**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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

**UNITED STATES' WRITTEN DIRECT EXAMINATION OF**

**NEAL BENOWITZ, M.D.**

**SUBMITTED PURSUANT TO ORDER #471**

**Q: Please state your full name for the record.**

A: Neal L. Benowitz.

**Q: Where do you currently work?**

A: I work at San Francisco General Hospital.

**Q: I want to talk about your educational and professional background. First, where did you receive your undergraduate training?**

A: Rensselaer Polytechnic Institute in Troy, New York.

**Q: What year did you graduate?**

A: I completed three years of undergraduate education in 1965. I was able to enter medical school because the University of Rochester had a policy where they would accept applicants with three years undergraduate training. I graduated from the University of Rochester School of Medicine in 1969.

**Q: Did you complete your medical studies there?**

A: Yes.

**Q: Are you board certified in any specialty?**

A: Yes. I am board certified in internal medicine, clinical pharmacology, and medical toxicology.

**Q: What does the specialty of clinical pharmacology involve?**

A: Pharmacology is the study of drugs, including how they act, their use for therapeutic indications and adverse effects. Clinical pharmacology is the medical specialty related to drug use in people. This includes drug development, studying how drugs work in people, studying and teaching optimal ways to use drugs in people, and evaluation and treatment of adverse effects of drugs.

**Q: What does the specialty of medical toxicology involve?**

A: Medical toxicology is, in a sense, a branch of clinical pharmacology. The specialty focuses on the evaluation and treatment of toxic or injurious effects of drugs or chemicals in people. Within the Division of Clinical Pharmacology at the University of California San Francisco, where I work, is the San Francisco Division of the California Poison Control Center. The activities of the Poison Control Center are medical toxicology.

**Q: Do you have any affiliation with the California Poison Control Center?**

A: Yes. I work as a consultant in the Poison Control Center.

**Q: Do you work in any other medical specialties?**

A: Yes. My clinical practice is in the areas of internal medicine and cardiovascular disease.

**Q: Getting back to your education and training, where did you perform your residency?**

A: I performed my residency in internal medicine at the Bronx Municipal Hospital Center.

**Q: What years were you in the residency program?**

A: The years of my residency were between 1969 and 1971.

**Q: What did your residency entail?**

A: For two years, I was involved in the care of patients with internal medicine problems. These patients consist of adults who have non-surgical diseases, such as heart disease, lung disease, kidney disease, and gastrointestinal disease, for example. I was directly responsible for inpatient and outpatient care under the supervision of one of the faculty attending physicians.

**Q: What did you do following the completion of your residency?**

A: After my residency, I joined the Clinical Pharmacology Postdoctoral Fellowship Training Program at the University of California San Francisco. This was a two-year training program that included training in research on drugs and six months of training in clinical areas with a focus on cardiovascular disease. Following my two-year fellowship, I spent one year in general

practice at a community clinic in Daly City, California. Subsequently, in 1974, I joined the faculty at the University of California San Francisco as an Assistant Professor of Medicine.

**Q: What did you teach?**

A: My appointment was in the areas of internal medicine and psychiatry and I taught in these general areas.

**Q: Were you later promoted beyond the rank of assistant professor?**

A: Yes. In 1981, I was appointed an associate professor also in internal medicine and psychiatry. In 1987, I became a full professor of internal medicine, psychiatry, and biopharmaceutical sciences.

**Q: In addition to your appointment as a full professor, have you been given any additional responsibilities at the University of California San Francisco?**

A: Yes. Since 1983, I have been chief of the Division of Clinical Pharmacology and Experimental Therapeutics. Also since 1983, I have been the director of the Postdoctoral Training Program in Clinical Pharmacology and Experimental Therapeutics. Finally, since 1994, I have been the Vice Chair of the Department of Biopharmaceutical Sciences in the School of Pharmacy.

**Q: What are your responsibilities in your present positions?**

A: My responsibilities include (1) teaching, (2) direct patient care, (3) research, and (4) administrative duties related to the positions I just told you about as head of the Division of Clinical Pharmacology and director of the Clinical Pharmacology Fellowship Training Program.

**Q: Let's begin with your teaching responsibilities. What students do you teach?**

A: I teach medical students, pharmacy students, medical residents, and clinical pharmacology and cardiology postdoctoral fellows.

**Q: What subjects do you teach?**

A: I teach therapeutics, cardiovascular medicine, and medical toxicology. These core areas are taught through several different avenues of instruction. For example, I organize an entire course in therapeutics for senior medical students, I give a number of lectures in the medical school to medical students and residents, and I do considerable bedside practical teaching.

**Q: With respect to the direct patient care you mentioned, what type of medical care do you provide?**

A: I have one half-day per week of a cardiology outpatient clinic. In this clinic, I follow patients over time, similar to that done in a private practice. I also spend one to two months per year as an inpatient attending physician working on either a cardiovascular disease or internal medicine inpatient service. I also provide care in the toxicology area as a medical consultant to the Poison Control Center. The toxicology care I provide can include either seeing hospitalized patients with toxicologic problems or doing consultation by telephone to other physicians and healthcare providers.

**Q: With respect to your activities as a researcher, in what areas have you conducted research?**

A: Most of my research has been in the area of tobacco and health, with a primary focus on the human pharmacology of nicotine, including addiction. I have also conducted research on other widely used stimulant drugs, including caffeine, cocaine, and ephedra-containing dietary supplements. I have worked on the issues of widely consumed drugs that can potentially cause injury to users.

**Q: What are some of the drugs that you have studied?**

A: The drugs I have studied include nicotine, caffeine, cocaine, and dietary supplements.

**Q: Can you explain to the Court the types of research you have conducted in the area of smoking and health?**

A: The overwhelming majority of my research on smoking and health has been in the area of the human pharmacology of nicotine, with an emphasis on nicotine addiction. The individual areas of study include: (1) the role of nicotine in controlling cigarette smoking and the use of other forms of tobacco; (2) individual variability in psychological and neuroendocrine responses to nicotine; (3) pathways and genetics of nicotine metabolism and pharmacologic activity of nicotine breakdown substances; (4) innovative therapies to aid smoking cessation; and (5) interactions between nicotine and illicit stimulant drugs such as methamphetamines and cocaine. My research activities include the review and consideration of the academic literature related to these issues, as well as substantial original research, much of which has been published.

**Q: Beyond the human pharmacology of nicotine and nicotine addiction, have you done other research in the area of smoking and health?**

A: Yes. I have also done smoking and health research in the areas of cardiovascular effects of smoking, biomarkers, the effects of smokeless tobacco, smoking and drug interactions, and second hand smoke, also known as Environmental Tobacco Smