, was more advanced than that of some of the leading researchers outside the tobacco industry.

Q: What documents, in addition to the ones you have already discussed, do you consider significant in terms of Defendants' knowledge of the addictiveness of nicotine from the 1980s?

A: Among the documents evidencing Defendants' internal recognition of nicotine's role in smoking addiction are the following:

- U.S. Ex. 34,328 – A February 13, 1980 Lorillard memorandum stated: "Goal – Determine the minimum level of nicotine that will allow continued smoking. We hypothesize that below some very low nicotine level, diminished physiological satisfaction cannot be

compensated for by psychological satisfaction."

- U.S. Ex. 21,794 – This is a March 1980 memo from Philip Morris's William Dunn to R.B. Seligman, Vice President of R&D, concerning the company's approach of keeping Philip Morris's nicotine receptor programs secret:

> Any action on our part, such as research on the psychopharmacology of nicotine, which implicitly or explicitly treats nicotine as a drug, could well be viewed as a tacit acknowledgment that nicotine is a drug. Such acknowledgment, contend our attorneys, would be untimely. . . . Our attorneys, however, will likely continue to insist upon a clandestine effort in order to keep nicotine the drug in low profile.

Dunn also stated Philip Morris's policy that "we must be officially heedless of the drug properties of nicotine."

- U.S. Ex. 21,557 – An April 11, 1980 BATCO document, entitled "What Three Radical Changes Might, Through the Agency of R & D, Take Place in this Industry by the End of the Century," stated that " . . . B.A.T. should learn to look at itself as a drug company rather than as a tobacco company."
- U.S. Ex. 34,273 – An August 12, 1980 internal memorandum from Philip Morris's T.S. Osdene to Dr. R.B. Seligman and Directors with the subject line "Evaluation of Major R&D Programs," contains the following statement under the sub-heading "Nicotine Program": "This program includes both behavioral effects as well as chemical investigation. My reason for this high priority is that I believe the thing we sell most is nicotine."
- U.S. Ex.* 75,975 – This is one of the papers in the compilation from a June 1984 internal

BAT conference. This was written by D.E. Creighton, entitled "Structured Creativity Group Presentation," and stated, at the top of page 400993196: "As suggested earlier, high on the list of product requirements is an adequate level of nicotine to sustain the smoking habit. Smokers have a nicotine threshold below which it is ineffective."

- U.S. Ex. 38,683 – This is a chart from a presentation made by a BATCo scientist in 1984, that describes a session at a "Smoking Behavior-Marketing Conference" in July 1984. The paper is titled "Session VI – Product Modification for Maximal Nicotine Effects," and the Summary states, "Sufficient is known to begin to improve the quality and characteristics of current products in terms of sensory and whole body effects based on nicotine modification." This another example of Defendants' focus on product development centered around nicotine.
- U.S. Ex. 64,512 – An August 24, 1987 Brown & Williamson document to M.J. McQue from H.B. Steele regarding "Future Consumer Reaction to Nicotine," stated: "Very few consumers are aware of the effects of nicotine, i.e., its addictive nature and that nicotine is a poison."

Of course, there are many other such documents from this time period. Indeed, there are entire research projects and groups within the Research and Development departments of Defendants, such as the Behavioral Research Group at Philip Morris, including the behavioral pharmacology laboratory run by Dr. Victor DeNoble, that were dedicated to studying the pharmacological effects of nicotine, and whose very existence underscore Defendants' acceptance of nicotine – because of its pharmacological effects, not its taste – as the most significant component of cigarette smoke. From my perspective, the only scientific reason why companies would do some of the research they did would be if they accepted nicotine as being

responsible for creating and sustaining people's addiction to smoking.

Q: What documents, in addition to the ones you have already discussed, do you consider significant in terms of Defendants' knowledge of the addictiveness of nicotine from the 1990s?

A: Examples of the documents from the 1990s that support my opinions are the following:

- U.S. Ex. 20,430 – A December 8, 1990 Philip Morris document to Cathy Ellis from Frank Gullotta regarding "Raison d'etre" stated, among other things: "We have known that there are optimal cigarette nicotine deliveries for producing the most favorable physiological and behavioral responses" and "Our laboratory has demonstrated that all forms of nicotine are not behaviorally or physiologically equal."
- U.S. Ex. 20,829 – A May 3, 1991 RJR report entitled "REST Program Review" stated, at Bates page 509479584, "We are basically in the nicotine business."
- U.S. Ex. 37,313 – This is a November 4, 1993 Philip Morris study protocol titled "The Effects of Nicotine Aerosols on the Pattern Reversal-Evoked Potential." It indicates it came from Philip Morris's facility in Neuchatel, Switzerland. The second page indicates that Philip Morris was testing the effects of a nicotine aerosol outside the context of smoking cigarettes. The third objective listed for the proposed study is "investigate the effects of aerosol pH on the magnitude of the physiological response." This shows that Philip Morris also understood the potential role of pH in influencing the physical effects of nicotine.

Q: Please explain why these documents from the 1960s through the 1990s are significant to your conclusions about Defendants' understanding of nicotine's addictiveness and its central role in maintaining smoking behavior.

A: The industry documents support the conclusion that the tobacco industry knew early on in its research that if a cigarette did not deliver a certain amount of nicotine, smokers would not be addicted. The tobacco industry also knew early on that there is some minimal dosage necessary to maintain dependence and that the industry needed to determine that dosage to ensure that smokers continue smoking.

In addition, internal documents indicate that the industry was investigating bioavailability. Such studies examine the dose effect of nicotine in the body as compared to the amount of nicotine in a cigarette. For instance, the tobacco industry was using many elaborate techniques to control the dosage of nicotine and measure its entry into the body; these studies did not just focus on the mouth or taste receptors in the tongue. Bioavailability studies are a hallmark in the investigation of drugs. These studies support the conclusion that the tobacco industry from an early date acted consistently with the understanding of nicotine's pharmacological properties.

Q: How did Defendants' knowledge of nicotine and addiction compare with what was known at NIDA at the time you worked at that agency?

A: The industry was years ahead of NIDA in its understanding of nicotine and addiction. For example, industry documents also indicate that tobacco manufacturers understood the importance of speed or rate of drug delivery, which I discussed above and which is a key concept to the addictiveness of smoked drug intake. In the case of nicotine, NIDA reached its understanding of this important concept decades after the tobacco industry had concluded that speed of delivery was an important determinant of the nicotine "kick."

Q: What effect would disclosure of this information by Defendants have had on your work at NIDA?

A: I believe that disclosure of Defendants' knowledge and the basis for their conclusions could have facilitated NIDA's efforts in understanding the importance of the speed of drug delivery in drug addiction in general.

NIDA research also could have benefitted from disclosure of information generated by Philip Morris on animal models of nicotine-seeking behavior. For example, in the early1980s when NIDA was trying to develop animal models to study the factors determining nicotine-seeking behavior, the industry was well aware of these efforts and was internally pursuing similar models. When those internal models appeared to be well on the road to providing useful verification for understanding the reinforcing effects of nicotine alone and in combination with other substances, the response of Philip Morris was to close the laboratory, kill the animals, and suppress publication of findings by its lead investigators, Dr. Victor DeNoble and Dr. Paul Mele. This effectively denied the public health community and researchers, such as those at NIDA, the benefit of public disclosure of their breakthroughs and findings.

Q: What was the industry's public position throughout this period on the addictiveness of smoking and nicotine?

A: Through the mid-1990s, all Defendants consistently denied publicly that smoking or nicotine was addictive.

Q: How did Defendants communicate their position denying that smoking or nicotine is addictive?

A: In many different ways, including paid newspaper ads, press releases, interviews on television news shows, congressional testimony, regulatory submissions, and submissions to scientific journals.

Q: Subsequent to the mid-1990s, did Defendants' public statements about smoking and

nicotine's addictiveness change?

A: In part. With the exception of Liggett, until 2000 no Defendant agreed without qualification that smoking is addictive. Beginning in 1997, Philip Morris recognized that smoking was addictive under some definitions; then in 1999, it recognized the overwhelming consensus that smoking is addictive; and then in 2000, it publicly stated that it agrees with that consensus.

However, even to this day, the Defendants have consistently refused to acknowledge publicly that nicotine is addictive, and the Defendants do not advertise their products as addicting or provide such information on the package – with the exception of Liggett/Vector on some its brands – or on the company websites.

While all of the companies acknowledge, to some degree, that smoking is addictive under certain definitions, none of them has clearly informed its consumers what it and the Surgeon General have concluded: that nicotine is an addictive drug. It makes it hard to determine if they have changed at all on this subject.

Q: Is it significant to you, as a psychopharmacologist with experience in drugs of addiction, that no Defendant tells customers directly, or the public on its website, that smoking is addictive because cigarettes deliver nicotine, an addictive drug?

A: Yes.

Q: Why is Defendants' failure to acknowledge directly that smoking is addictive because of nicotine significant to you?

A: One of the most fundamental concepts in helping people to attempt to break an addiction is recognition of the addiction. Similarly, one of the most fundamental concepts in providing drugs to consumers, whether over-the-counter or prescription, is clear information regarding risks

at point-of-sale and in the packaging. Not acknowledging the role of nicotine is leaving out vital information to consumers. It is leaving out information that could be helpful to their making more fully informed choices about their smoking. In order to give people a better chance in helping them quit it can be useful to tell them about the factors that are making it difficult to quit, not simply that it can be difficult, a fact that most people already know.

Understanding why it is difficult can help people decide and can help people prepare. This is not just for the area of tobacco. For example, to prevent the spread of malaria or West Nile Virus, we inform people about the role of the mosquito, and what to do to lessen the risk of infection, how to identify symptoms, and what to do if you display the symptoms. It would be considered irresponsible for CDC to just tell people that malaria and West Nile are risks if they go outside. The same concept applies to control of HIV, influenza, and other forms of drug addiction, including to prescription drugs.

Q: The public corporate website presenting BATCo's corporate positions on smoking and health issues currently has the following question-and-answer among its "Frequently Asked Questions":

> **IS NICOTINE ADDICTIVE?**
>
> **We accept the common understanding today that smoking is addictive. Certainly smoking is pleasurable and smokers can find it hard to quit even though they know that smoking is a real risk for serious diseases. Also under the diagnostic tools used today, which focus on behaviour, some smokers could be diagnosed as being dependent upon smoking. Anyone thinking about starting to smoke should consider that they may find it very hard to give up later. But**

smoking doesn't take away anyone's free will, and we believe it's important that smokers realise they can quit, provided they have the necessary motivation and self-belief.

The overwhelming majority of the millions of people who quit each year do so successfully without smoking cessation aids or treatment programmes. In the UK today, there are almost as many ex-smokers as smokers (usually giving up without external help). Many of us will know – or are ourselves – former smokers.

We think smokers who want to quit should be encouraged and supported to do so; it's the best way to reduce the risks.

What is your response to the substance and accuracy of BATCo's answer to the question, "Is nicotine addictive?"

A: It is significant for a few different reasons. First, the response never directly answers the basic question it posed. The answer did not even include the word "nicotine." This website poses an opportunity for BATCo to provide a clear and direct communication about nicotine as an addictive drug, but it skirts the issue. It is thus another example of the tobacco companies not providing important information about what it is about smoking that makes it so difficult to quit – cigarettes contain an addictive drug – to give smokers a realistic understanding of the challenges they face in quitting. Second, by saying that "some" smokers "could" be diagnosed as dependent, it vastly understates the body of evidence that show that the overwhelming majority of smokers show clear signs of addiction. Third, it uses aggregate statistics over 40 years to imply that the success rate for quitting is about 50%, ignoring the fact that only a few percent of smokers who try to quit each year actually succeed. Fourth, by ignoring nicotine, it is contrary to

what BATCo's own internal documents conclude about what makes smoking addictive.

Q: As one more example, the current website statement for Brown & Williamson on "Cigarette Smoking and Addiction" states:

> **Cigarette smoking is addictive by modern day definitions of the term. Many smokers find it difficult to quit. For some, it is very difficult.**
>
> **We believe that any person with the desire and determination to quit can do so. In 1990 the Surgeon General reported that there were nearly 45 million Americans who had quit smoking. In 1989 the Surgeon General noted that "Nearly half of all living adults who ever smoked have quit." According to the Surgeon General's 1988 report, "Approximately 90% of former smokers report that they quit smoking without formal treatment programs or smoking correction devices."**
>
> **In our opinion, it is inappropriate to call cigarette smoking addictive in the same sense as heroin, cocaine or other hard drugs. We believe that this defies common sense, is contrary to much scientific research and could lead people to believe they can't quit. In fact, cigarette smoking is not intoxicating like heroin and cocaine, nor does it interfere with a person's ability to function normally in society. For more information on what the U.S. Surgeon General and others have said about smoking and addiction click here.**

What is your response to the substance and accuracy of this statement?

A: This statement also provides selective information and poses the issue of cigarette

addiction in a misleading way. First, its statement about smoking being addictive by "modern day definitions" overlooks the fact that these "modern day" definitions are several decades old. In fact, the revised WHO definition was released four decades ago and the APA's DSM-III, which included tobacco use as a syndrome of dependence, is 24 years old. Furthermore, like the BATCo statement, it does not mention nicotine at all, and thus does not give any meaningful information here about why it is hard to quit. Also like the BATCo statement, it uses selective information from the Surgeon General's Reports about the population that has stopped smoking over decades.

In addition, its statements that implying that smoking does not meet the same criteria as addictive drugs as heroin and cocaine is contrary to the conclusions of the WHO, APA, Surgeon General, NIDA, College on Problems of Drug Dependence, American Society of Addiction Medicine, and every other major professional organization that has evaluated this question since the 1980s. Moreover, it incorrectly implies that quitting smoking is easier than quitting use of these other addictive drugs, when the widely published facts show clearly that quitting smoking is as difficult as, if not more difficult than, quitting other addictive drugs, for which abstinence is also commonly achieved outside of treatment. Its reference to intoxication and interference with a person's ability to function normally in society suggests that B&W is relying on the 1957 WHO criteria for addiction, ignoring that WHO itself – along with every other major scientific organization to look at drug addiction – has not considered "intoxication" to be a primary criterion to classify a drug as dependence-producing since 1964. Finally, by ignoring nicotine as the reason people are addicted to smoking, the website statement is contrary to B&W's own internal conclusions reached decades ago.

Q: How do Defendants' public statements denying nicotine addiction compare to the

knowledge and information reflected in Defendants' internal documents, including the documents concerning nicotine research?

A: Given the knowledge and understanding of nicotine's addictive effects as reflected in internal industry documents made available only in the last few years, it simply was not credible to publicly deny addiction, such as when an industry executive compared nicotine and its effects to gummy bears in 1994, and when the companies forcefully denied addiction to the FDA in their written comments on January 2, 1996. Such statements did not make any scientific sense at that time, and were contradicted by the understanding within the industry.

Q: Dr. Henningfield, I would now like to turn from your conclusions about Defendants' understanding of smoking and nicotine addiction and ask you some questions about what the outside scientific community understood about smoking and nicotine at various points in time. First, you have used the terms "addiction" and "dependence" in discussing nicotine. Please explain to the Court how those two terms relate to one another.

A: Consistent with a convention adopted by an Expert Committee of the World Health Organization in 1964, drug addiction is the common term for what is more technically referred to as "drug dependence." The term adopted by the WHO in 1964, "dependence," was never intended to imply a lesser condition than "addiction." Instead, it is a technical term that many of us in the field prefer to use in our writings. In fact, lead scientific organizations such as NIDA, the American Association of Addiction Medicine, and the College on Problems of Drug Dependence, use the terms "drug addiction" and "drug dependence" interchangeably. In the same way, oncologists talk about "neoplasms" or "neoplastic disorders" in their technical literature, while they use the term "cancer" when addressing larger audiences.

Q: For convenience, I will mainly refer to "addiction" in my questioning, but will use

the terms interchangeably. What types of organizations formally study whether a substance is addictive and classify drugs as addictive?

A: A variety of governmental, medical, and scientific bodies have examined the question of drug addiction, and identified those drugs that should be classified as addictive.

Under the U.S. Controlled Substances Act (CSA), the FDA, DEA, and NIDA jointly determine if a drug meets criteria as sufficiently addictive to merit control by the provisions of the Act. Tobacco products and alcohol are exempt from the CSA. When nicotine is not in the form of a tobacco product, then it is not exempt from control. The response of the pharmaceutical industry, therefore, has been to deliberately design its products so that they will not be so addicting as to precipitate the labeling and scheduling of addictive drugs as controlled substances under the CSA. One exception was a nasal nicotine spray, which DEA argued met criteria for control as an addictive drug, but was not scheduled and regulated as a controlled substance for a variety of public health-related reasons.

From another perspective, the American Psychiatric Association has examined whether specific clinical syndromes of "dependence," "withdrawal," "intoxication," etc., can be produced by various drugs and if the syndromes are of sufficient reliability, magnitude, and significance to warrant inclusion among other drug dependence-related disorders.

Thus, whereas, DEA and the WHO's Expert Committee focus more on the pharmacology of the drug in drug classification, the APA focuses on behavioral and clinical symptoms indicative of drug dependence.

Q: How many substances have been classified as addictive by these organizations?

A: Again, it depends upon the organization. The American Psychiatric Association officially recognizes 12 subtypes of drug dependence, including "alcohol," "cocaine," "opioids," and

"nicotine," – but not, by the way, "caffeine," carrots or some of the other substances which the tobacco industry experts have argued should be included if tobacco is listed.

Q: For any set of accepted criteria for addiction, must a drug meet every criterion to be classified as addictive?

A No.

Q: Within the group of drugs classified as addictive, do addictive drugs differ from one another in their chemical and pharmacological characteristics?

A: Yes.

Q: Within the group of drugs classified as addictive, do addictive drugs differ from one another in the severity of their particular effects, that is, the degree to which they satisfy different criteria of addiction?

A: Yes.

Q: Can you provide an example of how different drugs compare in whether they satisfy the primary criteria of addiction and in the degree to which they meet those criteria?

A: Yes. Morphine produces a pronounced withdrawal syndrome after a few weeks of daily use, whereas cocaine and amphetamines produce relatively mild withdrawal, and the vast majority of users of these drugs show no signs of withdrawal other than rebound sleepiness. Most alcoholic persons show frequent signs of intoxication which is not essential to their diagnosis but which makes their drug use obvious. In contrast, many stimulant- and even opioid-dependent persons can use their drug for months if not years and escape detection because behavioral signs, including intoxication, may not be readily evident. Nicotine as delivered by tobacco products shares with all of these drugs the characteristics of maladaptive use, frequently in the face of harm; frequent progression of use of the drug from initial sporadic use to regular

use; tolerance to many effects; and extreme difficulty in achieving and sustaining abstinence in many users. In addition, in contrast with cocaine and amphetamine, withdrawal from nicotine generally appears more prominently, frequently, and is generally a more debilitating feature than for cocaine and amphetamine use.

Q: Dr. Henningfield, can tobacco use be a form of drug dependence?

A: Yes.

Q: Are all tobacco users dependent under the APA criteria for dependence?

A: No**.**

Q: Do all heroin users meet criteria for dependence?

A: No.

Q: Do all cocaine users meet criteria for dependence?

A: No.

Q: How do these drugs compare in their liability to produce dependence or in the rates of dependence among people who use the drugs?

A: By virtually any measure, in all major studies, the risk of developing dependence following any use is higher for cigarettes than for these other drugs, and the probability of diagnosing dependence among people who use the drugs is higher for cigarettes than for these other drugs. For example, the 1988 Surgeon General's Report found that a much higher percentage of smokers met criteria for dependence than do alcohol or opioid users.

Q: What was the standard used in the 1988 Surgeon General's Report to distinguish occasional users of cigarettes from daily smokers meeting criteria for dependence?

A: The Report referred to smokers of five or fewer cigarettes per day as "chippers," which are recreational or intermittent users.

Q: For someone age 21, is that standard of smoking more than five cigarettes per day a scientifically supported predictor of addiction?

A: Yes, I would say it is a conservative measure for daily smokers.

Q: Is there currently a scientific consensus that tobacco use is a form of drug dependence?

A: Yes. Lead scientific, medical, and public health organizations in the U.S. and around the world that address addiction in general, and tobacco in particular, agree that this classification is appropriate.

Q: When did this consensus emerge?

A: By the 1980s, leading scientists and organizations with expertise in tobacco and drug addiction had come to the conclusion that nicotine was an addictive drug and that tobacco use was critically maintained by nicotine addiction.

Q: Prior to the 1980s, Dr. Henningfield, when had been the last previous evaluation of the scientific and medical evidence to specifically address the question of whether smoking or nicotine is addictive?

A: Before the 1980s, the 1964 Surgeon General's Report was the last major document to specifically consider whether smoking and nicotine are addictive.

Q: Dr. Henningfield, I have provided you with a copy of the 1964 Surgeon General's Report, previously admitted to evidence as U.S. Ex. 64,057. Are you familiar with this Report?

A: Yes.

Q: When did you first become familiar with this Report?

A: I believe I first read its chapter pertaining to addiction between 1978 and about 1981,

though I had seen its conclusions cited so many times even before that time that it is difficult for me to know when I first read it.

Q: What was the subject of this Report?

A: The title is Smoking and Health and the Report examined the major categories of health risk that were assumed to be plausibly attributed to cigarette smoking. Specifically, the Report addressed a number of questions, one of which was, "Is smoking addictive?"

Q: What was the conclusion in the 1964 Surgeon General's Report on the question of addiction?

A: At page 23 of the Report, the conclusion reached by the Surgeon General's Advisory Committee was:

> The tobacco habit should be characterized as a habituation rather than an addiction, in conformity with well accepted World Health Organization definitions. Since once established there is little tendency to increase the dose, psychiatric but not physical dependence is developed and the detrimental effects are primarily on the individual rather than society.

Q: How did the Surgeon General's Advisory Committee reach this conclusion?

A: It evaluated the evidence for determining if cigarette smoking was an habituation or addiction based on the criteria dating to a 1957 WHO Expert Committee report. Its conclusion was that cigarette smoking was primarily a psychological and social process, but it acknowledged that the behavior was reinforced and perpetuated by the pharmacological actions of nicotine. Thus, it did not exonerate nicotine, and it certainly did not ascribe nicotine's role to the sensory role or flavoring held by the tobacco industry in its public statements until a few years ago.

Q: What were the criteria for addiction that the Advisory Committee used in the 1964

Report?

A: In brief, the criteria were that the drug use would be associated with (1) periodic intoxication, (2) overpowering desire or need, (3) tendency to increase dose, (4) psychic and physical dependence, and (5) detrimental effect on society. Additional factors discussed included the observation of "serious personality defects" and "psychiatric disorders," and the absence of a pure nicotine substitute for smoking.

Q: Were these the generally accepted prevailing criteria for addiction at the time?

A: They were the 1957 WHO criteria relied upon by the Report and so their use was not inappropriate. However, those criteria had already been criticized as outmoded and inconsistent in other contexts, including by the Advisory Committee's addiction expert, Dr. Maurice Seevers. Indeed, the WHO was already well along in the process of reevaluating its own criteria, and it published its revised criteria in 1964 and 1965. However, the revised WHO criteria were announced too late for consideration by the Advisory Committee to the Surgeon General, which issued its landmark report earlier in 1964.

Q: Dr. Henningfield, how does the characterization of nicotine as an habituation by the Surgeon General in 1964 compare with the scientific community's understanding of nicotine at that time?

A: In 1964, there was not general agreement among the independent scientific and medical community that nicotine is addictive. The Surgeon General's conclusion reflected that view.

Q: What in your view explains the lack of consensus?

A: First, the criteria for addiction used in that report emphasized the prevailing view of the 1950s that drug addiction reflected an underlying personality disorder which made the individual more vulnerable to the effects of the drug, and it included the observation of intoxication as a

critical feature of drug use.

Second, there were serious gaps in the evidence available to the Advisory Committee. The experts did not have the benefit of the tobacco industry's own evidence and conclusions that nicotine was addictive. At the time of the 1964 Report, the publicly available evidence of nicotine's importance to behavior was limited.

Q: What was the public health community's understanding of nicotine at that time?

A: Nicotine was understood to be a powerful and potent nerve acting drug, as evidenced by a perusal of the Larsson, Haag, and Silvette compendium.

Q: What is the Larsson, Haag, and Silvette compendium?

A: It is a two volume work summarizing much of the world literature on the effects of tobacco and nicotine, developed at the Medical College of Virginia, with support by Philip Morris. It was published in 1962.

Q: Was addiction a recognized field of medical and scientific inquiry at that time?

A: Yes, but at that time the field of addiction science was young and focused primarily on opioids and alcohol.

Q: Dr. Henningfield, earlier you testified that "the available non-industry evidence of nicotine's importance to behavior" was limited. How so?

A: Until the 1980s, there was suggestive evidence that nicotine could serve as a reinforcer for monkeys, generated by work in the late 1960s at the University of Michigan; suggestive evidence of a nicotine withdrawal syndrome dating to at least the Finnegan, Larson, and Haag study in 1945; and suggestive evidence that injected nicotine could mimic key pleasurable effects from the Johnston study of 1942. However, all of these studies had limitations and left alternate explanations which seemed at least as possible an explanation as the addiction hypothesis.

Indeed, even much later on, in various conferences sponsored by the National Institute on Drug Abuse in the late 1970s, the possibility that nicotine might be a prototypic dependence producing drug was raised, but it was also recognized that several significant gaps questioned such a conclusion. This possibility, and the gaps in knowledge, led to the growth of NIDA's research program to resolve the questions.

Q: For purposes of illustration, I want to focus on one of the studies you just mentioned. What was the 1942 Johnston study?

A: The 1964 Report cited, in support of its findings, the 1942 Lennox Johnston study, which showed that intravenous injections of nicotine could cause psychoactive effects and provide a substitute for tobacco. In his study, Dr. Johnston observed that smoking tobacco is essentially a means of administering nicotine, just as smoking opium is a means of administering morphine.

Q: How did the Surgeon General's Advisory Committee treat this study in 1964?

A: Because Dr. Johnston's study was the sort of initial clinical study that did not employ a placebo condition and other characteristics of a definitive scientific study, the Advisory Group in 1964 considered it to be an "anecdotal" source of information.

Q: How would you characterize the Advisory Committee's decision to characterize smoking as an "habituation" based on the evidence available at that time?

A: The limitations in studies that were available, and gaps in areas of study, resulted in the Advisory Group taking a very cautious approach in the 1964 Surgeon General's Report.

Q: How was the approach taken "cautious"?

A: "Cautious" is my term, "conservative" would be another that would be consistent with the discussion by the Committee at the beginning of the report that definitive conclusions would require definitive proof. The evidence that the Committee had at hand was suggestive, but not

definitive.

While the Surgeon General recognized that nicotine played a role in tobacco use, he concluded that based on the limited research that had been performed and the gaps in areas of study that existed that nicotine's role appeared too limited to warrant the designation "addictive."

Q: Were there substances other than nicotine that also did not fit the 1957 WHO definition of addictive, but that nonetheless were considered addictive at that time?

A: Yes, cocaine is one example of a drug recognized as addicting but not clearly meeting the 1957 WHO criteria. Dr. Maurice Seevers, the Advisory Committee's addiction expert who had been approved by the industry, himself had in 1962 indicated that the 1957 WHO criteria were problematic since it was universally recognized that cocaine was addictive, even though cocaine did not meet all of the 1957 criteria. He discussed the fact that cocaine should be categorized as addicting even though the evidence available at the time showed that it did not meet the those 1957 criteria.

Q: Which of the 1957 WHO criteria did cocaine not appear to fulfill at the time?

A: The two key criteria that cocaine did not meet were (1) physical dependence that would have led to a withdrawal syndrome upon discontinuation of drug taking, and (2) apparent lack of tolerance. It also was more limited in its "psychotoxic" or "intoxicating" effects than alcohol, sedatives, and opioids.

Q: Why was cocaine still considered addicting even though it did not meet all of the WHO criteria?

A: The main factors were the observation that many people found it extremely difficult to stop using cocaine and hence met criteria for "overpowering desire or need" to take the drug, and that this could lead to detrimental effects to society, including crime.

Q: How did the evidence available to the Surgeon General's Advisory Committee compare to the information possessed by Defendants about the addictiveness of nicotine?

A: As indicated by some of the pre-1964 documents, including the BATCo documents discussing the HIPPO research, the contrast was quite stark. The internal documents reveal that the tobacco companies understood that nicotine was addictive by the early 1960s. The industry understood the fact that many smokers were addicted and would make great sacrifices to sustain their addictions, and that nicotine was critical for most smokers. They clearly understood their market and their consumers.

Q: Dr. Henningfield, you have been shown Joint Ex. 46,579. What is this document?

A: It is a February 1962 BAT document discussing nicotine-related studies it had contracted for with Battelle, an outside laboratory.

Q: Please identify any portions of this document you consider significant.

A: There are many parts of this document, but beginning toward the bottom of page 7, the author states: "What we need to know above all things is what constitutes the hold of smoking, that is, to understand addiction. . . . These are the reasons for the study of the physiological effects of nicotine carried out under the MAD HATTER and HIPPO contracts." And on the top of page 9, the document states: "As a result of these various researches we now possess a knowledge of the effects of nicotine far more extensive than exists in published scientific literature."

Q: Why do you consider this important?

A: Because BATCo clearly believed it had learned important scientific information about the physiological effects of nicotine and addiction that was unknown outside of the tobacco industry.

Q: Did BATCo share the information it had learned about nicotine from these projects

with the outside scientific community?

A: No.

Q: How do you know that?

A: A few documents from that time indicate that B&W and BATCo discussed, but decided not to provide this information to the Surgeon General's committee. For example, U.S. Ex. 54,273 is a letter dated June 28, 1963, to A.D. McCormick, a BATCo lawyer. This document reflects the internal discussion about whether any of the research they had in their possession at this time should be submitted, including "Battelle's work." Then, U.S. Ex. 22,734, a note from "Yeaman" of Brown & Williamson to Mr. McCormick dated July 3, 1963, states, "Finch agrees submission Battelle or Griffith developments to Surgeon General undesirable . . . ."

Q: As a research scientist, do you believe the Surgeon General's committee would have considered carefully scientific information bearing on nicotine and addiction submitted by Defendants?

A: Yes.

Q: Why?

A: The industry would have been assumed to have been most knowledgeable about the role of nicotine in the use and persistence of use of its product. An admission by the industry that nicotine was critical and essential and appeared to function as an addictive drug would have been likely to have been considered very seriously by the committee.

Q: In your opinion Dr. Henningfield, would the conclusion reached by the Surgeon General have been different if the Surgeon General's Advisory Committee knew what the industry knew?

A: It is plausible that had the Surgeon General's Advisory Committee had full knowledge of

what the industry knew and the industry's conclusions, that information could have tipped the balance and placed nicotine into the addiction rather than habituation category. But of course, there is no way of knowing for sure. Nonetheless, as an addiction expert who has served on many advisory panels and expert committees charged with making decisions in the face of some uncertainty, I believe that my conclusion is reasonable.

Q: What leads you to this conclusion?

A: The Committee did recognize the importance of the pharmacologic effects of nicotine. However, it did not see these pharmacological effects as being as strong as they are because of the limited data available to the Advisory Committee. Knowledge of available industry data would have provided the additional information that would likely have made the difference in placing nicotine in a different category.

Q: What industry information would have been given serious consideration by the Committee?

A: Its knowledge on the critical importance of nicotine, reflected in the HIPPO documents and other documents; other information about the importance of nicotine dose; the tobacco companies' assumptions that there was what we now term a "withdrawal syndrome" as evidenced, in part by its studies to better understand the underlying physiology of the withdrawal syndrome; its efforts to more effectively control the nicotine levels delivered to the bloodstream; and so much more that has come to light in other internal tobacco industry documents.

Q: Are the 1957 WHO criteria applied in the 1964 Surgeon General's Report considered scientifically valid today?

A: No. The standard used in the 1964 Surgeon General's Report was replaced by the WHO's new criteria in 1964.

Q: Why was the 1957 set of criteria replaced?

A: While the 1964 Surgeon General's Report was being prepared, the World Health Organization Expert Committee was revising the criteria for addictive drugs. Also released in 1964, the WHO report recommended that the distinction between "addiction" and "habituation" be dropped as meaningless, and recommended that the term "dependence" be used as a more neutral term that would not carry the baggage of "addiction," including the early and mid-century baggage that addiction implied immorality and criminality.

The criteria continue to advance with advances in drug addiction related science. This is evidenced by evolving criteria and tests used to assess "abuse liability" or "addictiveness" which are required by WHO, FDA, and DEA, including my own former laboratory at NIDA, which was the nation's lead laboratory for conducting such assessments and refining the methods of assessment.

For example, in the late 1960s, national and international agencies involved in determining whether a substance was sufficiently addicting to merit control would not have accepted arguments against such categorization – also called "scheduling" – from a pharmaceutical company based on the 1957 WHO criteria.

Q: Has it been commonplace to modify scientific and medical definitions over time in areas other than drug addiction?

A: Yes. As is the case in virtually all areas of medical science, including diagnosis of cancer, stroke, hepatitis, and HIV/AIDS, the criteria and terminology advance with advances in scientific evidence. In these other areas it would seem ridiculous to rely upon decades-old criteria, in the face of new evidence that have greater validity.

Q: After the 1964 Surgeon General's Report, when was the next time a major medical

or scientific organization considered the question of whether smoking or nicotine is addictive?

A: In 1980, the American Psychiatric Association (APA) recognized "tobacco dependence" and "tobacco withdrawal" as mental disorders meeting similar criteria as "opioid dependence" and other drug dependence disorders in its Diagnostic and Statistical Manual, 3rd Edition**.**

Q: I will return to the APA and DSM-III in a moment. Were there changes in the public health community's understanding of nicotine between 1964 and the APA's release of the DSM-III in 1980?

A: Yes, there were incremental advances.

Q: What were they?

A: There was a gradual increase in knowledge suggesting that nicotine played a modulating role as evidenced by the conditions under which compensation appeared to occur. Though, the role of nicotine was also questioned due to the imprecise nature of compensation and the failure of some studies to document compensation. There was also some animal work confirming that nicotine was behaviorally active and produced effects that overlapped with stimulants and sedatives, perhaps related to the dose, but that nicotine was not characterized simply as a stimulant or sedative.

Q: What do you mean that there was evidence that nicotine played a "modulating role"?

A: For example, giving people different forms of nicotine while they were smoking could reduce smoking. Smoking rates appeared to be crudely but generally decreased when given high nicotine yielding cigarettes, and giving a drug that blocked nicotine's effects in the brain altered smoking, whereas a similar drug that did not enter the brain had no effect on smoking.

Q: Please briefly describe what the APA does as an organization.

A: The American Psychiatric Association is the world's major professional organization of scientists and clinicians focused on psychiatric or mental disorders by advancing science, education, and treatment.

Q: What is the purpose of the DSM?

A: The Diagnostic and Statistical Manual of Mental Disorders enables clinicians to recognize disorders or diseases, provide objective diagnostic methods for identifying persons with psychiatric diseases, and thereby provide the foundation for treatment and research.

Q: Why in DSM-III was the condition called "tobacco" dependence and withdrawal rather than "nicotine" dependence and withdrawal?

A: The syndromes were designated "tobacco dependence" and "tobacco withdrawal" rather than nicotine dependence and nicotine withdrawal, respectively, because of insufficient knowledge and understanding regarding the specific role of nicotine in smoking, whereas it was clear at that time that smoking could lead to dependence and withdrawal. It was clear to the developers of that manual that nicotine was involved in smoking, but there were important unresolved questions as to how important the role of nicotine itself was, as opposed to the myriad other constituents of tobacco smoke.

Q: Dr. Henningfield, in 1980, after APA identified "tobacco dependence" in the DSM-III, did Defendants state publicly that they agreed that smoking or tobacco use was properly characterized as a "dependence"?

A: No. In fact, the industry later argued through its experts who testified before the U.S. Congress, under sworn oath in trials, and in their statements to FDA in the 1990s that neither tobacco dependence nor withdrawal should be recognized among other drug dependence and

withdrawal disorders.

Q: At that time, did Defendants make any statements informing consumers or the public directly that smoking was a drug-dependent behavior, or that nicotine was a drug of dependence?

A: No.

Q: How did the independent research community's understanding of nicotine and compensation in 1980 compare with what the industry knew?

A: The public health community by and large did not view nicotine as addicting and was supporting research to ascertain the role of nicotine in modulating smoking. Smoking cessation was largely behaviorally focused, with relatively little attention given to the possibility that there was a true nicotine withdrawal syndrome, mental impairment mediated by nicotine deprivation during withdrawal, or physiologically driven pressure to relapse.

Before the 1980s, even though there was considerable evidence suggesting an important role of nicotine, that role was unclear and far from agreed upon by leading experts. The pre-1980s uncertainty about the role of nicotine stemmed from gaps in information available to researchers such as the lack of clear animal data showing that nicotine would serve as a positive reinforcer.

For example, in 1979, Michael Russell, one of the most well-regarded of the public health researchers on nicotine, wrote a chapter published in a NIDA monograph about smoking titled, "Tobacco Dependence: Is Nicotine Rewarding or Aversive?" This is U.S. Ex. 65,420. In it, Russell explored whether nicotine was an important factor in smoking. While Russell stated that "We know that tobacco smoking is highly dependence-producing," he wrote that it remained unproven "that nicotine is what smokers seek." In fact, Dr. Russell even raised the possibility

that the main role of nicotine might be to limit tobacco intake by virtue of its aversive effects that would occur when high dosages were achieved. Dr. Russell noted key gaps in knowledge, including that results with animal models of nicotine self-administration were inconclusive.

Meanwhile, the tobacco industry, with its assumption that nicotine was critical to sustaining compulsive smoking and was addictive, was at a whole different level of research: it was examining the mechanisms of nicotine addiction, studying the minimum satisfying or addictive dose of cigarettes, and studying ways to increase the kick per milligram of nicotine in the tobacco. The public health community was far behind the tobacco industry in its understanding of the role of nicotine in smoking and its efforts to advance public health, tobacco use prevention, and therapy to enable cessation on this premise.

Q: Did you personally share the uncertainty expressed by Dr. Russell?

A: Yes. I questioned the specific role of nicotine – apart from tobacco – in the withdrawal syndrome that usually accompanies abrupt tobacco deprivation. I raised the same issues that had been raised by the APA, because although the occurrence of a tobacco withdrawal syndrome accompanying tobacco deprivation had been recognized by the APA in 1980, the specific role of nicotine among the many constituents of tobacco smoke had not been thoroughly studied.

Q: In performing its evaluation of the addictiveness of nicotine, what criteria did the APA use?

A: The APA, because it is concerned with clinical treatment of behavioral and psychiatric conditions, relied primarily on behavioral measures for assessing drug dependence – such as the amount of time spent engaged in drug-seeking or drug-related behavior, the drug's effect on a person's life and ability to function, and effects on behavior when the drug-taking stops.

For dependence, the same criteria are applied across drugs, although the specific pattern

of signs differs somewhat from drug to drug for the simple reason that although morphine, cocaine, pentobarbital, marijuana, and nicotine are all meet basic criteria as addictive drugs by the APA or the DEA or the WHO, they all can be distinguished on the basis of their pharmacology in certain respects.

Q: Were these the correct criteria to use at that time?

A: Yes.

Q: Are these the criteria in use by the APA today?

A: Today's APA criteria are fundamentally the same, but if you examine the DSM-III, DSM-III-R, and DSM-IV you will see that there has been an evolution of the criteria as the scientific and clinical understanding of addiction have continued to advance. I understand that the same is true with respect to disorders such as depression and HIV, although I do not claim expertise in the diagnostic criteria for those disorders.

Q: Were the criteria by which tobacco use and withdrawal were evaluated in the DSM-III unique to smoking and tobacco?

A: No, the same criteria have historically been applied to alcohol, opioids, sedatives, and other widely accepted dependence-producing substances. The clinical and scientific evidence available for tobacco was simply evaluated against the existing DSM criteria.

Q: Was the APA's approach in the DSM-III of listing the substance – tobacco – rather than the chemical entity – nicotine – unique to tobacco?

A: No, cannabis – and not THC or tetrahydrocannabinol – was listed with respect to what is more commonly known as marijuana.

Q: Did the APA eventually resolve its questions about nicotine's role in smoking?

A: Yes. By its 1987 revised version of the DSM-III, known as DSM-III-R, the APA

recognized the specific and critical role of nicotine in dependence and withdrawal and it changed the terminology to refer to "nicotine dependence" and "nicotine withdrawal."

Q: Have you been personally involved in any work with the APA on the issue of addiction?

A: Yes. I worked on the APA Advisory Committees that contributed to the drug-dependence sections of the DSM-III-R and to the DSM-IV, which was issued in 1994.

Also, our research at NIDA contributed to the conclusion that the syndromes formerly called "tobacco" withdrawal and dependence by the APA could be termed "nicotine" withdrawal and dependence because our research helped to confirm that nicotine was the key pharmacologic agent in tobacco dependence and withdrawal. Additionally, our research provided additional support for the inclusion of concentration- and attention-related deficits as symptoms of nicotine withdrawal.

Q: Dr. Henningfield, around the same period of time as the 1980 issuance of the DSM-III by the APA, did any other organizations similarly address the issue of tobacco use as a condition related to dependence?

A: Yes. In 1978, the WHO had included "tobacco dependence" in its International Classification of Diseases, 9th Revision, known as the ICD-9.

Q: How does the WHO's ICD-9 relate to the WHO Expert Committee you referred to earlier in your testimony?

A: The ICD-9 provided an internationally recognized system for diagnosing and categorizing diseases. Like APA's DSM, the ICD is focused on diagnosis of diseases to guide research and clinical treatment. Unlike the APA's DSM, the ICD is not limited to psychological or psychiatric conditions. By contrast, the WHO Expert Committee on Drug Dependence is more focused on

examining the scientific properties of chemical substances to determine whether they meet the WHO's criteria for classifying a substance as dependence-producing.

Q: What do you mean by "internationally recognized"?

A: Generally, Member States of the United Nations' WHO officially recognize the disease categorizations and diagnostic criteria provided by the ICDs, although all nations can use them and in practice most nations do.

Q: Are you familiar with the ICD-9?

A: Yes.

Q: How did you become familiar with this report?

A: I consulted it when working on the Surgeon General's Reports on smokeless tobacco and on nicotine addiction.

Q: Does the ICD discuss drug dependence?

A: Yes.

Q: How was the issue of tobacco addressed in the ICD-9?

A: The ICD-9 included tobacco dependence as a disease entity. However, the ICD-9 listed tobacco dependence separately from drugs such as heroin, in part, apparently, because tobacco use rarely appeared to lead to "psychotoxic" – that is, intoxicating – effects and such effects were considered important aspects of the clinical disorder of dependence by the WHO at that time.

Q: How did the ICD-9's consideration of "intoxication" as a criteria of drug dependence compare to the approach of the WHO's Expert Committee on Addiction Producing Drugs to intoxication?

A: By 1964, the WHO Expert Committee on Addiction Producing Drugs did not consider "psychotoxicity" or "intoxication" as defining criteria for dependence-producing drugs.

Q: Has the WHO issued a subsequent version of the ICD?

A: Yes. In 1992, ICD-10 was published.

Q: Did ICD-10 discuss smoking and addiction?

A: Yes.

Q: How, if at all, did ICD-10's conclusions about smoking and addiction differ from the conclusions reached in ICD-9?

A: In 1992, the ICD-10 dropped the criteria of psychotoxicity or intoxication for dependence-producing drugs. As a result, tobacco was included along with other dependence-producing drugs such as cocaine and heroin.

Q: Why did ICD-10 drop the criteria of psychotoxicity or intoxication for dependence-producing drugs?

A: By then it was overwhelmingly clear that intoxication was neither a necessary nor sufficient condition to cause or define dependence, because many dependence-producing drugs were often used with little or no evidence of intoxication, such as cocaine and morphine, and because other drugs that were rarely dependence-producing, such as major tranquilizers and antihistamines, could produce behavioral disruption and "intoxication."

Q: Can nicotine produce intoxication?

A: Yes, when a person takes higher doses than he or she is tolerant to, particularly upon initial episodes of smoking or using smokeless tobacco.

Q: Do you consider it significant that ICD-10 lists "tobacco" dependence and withdrawal disorders while DSM-III-R listed "nicotine" dependence and withdrawal disorders?

A: No. ICD recognizes that it is the tobacco-delivered forms of nicotine that are the most

addictive and likely to lead to withdrawal as well as being extremely harmful. In contrast, DSM-III-R emphasized that because nicotine is the drug in tobacco that defines the syndromes, the syndromes are designated by nicotine.

They are both based on the science. Tobacco-delivered nicotine, as also discussed in the UK's Royal Society of Physicians Report in 2002 and the 1988 Surgeon General's Report, is far more deadly and addictive than pure nicotine-based medicines such as nicotine gum and patches. On the other hand, there are merits to defining the disorders with respect to the main chemical constituent that defines the addictive disorder. I believe that both approaches have merit and do not see them as contradictory.

Q: What do you consider the next significant development in the independent scientific and medical community's understanding of smoking and nicotine following the 1980 APA decision to include "tobacco dependence" and "tobacco withdrawal" in its DSM-III?

A: In 1982, NIDA concluded that scientific evidence demonstrated that nicotine is addictive.

Q: How did NIDA communicate its conclusion in 1982 that nicotine is addictive?

A: The Director of NIDA, Dr. William Pollin, gave testimony before Congress in 1982 and 1983.

Q: Were you personally involved in NIDA's research and conclusions on this issue?

A: Yes. In fact, I was part of the NIDA team involved in the development of Dr. Pollin's testimony.

Q: Was Dr. Pollin's testimony officially given on behalf of NIDA?

A: Yes.

Q: The May 5, 1983 version of Dr. Pollin's testimony has been marked as Joint Ex. 58,808. Please briefly summarize Dr. Pollin's testimony.

A: Dr. Pollin testified before the U.S. Congress about the findings of the Institute that nicotine met all standard criteria used by NIDA, the Drug Enforcement Agency, and the WHO for a dependence-producing drug. Among the NIDA conclusions in Dr. Pollin's testimony were that scientific studies showed nicotine to meet the criteria for the "abuse liability of a substance" – "psychoactive and behavioral effects, reinforcer properties (e.g., demonstrated euphoriant effects), and that its use maintains drug-seeking behavior." He also stated that "not only has tolerance to some of the effects of smoking been demonstrated, but metabolic tolerance to various components of cigarette smoke, including nicotine, has been documented." Dr. Pollin also communicated that smoking met the criteria for nicotine drug dependency – "(1) persistent, regular use of a drug, (2) attempts to stop such use which lead to discomfort and often result in termination of the effort to stop, (3) continued drug use despite damaging physical and/or psychological problems, and (4) persistent drug-seeking behavior."

Q: What were the standard criteria used by NIDA for a dependence-producing drug at that time?

A: In brief, they were the same as those used to enable FDA and DEA to determine if a substance should be officially designated a "controlled substance," which is the legal term for an addictive drug adopted by the Controlled Substance Act of 1970.

Q: What were the standard criteria used by the DEA for a dependence-producing drug at that time, that were applied by NIDA?

A: There are 8 factors specified by the Controlled Substances Act which include determination of the actual or relative potential for abuse compared to known dependence producing drugs, scientific evidence of pharmacological effects relevant to abuse, the history and pattern of abuse of the chemical or substances containing the chemical, the psychic or

physiological dependence liability, and its risks to public health. Evidence of addiction potential on any of these factors can trigger categorization as a "controlled" or "scheduled" substance; however, in practice scheduling decisions are based on the convergence of evidence and the overall strength of the effects on key measures such as self-administration and human abuse liability tests.

Q: What data did NIDA rely upon in concluding that smoking was a nicotine-driven drug dependency?

A: As evidenced by Dr. Pollin's testimony, NIDA relied on previously existing data as well as intramural findings from the Addiction Research Center showing that nicotine met key criteria as a reinforcing and euphoriant drug in animal and human studies. NIDA determined that the convergence and strength of the evidence across the criteria used for drug scheduling decisions was sufficient to conclude that nicotine met the same criteria for an addicting substance as prototypic addicting substances such as morphine and cocaine.

Q: What role, if any, did Defendants play in the hearings?

A: The various companies provided testimony through their experts. Dr. Theodore Blau was their lead expert concerning addiction.

Q: What was the substance of that testimony?

A: In brief, that Dr. Pollin was trivializing the concept of dependence and that listing tobacco as dependence producing was inappropriate. The testimony claimed that NIDA was wrong, that the primary role of nicotine in tobacco was as a naturally occurring substance that added to the sensory pleasures of smoking, and that cigarettes were more like hamburgers and potato chips than addictive drugs.

Q: After NIDA concluded, and stated publicly in 1982, that smoking was drug

dependent behavior and that nicotine delivered by cigarettes met established criteria for dependence-producing drugs, did Defendants inform consumers or the public directly that smoking was a drug-dependent behavior, and that nicotine was a drug of dependence?

A: No. Furthermore, the industry opposed NIDA's conclusions and its efforts, along with CDC's Office on Smoking and Health, to label cigarettes as addictive.

Q: At that point in time, did you have access to the internal documents of Defendants that discussed their research and understanding about nicotine?

A: No.

Q: Based upon your subsequent review of Defendants' internal documents, was the testimony of industry representatives in 1982 consistent with their internal approach and conclusions about nicotine at that time?

A: No.

Q: How did external statements from Defendants' representatives differ from the perspective held internally by Defendants about nicotine's role in smoking?

A: None of the public statements included any of the conclusions that we now know the industry itself had come to. The public statements were absolutely contrary to their internal conclusions and their assumptions guiding their product research, such as the importance of sustaining the impact of nicotine while decreasing the amount that would be measured in FTC machine testing. Yet in their public statements, the industry and its experts trivialized NIDA's conclusions that cigarette smoking was a true form of drug dependence and that nicotine met the same criteria for an addictive drug that any other drug labeled addictive – or more technically, dependence-producing – would be expected to meet. Defendants stated publicly that NIDA's conclusions were not scientifically motivated, that NIDA was biased, and that the evidence was

not conclusive.

Q: How, if at all, did Defendants' response to NIDA's conclusions in 1982 affect researchers like yourself who were working in the smoking and health field at that time?

A: In hindsight, it was a lost opportunity that delayed progress in the field of tobacco and nicotine addiction research. This was an opportunity for the industry to come forward with its conclusions and studies that were not uncovered until the 1990s to help NIDA, APA, and other organizations more fully understand the addictive process, including the mechanisms by which nicotine dose is manipulated in cigarettes, but it did not. Instead, the tobacco companies simply rejected the conclusions of those organizations.

Q: Dr. Henningfield, were there independent scientists who disagreed with NIDA's characterization of smoking as a nicotine-driven drug dependence in 1982?

A: Yes, as is typical in any area of science, there were some who questioned what was becoming overwhelmingly established. This is the case even to this day.

Q: So was it similarly reasonable for Defendants in 1982 to deny that smoking is addictive because of nicotine?

A: No.

Q: Why not?

A: Because, as the industry documents make clear, the tobacco companies themselves had concluded by the early to mid 1960s that nicotine is the critical pharmacological agent in cigarette smoke that makes smoking addictive.

Further, the main authoritative expert bodies in the U.S. which address the issue had come to firm science based conclusions, namely APA and NIDA.

Q: How, if at all, did the U.S. Public Health Service respond to Dr. Pollin's testimony?

A: The testimony prompted the development of a pamphlet called "Why People Smoke" that discussed smoking as an addiction, and that nicotine played the key physiological role that strengthened the desire to smoke and kept people smoking. It concluded that "smoking can be more than just a "bad habit", that it can be a drug dependence, an addictive behavior."

Q: Was this the first time the Public Health Service issued such a public statement that nicotine was addictive?

A: I believe it was the first official PHS advisory, based on analysis from the National Institute on Drug Abuse, concluding that cigarette smoking met criteria as a form of drug dependence.

Q: After NIDA announced its conclusion about nicotine addiction in 1982, what was the next major event in the development of the independent scientific and medical community's view concerning smoking, nicotine, and addiction?

A: For cigarettes, the Surgeon General confirmed this conclusion in the 1988 Report entitled "The Health Consequences of Smoking: Nicotine Addiction."

Q: Why did you limit your answer to cigarettes in your previous response?

A: Because in the 1986 Surgeon General's Report dealing with smokeless tobacco, the Surgeon General addressed the question of the addictiveness of smokeless tobacco.

Q: Dr. Henningfield, I have provided you a copy of the 1986 Surgeon General's Report on the Health Consequences of Using Smokeless Tobacco, previously admitted into evidence as U.S. Ex. 60,599. Are you familiar with this report?

A: Yes.

Q: How did you become familiar with this report?

A: As I noted earlier, I was part of the NIDA team that was directed to address the addiction

question concerning smokeless tobacco for this report.

Q: Who authored this Report?

A: An advisory committee to Surgeon General Dr. C. Everett Koop, under the direction and general editorship of Dr. Joseph Cullen of the National Cancer Institute, who chaired the Committee.

Q: What specifically did the Report say about nicotine and addiction?

A: On the question of addiction, the Report stated:

> A number of studies have shown that nicotine exposure from smoking cigarettes can cause addiction in humans. In this regard, nicotine is similar to other addictive drugs such as morphine and cocaine. Since nicotine levels in the body resulting from smokeless tobacco use are similar in magnitude to nicotine levels from cigarette smoking, it is concluded that smokeless tobacco use can be addictive. Besides, recent studies have shown that nicotine administered orally has the potential to produce a physiologic dependence.

Q: What is the significance of this statement?

A: This Report represents the first time a clear consensus statement was made in a Surgeon General's Report that nicotine causes addiction. In addition, the conclusion was based largely on consideration of cigarette-related data.

Q: What data did the Advisory Committee rely on in preparing the 1986 Surgeon General's Report on smokeless tobacco?

A: Much of the same data relied upon earlier by NIDA that led NIDA to conclude that nicotine was an addicting drug and cigarette smoking an addictive behavior. In addition, data

concerning patterns of use of smokeless tobacco, nicotine intake, and nicotine withdrawal were available.

Q: In performing its evaluation of the addictiveness of nicotine, what criteria did the Committee use?

A: The approach of the 1986 Report was to compare nicotine, cigarette smoking, and smokeless tobacco use to relevant data on prototypic addictive drugs along the same dimensions used by NIDA to assess any substance as a potentially addicting substance. These are the same as I summarized above for the Controlled Substance Act.

Q: Were these the correct criteria to use at that time?

A: Yes.

Q: Are these the criteria in use today?

A: These general criteria have been the mainstay of evaluations over several decades since the Controlled Substances Act codified the foundation for determining if a substance is appropriately controlled by the DEA as an addictive substance. Of course, the precise wording varies and the specific nature of the tests continues to evolve with advances in science and experience.

Q: Returning to the 1988 Surgeon General's Report, Dr. Henningfield, were you personally involved in the preparation of the 1988 Report?

A: Yes. As I stated earlier in my testimony, I was invited to serve as one of the four scientific editors early in 1987, I believe it was in February but it could have been March.

Q: Earlier you used the word "charge" to describe the 1964 Advisory Committee's purpose. What was the "charge" as you understood it for the 1988 Report?

A: To thoroughly examine the scientific foundation for the conclusions that had been drawn

earlier by the American Psychiatric Association, NIDA, the Surgeon General's Advisory Committee on Smokeless Tobacco, and other reports in the 1980s that had concluded that nicotine was addicting, and to determine the overall strength of evidence, potential implications for public health, tobacco use prevention, treatment development, cigarette labeling, and policy. This was my understanding.

Q: Was it your "charge" to address whether smoking was addictive?

A: No, that had already been established. Of course, had our extensive review of the evidence concerning nicotine addiction and smoking led to an alternate conclusion and not been supportive of the earlier conclusions of NIDA and other organizations, the Report's conclusions would have reflected that. In fact, the key charge of the reviewers to any Surgeon General's report is to determine if the conclusions are supported by the data and the analysis.

Q: How did the 1988 Report's overall objective compare to that of earlier Reports?

A: The approach of different Surgeon General's Reports has varied depending upon the state of the science when they were prepared. Some Reports have examined the state of scientific evidence to determine whether or not there is evidence to conclude there is a causal relationship between some aspect of smoking and disease. For example, one of the 1986 Reports examined the evidence in order to determine whether or not environmental tobacco smoke was appropriately considered a cause of cancer and other disease; the other 1986 Report, on smokeless tobacco, examined whether or nor smokeless tobacco caused oral cancer and addiction and other diseases.

Other Reports represented a compilation of evidence where clear conclusions had already been reached. For example, at the time that the 1982, 1983, and 1984 Reports were done on cigarette smoking and cancer, heart disease, and lung disease, respectively, it had already been

well established that smoking caused these diseases. The purpose of these Reports was to thoroughly assess the overall state of the science to determine additional potential conclusions of consequence for public policy, research, and communications to the public about the health risks of smoking. The purpose and approach of the 1988 Report was analogous to these Reports, but in the area of nicotine.

Q: How was this examination carried out for the 1988 Report?

A: Surgeon General C. Everett Koop worked with CDC staff to assemble major institutions with jurisdiction over these issues such as NIH, NCI, and NIDA to address nicotine addiction as it relates to cigarette smoking.

Q: How were the chapters drafted?

A: We assembled groups of section authors since no chapter could be completed by any single expert on a timely basis, with the exception of the chapter on "pharmacokinetics, metabolism, and pharmacodynamics" which Dr. Benowitz primarily drafted, and the appendix on the "toxicity of nicotine," which Dr. Benowitz also drafted. I believe that "tobacco use as drug dependence" and "tobacco use compared to other drug dependencies" each involved at least 10 section authors with specialists covering subtopics such as drug discrimination studies, nicotine self-administration, relapse to drug use across addictions, and so forth.

Q: How were the draft sections reviewed?

A: The draft sections were each reviewed by approximately 5-10 outside peer reviewers who were national and internationally recognized leaders in the areas they were asked to review. They were asked to examine the draft conclusions particularly rigorously.

Q: What occurred after the review of the individual sections?

A: The chapters were revised, taking consideration of every suggestion with the editors often

working together, going back to contributors, and sometimes seeking additional opinions to resolve topics in which the reviewers differed substantially with a contributor. Dr. Davis and other editors and staff at CDC were also involved in assuring oversight and integrity of the process. The chapters were then assembled into a single draft volume with draft major conclusions included.

Q: Once a single draft was assembled, what happened next?

A: The volume was sent to senior scientists and leaders in the addiction and tobacco fields, editors and senior reviewers of previous Surgeon's General's Reports, as well as many federal agencies including NIH institutes and FDA. This review process resulted in the discovery of further gaps and suggestions to strengthen the report and the clarity of its communication.

Q: What is an example of such a "gap"?

A: One initial gap was the omission in the first chapter of a summary articulation of the criteria used to determine that nicotine was an addictive drug. As I stated earlier, that conclusion had been drawn by the American Psychiatric Association in 1980 and 1987 from the clinical perspective. We also summarized the key criteria used by NIDA to determine whether or not a substance is appropriately categorized dependence producing or a "controlled" substance to use the technical term applied to substances other than tobacco or alcohol. These criteria are summarized at the beginning of the report and they are consistent with criteria of these other organizations.

Q: How long did the entire process of developing the 1988 Report take?

A: My involvement was about a year and a half, from the time of my first contact in about February or March of 1987 until the release in May of 1988.

Q: Why did it take so long?

A: The subject matter was complex, crossed many disciplines, and it took time to get reviews and rework the sections. This was exacerbated by the fact that many of the required experts were NIDA-funded scientists and NIDA had seen a great increase in funding and research beginning in about 1986, in response to HIV/AIDS and the then-growing cocaine problem. Thus, many of the experts were already overburdened. The editors concurred that the importance of the report justified taking more time if that is what it would take to issue a report that would stand the test of time and the expected intense criticism and scrutiny from the tobacco industry.

Q: Was there new scientific evidence available to the public health community compared to that available to the Surgeon General's Advisory Committee in 1964?

A: Much more. The section evaluating the addiction issue in the 1964 Report was 10 pages long and included 36 references. By comparison, the 1988 Report on nicotine was over 600 pages long and included more than 2,000 references.

Q: What were the specific findings of the 1988 Report, which has been previously admitted into evidence as U.S. Ex. 64,591?

A: In particular, the 1988 Surgeon General's Report reached three main conclusions regarding the addictiveness of tobacco products: (i) cigarettes and other forms of tobacco are addicting; (ii) nicotine is the drug in tobacco that causes addiction; and (iii) the pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Q: I want to first address the committee's first finding, that cigarettes and other forms of tobacco are addicting. What was the basis for that conclusion?

A: The Report concluded that tobacco use met three primary criteria for drug addiction: (i) use is highly controlled or compulsive; (ii) nicotine in tobacco products produces psychoactive or

mood-altering effects; and (iii) nicotine reinforces behavior that results in continued intake of nicotine in the form of tobacco products. These key criteria are embodied in those of the APA and WHO definitions.

Q: What evidence supported the conclusion that use is highly controlled or compulsive, the first criterion of addiction that you identified?

A: This conclusion was supported by several lines of evidence, including laboratory studies with humans involving means of administering nicotine; giving cigarette smokers nicotine by way of intravenous infusions, nicotine gum, and other forms, to determine if subsequent smoking was decreased; animal and human studies of behavioral effects; studies of nicotine dosing to determine if nicotine dose was of significance in cigarette smoking as it is for other forms of addictive drug self-administration; and human studies of rates and patterns of smoking in the real world.

Q: What evidence supported the conclusion that nicotine produces psychoactive or mood-altering effects, the second criterion for addiction that you identified?

A: Again, different types of evidence, including human studies showing that a variety of forms of nicotine, including in the form of cigarettes, produced dose-related changes in ability to feel the drug, and mood alteration, as well as feelings that were similar in key respects to other addictive drugs as measured on rating scales developed in studies with prototypic addictive drugs in the 1960s and 1970s. Animal studies showed that nicotine produced behavioral effects on measures considered to be models for human psychoactive effects.

Q: What evidence supported the conclusion that nicotine reinforces behavior that results in continued intake of nicotine in the form of tobacco products, the third criterion for addiction that you identified?

A: A variety of methods of nicotine dose alteration in tobacco products and giving volunteers either nicotine or nicotine blocking drugs converged to demonstrate that nicotine was a major determinant of the desired effects of smoking and of patterns of smoking and smoke intake. Animal self-administration models, by that point, had also demonstrated that nicotine could serve as an effective biological reinforcer.

Q: You just testified that nicotine was a "major determinant." What are the other factors determining patterns of smoking and smoke intake?

A: As discussed in the 1988 Surgeon General's Report and elsewhere, many factors influence cigarette smoking patterns, including sensory factors, the so-called "tar" fraction of the smoke, social factors, and even environmental stimuli, which can trigger craving for cigarettes and cigarette smoking.

Q: You identified three "primary criteria" for addiction in the 1988 Report. Did the 1988 Report identify criteria for addiction other than the three you have identified?

A: The 1988 Report also referenced the APA's DSM criteria for nicotine dependence and withdrawal and verified that patterns of cigarette smoking indeed met such criteria. It also compared cigarette smoking to prototypic addictive drugs including morphine, cocaine, and alcohol, along key dimensions including risk of developing dependence, persistence of use, patterns of relapse following treatment, and patterns of self-achieved abstinence or "spontaneous remission."

Q: Why didn't the primary criteria include "intoxication" as the 1964 Surgeon General's Report had?

A: First, it was acknowledged that nicotine can produce intoxication; however, intoxication, along with personality disorder and harm to society cited in the 1964 Report, were hold-over

criteria from the 1950s WHO Expert Committee, and were not criteria used by national or international agencies for determining if a drug was addictive. As I testified earlier, these 1957 WHO criteria had been eliminated decades earlier by the WHO itself, DEA, FDA, and others organizations as neither necessary or nor sufficient to define an addictive, or more technically "dependence producing" or "controlled" drug or substance, respectively.

Q: How do you respond to the charge by Defendants that the definition of addiction utilized in the 1988 Report was not based on any significant scientific information not known at the time of the 1964 Surgeon General's Report?

A: By 1988, our scientific and medical understanding of drug addiction had advanced considerably since the release of the 1964 Surgeon General's Report. One only need compare the 10 pages and 36 references in the 1964 Report with the over 600 pages and more than 2,000 references of the 1988 Report to get a sense of the tremendous advances in the science.

Q: Dr. Henningfield, I want to refer you back to the 1942 Lennox Johnston study. You earlier described that the 1964 Surgeon General's Report viewed that study as an "initial" study that provided "anecdotal" evidence. Was the Johnston study discussed again in the 1988 Report?

A: Yes, in the 1988 Report that the Surgeon General reevaluated Dr. Johnston's study in light of data collected primarily by government-supported researchers in the 1980s, and came to essentially the same conclusion as Dr. Johnston.

Q: What conclusion was that?

A: The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Q: How do you respond to the charge that the definition of addiction used in the 1988

Surgeon General's Report was not based on science, but rather was intentionally crafted to include nicotine?

A: Contrary to tobacco industry claims, scientific and medical uncertainties concerning the addictiveness of tobacco products that had existed in the 1960s and 1970s were not resolved by changing definitions to fit nicotine; moreover, the definitions of WHO and APA, which were relied upon in the 1988 Report and summarized in its first chapter, did not evolve to fit nicotine. The conclusion that nicotine is addictive was resolved on science and expert consensus. The National Institute on Drug Abuse and the lead national and international organizations in the addictions field concurred with the Surgeon General's conclusions.

Q: Finally, I want to ask you about the Committee's third finding, that the pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine. What evidence supported this finding?

A: Animal and human studies showing that nicotine met the same criteria as an addictive drug as heroin and cocaine, as well as epidemiological studies of the patterns of use, cessation, and relapse of these drugs in the real world setting.

Q: How do the criteria used in the 1988 Surgeon General's Report compare with the criteria adopted by the APA in DSM-III and the WHO in the ICD-10?

A: The APA's DSM-III and WHO's ICD-10 criteria were developed to determine if addiction can occur at the level of being a serious clinical problem warranting categorization. They were not specifically directed at whether or not a "drug" or "substance" meets criteria as being addicting, although it is presumed that if drug dependence and withdrawal can develop that a dependence-producing drug must be involved. Therefore, the 1988 Surgeon General's report

relied, in part, upon the APA and WHO findings that nicotine/tobacco dependence and withdrawal could occur with tobacco use and that nicotine was the key pharmacological agent.

In addition to these clinical criteria, the 1988 Report considered the chemical and pharmacological evidence considered by NIDA, DEA, and FDA in determining if a drug is addictive. Bluntly put, nicotine met criteria as an addictive drug by any and all of these measures, none of which had been conceived by our committee or developed to accommodate tobacco and nicotine.

Q: Were there independent scientists who disagreed publicly with the Surgeon General concluding in 1988 that smoking behavior is maintained primarily by nicotine addiction?

A: Yes. As I said before, there are always dissenting scientific voices. However, by 1988, most of the vocal dissenting voices were scientists acting on behalf of the tobacco industry who had grants, contracts, or consultancies with it.

Q: Was it credible for Defendants in 1988 to disagree publicly that smoking behavior is maintained primarily by nicotine addiction?

A: No.

Q: Why not?

A: For the same reasons it was not credible even in 1980 or 1982 – the tobacco companies had long before concluded internally that nicotine is addictive and is responsible for creating and sustaining smoking behavior.

Q: Dr. Henningfield, now that you have explained some of the history relating to the evolution of the independent research community's understanding of addiction to smoking and nicotine, how does this history compare to the tobacco industry's own understanding of nicotine over the same time period?

A: Within the tobacco industry, the addictive nature of nicotine was understood well by the 1960s. However, as reflected in the 1979 Michael Russell article I referred to earlier, in the 1970s and early 1980s the independent research field was still trying to determine if cigarette smoking was addictive and if nicotine really did function critically to maintain smoking analogously to the role of morphine in opium product use and cocaine in coca product use.

By contrast, the tobacco industry already knew the answer – that nicotine was primarily responsible for maintaining smoking behavior – and its own research was addressing issues based on that assumption. Tobacco industry documents show that the industry was exploring the minimum threshold dose to make cigarettes acceptable and sustain addiction. They were also exploring ways to provide ever lower levels of nicotine in FTC tests without actually reducing the nicotine obtained by the smoker.

Q: Dr. Henningfield, now that you have seen internal documents describing Defendants' research and understanding of nicotine, is the information contained in those documents relevant to your work as a researcher?

A: Yes.

Q: Had you been aware of this information earlier in time, how would you, as an addiction researcher, have responded?

A: Researchers such as myself and research organizations such as NIDA would have quickly moved ahead to studies of how to prevent and treat smoking more effectively based on the knowledge that nicotine actually was critical and addictive.

Q: How was the 1988 Surgeon General's Report received by the medical and scientific community?

A: It was considered of major significance because even though many leading addiction

experts and organization that had examined tobacco and nicotine had come to the conclusion that nicotine was addicting, the Surgeon General's Report brought the level of awareness, understanding, and confidence in the conclusion to a much higher level – in fact, to a level that prompted many organizations in the United States and around the world, ranging from the American Lung Association to the American Society of Addiction Medicine, to develop communications for their own constituents.

Q: Why did the 1988 Surgeon General's Report have such an impact if NIDA and APA had already come to some similar conclusions years earlier?

A: Although I do not know the complete answer, as an expert in public health myself, I put great stock in Surgeon General's Reports because I understand that they are laboriously and conservatively evaluated, reviewed, and re-reviewed, and that the conclusions tend to stand the tests of time, generally evolving and rarely being refuted outright. In fact, such has been the case with the 1988 Report on nicotine addiction.

Q: How did Defendants respond to the 1988 Report and its conclusions?

A: The Defendants undertook an immediate, aggressive, and sustained attack on the Report's conclusions in the media through spokespersons, newspaper ads, press releases, and testimony at congressional hearings held in July 1988 and in 1994; in 1996 in their comments to the FDA on its proposed tobacco rule; and in the courts in many trials where the 1988 Report has been invoked to support the premise that cigarette smoking is addictive. I discuss a few examples of those statements below.

For example, Defendants claimed that the Report discounted tolerance, physiological dependence and withdrawal, and intoxication in order to come to its conclusion.

Q: Were Defendants' claims accurate?

A: No. The fact is that the Report documented these effects for nicotine and concluded that nicotine met these additional criteria. However, neither tolerance nor physiological dependence are primary criteria for producing or diagnosing dependence as defined by the WHO, the APA, or the DEA. Furthermore, the 1988 Surgeon General's Report accepted and followed the convention previously used by the WHO in the 1960s and the APA in the 1980 DSM-III that you do not need "intoxication" to call drugs addicting because many intoxicating substances are not addicting and because many drugs of abuse and addiction are used at doses that do not cause intoxication.

Q: Dr. Henningfield, you have been shown U.S. Ex. 64,514 for review. Please describe this document.

A: It is a May 16, 1988 "news release" from the Tobacco Institute titled "Claims that Cigarettes are Addictive Contradict Common Sense."

Q: Do you know what the Tobacco Institute is?

A: Yes.

Q: What is your understanding of what the Tobacco Institute is?

A: Ostensibly it was a trade organization representing the tobacco industry that claimed to be dedicated to investigating the health effects of smoking and disseminating the truth to smokers.

Q: What if anything is notable about the date of the press release?

A: It was released soon after the 1988 Surgeon General's Report was released.

Q: The second paragraph begins, "Smoking is truly a personal choice which can be stopped if and when a person decides to do so." Based on your understanding of addiction and your research on smoking, what is your reaction to that statement?

A: It is a contradiction in terms. The reason that addictive drugs, including nicotine, are

treated differently from nonaddictive drugs is because they do compromise personal choice due to their biological actions on the body. That is, addiction impairs freedom of choice. Moreover, nicotine, like some other addictive drugs, is potent and powerful and alters brain function. This leads the individual to a state in which they do not feel or function right without the drug.

Q: The next sentence states, "The Surgeon General's own Public Health Service figures indicate that about 40 million Americans are former smokers and that 95 percent of them quit smoking without help. These figures, and common sense, contradict any claim that smoking is an 'addiction.'" Based on your understanding of addiction, Dr. Henningfield, how do you respond to this statement?

A: In the absence of treatment for most diseases, people recover spontaneously, and hopefully that will be true for the vast majority of people who are exposed to the flu virus this year. The observation that many people recover from disease without treatment does not lead to the conclusion that the diseases are not real, or significant. To provide additional perspective, despite the fact that the vast majority of smokers have already made the choice to quit smoking and have attempted quitting at least once, only a few percent of smokers achieve the interim goal of one year abstinence annually, and of those who do, many go back to smoking. By the standards of any drug addiction, these are very poor overall success rates. In fact, many studies have shown that smoking is comparable to heroin addiction and alcoholism in ability to quit and sustain abstinence.

Q: Is that statement, in your view, consistent or inconsistent with Defendants' internal documents about smoking and nicotine?

A: These blunt statements were in direct contradiction to what the industry itself had already concluded.

Q: In the next paragraph, the Tobacco Institute states: "The claim that cigarette smoking is a drug addiction similar to cocaine or heroin use, or alcohol abuse, is unfortunate and unwarranted. The message to the American public is that using illegal drugs, such as crack or heroin, has the same risk of addiction as smoking." Based on your professional education, training, and research, including at NIDA, what is your response to Defendants' statement that a comparison of nicotine addiction to other drug addictions is "unfortunate and unwarranted?"

A: First, it contradicts both the scientific data and the industry's own comparison of smoking to narcotics and other addictive drugs. Second, the concept of motivating smokers to quit smoking with science-based information should be welcomed by any person or entity that puts life over profit. The first step in overcoming addictions is recognizing them.

Q: Do you agree that the second sentence in that passage quoted in the previous question criticizes the suggestion in the 1988 Report that smoking poses the same risk of addiction as crack and heroin?

A: Yes.

Q: What, if anything, did the scientific and medical data in the 1988 Report say about the relative risks of addiction among different types of dependence-producing drugs?

A: The risk of dependence among tobacco users is as high or higher than that observed for other addictive drugs.

Q: The second to last paragraph states:

> **The claim that cigarette smoking causes physical dependence is simply an unproven attempt to find some way to differentiate smoking from other behaviors. In fact, any feelings persons might have upon giving**

up smoking are those that would be expected when one is frustrated by giving up any desired activity. It should be noted, however, that a physical dependence to caffeine has also long been claimed, as well as the resulting "physical withdrawal" symptoms.

Are the statements in this paragraph consistent with your understanding of addiction in 1988?

A: No. The tobacco companies fabricated criteria for addictive drugs that were not recognized by WHO or APA or NIDA or DEA or FDA at that time. Not only is the above statement medically and scientifically false, the tobacco industry understood that it was not true even as it was writing the statement. The conclusions about physical dependence had been drawn by the industry decades earlier in its studies of the consequences of reduced nicotine cigarettes and smoking cessation.

This is just one example of statements that Defendants released after the issuance of the 1988 Surgeon General's Report on nicotine addiction. We all knew there were many layers of oversight on this report. The Report was, as it had to be, based on the strongest possible science, because we knew it would be looked at and scrutinized very carefully. There are thousands of studies cited in it. As to the particular statement about caffeine, the fact that caffeine can produce physical dependence and a mild withdrawal has not been sufficient for the APA to designate a caffeine dependence disorder.

Q: Based on your review of Defendants' internal documents about smoking and nicotine's role in smoking, how do these 1988 public statements of the Tobacco Institute compare to the internal knowledge and understanding of Defendants on the question of addiction?

A: The contrast between what they knew and what they told the public in 1988 and provided to Congress in July 1988 could not be greater. Their public statements and testimony provided not the slightest inkling that there could be any basis for the truth of the Surgeon General's conclusion. Yet their internal statements reveal not the slightest doubt that the effects of nicotine on the brain and nervous system are crucial to sustaining cigarette smoking.

Q: Dr. Henningfield, I have shown you U.S. Ex. 64,513 for review. This is a January 11, 1989 transcript of the television show Good Morning America. Have you seen it before?

A: Yes.

Q: Do you see that on the first page, that the transcript indicates the show included the assistant to the president of the Tobacco Institute?

A: Yes.

Q: Is there anything significant about the timing of this show, January 1989?

A: This show occurred soon after the release of the 1989 Surgeon General's Report.

Q: Please turn your attention to page 3 of the transcript, in which the Tobacco Institute spokesperson said the following:

> **I can't allow the claim that smoking is addictive to go unchallenged. As you correctly pointed out in the beginning of the segment . . . more than forty million Americans have quit smoking, and the Surgeon General tells us that ninety-five percent of those people have done it on their own, they haven't gone for formal treatment or even asked for the help of their friends of family. These are people who made a decision to quit smoking, put down their cigarettes and walked away**

from it.

The majority of people who smoke make that decision, they can quit if they want to []. It's a matter of willpower.

Dr. Henningfield, in light of your research and understanding of addiction, what is your response to that statement by the representative of the Tobacco Institute in 1989?

A: It is an attempt to mislead the public that smoking and smoking cessation are simple matters of choice, when in fact the industry already understood what the health community was also stating – namely, that the vast majority of smokers continue to smoke despite their desire to quit, and that nicotine addiction was a key obstacle to quitting. Furthermore, the industry spokesperson is leaving out the fact that those approximately 40 million former smokers were the net result of a few percent of smokers becoming nonsmokers each year over approximately 40 years since the release of the 1964 Surgeon General's Report. In fact, for most of those persons, lasting cessation had only come after several cessation attempts, and because it had come so late in their smoking careers, many would experience premature death and disease – though at reduced risk compared to persons who never quit at all.

Q: What, if anything, does the fact that people have quit smoking say about whether smoking is a drug-driven behavior of dependence?

A: That smoking is like other drug addictions, in that if people live long enough, many will eventually quit and will do so outside of a treatment program, as so-called "self quitters."

Q: Does this happen with other addictions?

A: Yes.

Q: Please provide an example.

A: It happens every day in the real world with alcohol, cocaine, and heroin, as is documented

in considerable detail in the 1988 Surgeon General's Report and elsewhere in the scientific literature. Perhaps the most dramatic and well-documented example is the Vietnam Veterans study which found that approximately 90% of persons dependent on or abusing heroin and heroin-like drugs were "clean" within three years of return to the United States. For most of these people, treatment was minimal and they maintained abstinence even though they were able to obtain drugs if they chose. Although some might interpret these data as implying that heroin addiction is not real or meaningful, leading addiction experts and organizations conclude that what it actually demonstrates is that given some incentive and support, most drug-addicted persons can eventually achieve abstinence. The fundamental first step in achieving abstinence in any addiction is recognizing that the addiction exists and is real and needs to be taken seriously as plans are made to achieve and sustain abstinence.

Q: Based on your review of Defendants' documents, is this statement from the Tobacco Institute in 1989 consistent with Defendants' internal research and understanding about nicotine's role in smoking behavior?

A: No.

Q: Dr. Henningfield, are you familiar with the statements that Defendants' Chief Executive Officers made in televised hearings before Congressman Waxman's Subcommittee on Health and the Environment in 1994?

A: Yes.

Q: Do you recall whether Defendants' CEOs stated their positions on whether nicotine is addictive?

A: Yes.

Q: What did Defendants' CEOs state about whether nicotine is addictive?

A: They denied under oath that nicotine is addictive.

Q: Was it reasonable for Defendants in 1994 to deny that nicotine delivered in cigarette smoke is addictive?

A: No.

Q: Why not?

A: For the same reasons I've stated previously – those statements were inconsistent with Defendants' internal conclusions about the role of nicotine in cigarette smoking.

Also, by 1994, the evidence was even stronger that nicotine was addictive, just as it was stronger in 1988 than in 1980, and stronger than in 1964. The evidence has continued to mount even to this day – as we see in the most recent issue of the journal *Science*, which reports still more breakthroughs in understanding the biological mechanisms of addiction.

Q: At any time after the 1988 Surgeon General's Report concluded that nicotine was the addictive agent in cigarettes, have Defendants told the public that nicotine is not addictive because it is properly characterized as a "drug of dependence?"

A: No.

Q: In their statements to their consumers or the public, have Defendants ever referred to cigarette-delivered nicotine as a drug that causes dependence?

A: I am not aware of any direct communications to consumers by the industry indicating that nicotine is dependence producing.

Q: To this day, have Defendants ever told the public that they disagree that nicotine is "addictive" because they believe the scientifically correct term to describe nicotine's pharmacological effects is "dependence-producing"?

A: Not that I am aware of.

Q: To your knowledge, have Defendants' public statements denying that nicotine is addictive rested on any substantive distinction between the terms "addictive" and "dependence-producing"?

A: No. Rather, the industry used half-century old definitions of addiction as though they were the current gold standard and attempted to discredit modern concepts of addiction and dependence, and their application to nicotine. By the tobacco industry's logic, many drugs considered addictive and regulated as controlled substances by DEA and FDA and internationally by the WHO would be exempt from such controls.

Q: Dr. Henningfield, what is the most important recent evaluation that has been done of the scientific evidence relating to nicotine and addiction?

A: The 1996 FDA Final Tobacco Rule.

Q: While you have mentioned it earlier in your testimony, please briefly explain what the 1996 FDA Final Tobacco Rule was.

A: In 1996, the FDA published its final regulatory rule asserting jurisdiction over tobacco products based on Defendants' intentional manipulation of nicotine in cigarettes. In my testimony, I am specifically referring to the FDA's Jurisdictional Determination, which was an extensive review of the scientific evidence, including consideration of Defendants' internal documents, that was the basis for its claim of jurisdiction over cigarettes.

Q: Why do you consider the 1996 FDA Final Tobacco Rule, which has been admitted to evidence as U.S. Ex. 64,323, important?

A: Its conclusions expressed in the Jurisdictional Determination of the Final Rule make it so important.

Q: What are these conclusions?

A: The key conclusions in the 1996 FDA Jurisdictional Determination, in the executive summary at page xv, are as follows:

> In the case of cigarettes and smokeless tobacco, no reasonable manufacturer could fail to foresee that these products will have significant pharmacological effects on consumers and be widely used by consumers for pharmacological purposes. All major public health organizations in the United States and abroad with expertise in tobacco or drug addiction now recognize that the nicotine delivered by cigarettes and smokeless tobacco is addictive. The first major organization to do so was the American Psychiatric Association, which in 1980 defined the "tobacco dependence disorder" and the "tobacco withdrawal syndrome." Since 1980, nicotine in tobacco products has also been recognized as addictive by the U.S. Surgeon General (1986 and 1988), the American Psychological Association (1988), the Royal Society of Canada (1989), the WHO (1992), the American Medical Association (1993), and the Medical Research Council in the United Kingdom (1994). Every expert medical organization that submitted comments to FDA on whether nicotine is addictive concluded that it is. The tobacco industry's public position that nicotine is not addictive is simply not credible in light of this overwhelming scientific consensus. The scientific consensus that cigarettes and smokeless tobacco cause addiction to nicotine makes it foreseeable to a reasonable manufacturer that these products will affect the structure and function of the body. This scientific consensus also makes it

foreseeable that cigarettes and smokeless tobacco will be used by a substantial proportion of consumers for a pharmacological purpose namely, to satisfy their addiction.

It is also foreseeable that the nicotine in cigarettes and smokeless tobacco will cause, and be used for, other significant pharmacological effects. . . . Because a reasonable manufacturer would foresee that cigarettes and smokeless tobacco will cause and be used for these well-established pharmacological effects in a substantial proportion of consumers, the Agency finds that these drug effects and drug uses are intended by the manufacturers.

Q: Do you agree with FDA's conclusions?

A: Yes.

Q: Did FDA come to significant conclusions beyond those of the 1988 Surgeon General's Report?

A: Yes.

Q: What were they?

A: The three most important conclusions in my opinion were, first, that the cigarette companies knew their products were addictive decades earlier; second, that in their cigarette development and marketing they intend to increase the risk of addiction to their products; and third, that the addictiveness of the cigarette is accounted for by more than just the pure nicotine, that it is related to the various chemicals and design features that could enhance the addictive effects of the cigarette.

Q: Dr. Henningfield, in addition to examples where the industry has affirmatively

denied and challenged the evidence of nicotine's addictiveness and its role in smoking, are you aware of any instances in which the industry has withheld or suppressed information that would have been valuable to public health researchers, like yourself, who were involved in researching cigarettes?

A: Yes.

Q: How did you become aware of such instances?

A: Through documents released in litigation against the tobacco industry, as in the 1986 smokeless tobacco case in which I served as an expert, and then in the 1990s working with FDA and serving as an expert for plaintiffs against the tobacco industry.

Q: What is a specific example of a Defendant withholding or suppressing from the public important information?

A: Philip Morris had one of the first laboratories that demonstrated what would have been an important breakthrough – that rats press levers and work for nicotine. This was important because there had not previously been a valid rat model. Philip Morris was one of the first to develop a valid rat model of nicotine self-administration, as reported internally in U.S. Ex.* 35,632, an August 24, 1981 "Progress Report" of the work in the Behavioral Pharmacology Laboratory, sent from Victor DeNoble to William Dunn. In addition, the suppressed studies showed that nicotine in combination with another smoke constituent, acetaldehyde, was more reinforcing than either substance alone.

Q: What is the importance to the scientific community of such a valid rat model of self-administration?

A: An animal model for addiction research is one of the foundational tools used by scientists trying to discover whether a substance is safe, and how substances can either cause or treat a

dependence disorder. Pharmacology is complicated, and living bodies, whether the living body is a human living body or an animal living body, are more so. The only way you can really know how a drug interacts with a living body is to put it into a living body. So researchers like myself are very reliant on animal models to make progress in science and medicine. Rat models in particular enable rapid progress because many types of factors can be quickly and economically studied. Moreover, rats tend to self-administer the same drugs that are abused by humans and to reject drugs that are not abused by humans – that is, they can provide very useful initial models for evaluating the effects of a wide range of drugs and test conditions.

The concept of addiction has at its core the idea of compulsive use, as reflected in powerful drug-seeking and drug-taking behavior. In intravenous self-administration experiments, animals learn to administer drugs to themselves. Typically, the animal has the opportunity to press a lever; when it does so, it receives an automatic intravenous infusion of a drug, through a chronically indwelling venous catheter. Several animal species, notably rats, will press levers to obtain injections of the "classical" addictive drugs such as morphine, heroin, amphetamines, cocaine, barbiturates, and benzodiazepines. Large amounts of these drugs can be self-administered in this way. Furthermore, animals will work very hard to obtain the drugs, for example, pressing a switch thousands of times, for hours on end, to obtain drugs. This drug-seeking and drug-taking behavior can dominate the animals' behavior repertoire to the detriment of normal behavior, just as in cases of serious drug abuse in humans. Therefore, intravenous self-administration is a suitable animal model for the study of drug dependence in humans.

For this reason, one of the tests that drug companies use to determine if a drug has addictive potential is a self-administration study. Laboratory animals are given the drug and researchers study whether animals will press the levers and give themselves intravenous

injections of the drug. If so, this is strong evidence that the drug has a biological effect on the brain as a reinforcer. The test thus helps the company to determine if this is an effect that will have to be addressed in the labeling and regulation of the drug. Finding that the drug is self-administered sometimes leads companies to terminate further development of the drug because the potential addictive effect will limit the use of the drug.

This test may be required by FDA if there is concern that a drug might have an addictive potential and the test is also relied upon by WHO, DEA, and other organizations involved in evaluating, regulating, and controlling addictive drugs.

Q: Do you know who at Philip Morris developed the valid rat model of nicotine self-administration?

A: Yes. Victor DeNoble and Paul Mele.

Q: How do you know this?

A: Prior to its scheduled publication in about 1982 or 1983, Dr. DeNoble had sent me a prepublication copy of the study, thinking that it was going to be published and eager to share what he appropriately considered to be a breakthrough finding with the scientific community. He knew that in my position at NIDA, I would be able to see that the study was disseminated more quickly and broadly than might have occurred through the journal publication alone. In fact, I cited the paper intended for publication in several reports that I was working on at the time.

Q: Was the DeNoble and Mele article published?

A: No.

Q: Why not?

A: After it was accepted for publication Philip Morris requested that Dr. DeNoble withdraw it from publication.

Q: How did you learn this?

A: I received a telephone call from him that I should not cite the work. For better or for worse, I had already included a brief reference to the unpublished paper in a 1984 review article published in *Advances in Behavioral Pharmacology*, where I had inadvertently failed to retract a comment about the work. Unfortunately, that comment did not contain the information necessary for anyone to replicate the findings, and the comment was so tentative due to the fact that the findings had not been replicated that this comment could hardly have been expected to generate much interest in Dr. DeNoble's work.

Q: Did a paper describing the development of a valid rat nicotine self-administration model eventually get published?

A: Yes.

Q: How long after you received the prepublication copy from Dr. DeNoble did that publication occur?

A: It was not until 1989, seven years after Dr. DeNoble's rat study, that Drs. Corrigal and Coen succeeded in developing a rat model for nicotine intravenous self-administration.

Q: Dr. Henningfield, from your perspective as an addiction researcher, what do you conclude was the effect of Defendants' conduct concerning smoking, nicotine, and addiction?

A: From a research perspective, scientists are in an ongoing struggle to prioritize their research endeavors because of limited research funding. Since resources are so limited, funding institutions must allocate research monies to issues of recognized scientific merit; and scientists must dedicate their limited time to seek answers to questions of apparent and widespread significance to the field and community.

From a clinical perspective, health care providers and insurers as a group did not take the difficulties of quitting smoking and the importance of treatment to help people quit smoking as seriously as they do now that a medical consensus regarding addiction has been reached. Until tobacco addiction, or more technically, "dependence," was an officially recognized diagnosis, effective treatments were far less likely to be researched, developed, and marketed. A specific example is that the 1988 Report triggered the process of the U.S. Agency for Health Care Policy Research to develop a clinical practice guideline to set the gold standard for treatment of dependence by health professionals, and to help legitimize their efforts to provide such treatment. This was published in 1996 and updated in 2000.

As a public health scientist studying the issue of nicotine and addiction on behalf of NIDA in 1982, I had not seen any of the tobacco industry's internal documents that revealed that the industry knew nicotine was addictive. Had the tobacco industry been forthcoming with that knowledge, research would have been advanced tremendously at a much earlier date. The tobacco industry's failure to disclose the results of emerging industry research on important aspects of nicotine addiction caused numerous research scientists to waste precious research dollars chasing what we now know were really not the key measures of addiction, such as the extent to which smokers adjusted their smoking behavior in response to changes in FTC cigarette yield. Had the industry been forthcoming with its studies and findings, we could have spent time and research dollars studying real issues, such as applying the rat self-administration model to develop new treatments. Such research could have been done at an earlier date if the industry had not challenged fundamental principles such as whether nicotine is truly addictive and the critical role of nicotine in tobacco, and had not suppressed its own research findings.

In fact, the tobacco industry could have resolved much earlier the biggest issue the

scientific community had in the 1970s and 1980s – that is, the role of nicotine in cigarette smoking. We were spending a lot of time and effort trying to understand if nicotine is critical for cigarette smoking and what the role of nicotine is in regulating smoking. Full and early disclosure of knowledge concerning these issues would have enabled researchers such as myself to justify turning our attention more aggressively to understanding how better to treat and prevent the addiction.

Q: You have testified about the effect that Defendants' activities had on the research community, and the potential development of smoking cessation therapies. Are you aware of any instances in which any of the Defendants sought to influence a maker of a smoking cessation product?

A: Yes.

Q: You have been provided U.S. Ex. 37,048 for review. What is this document?

A: It is a memorandum dated October 25, 1984 from R.D. Latshaw of Philip Morris titled "Dow-Nicorette Meeting, October 23, 1984."

Q: Please describe the document and identify any portion of this memorandum that you consider significant to your testimony.

A: The document discusses a meeting between representatives of Dow, later "Marion Merrell Dow," which was the U.S. marketer of nicotine gum for smoking cessation and a large chemical supplier to Philip Morris, and Philip Morris, after Philip Morris evidently expressed its objection to the tone of advertising for Dow's nicotine-replacement smoking cessation product. The memorandum states that:

> Nicorette smoking cessation clinics and doctors' generous distribution of Nicorette pamphlets are not part of Dow's marketing program, but are

attributed to the zealousness of some members of the medical profession. Sharrock [of Dow] said he has been carefully screening advertising and promotional materials to eliminate any inflammatory anti-industry statements. He intends that sales be maintained on a basis of Nicorette being a product for those who want or need to stop smoking. Examples were cited where ad agencies pushed anti-smoking themes and Sharrock vetoed the ideas.

The document also indicates that Philip Morris linked Dow's ability to continue to supply chemicals to Philip Morris to how aggressively Dow marketed Nicorette: "future purchases would be predicated on Dow's performance as a supplier as well as the course of the Nicorette program."

Q: Why are these passages significant to you?

A: Rather than applauding a company for attempting to give smokers one more choice – the choice to quit smoking – this document shows that the company was willing to go to great lengths to impair the marketing efforts of the company.

Q: Do you have any personal knowledge of these efforts?

A: Yes, I interacted with Marion Merrell Dow representatives who were attempting to work with NIDA and the U.S. Public Health Service to increase awareness that smoking was addictive and to encourage attempts to quit smoking. They made it clear that there were concerns in their company, but that the company had made what it considered to be the ethically right decision not to cease marketing the product and not to cease efforts to disseminate the truth, even though it might hurt other portions of their business.

Q: Dr. Henningfield, has the internal information from Defendants that you have

obtained, including through review of Defendants' documents, influenced your work?

A: Yes.

Q: How so?

A: The tobacco industry documents have had substantial impact on my recommendations and the recommendations of expert panels for research. As an example, one major area of impact has been that we now understand much more that cigarette design features have been geared to enhance the dosing flexibility and addictive potential of cigarettes. This has caused myself and advisory panels to recommend increased research on chemical, physical, and manufacturing factors that influence the addictiveness and toxicity of cigarettes.

This was summarized in the 2001 British Physicians' Report – the British equivalent of a Surgeon General's Report – as well as by the WHO's Scientific Advisory Committee on Tobacco Product Regulation, both of which focused on "tobacco-delivered nicotine" as a means of emphasizing the importance of this highly engineered chemical cocktail.

Q: Thank you, Dr. Henningfield.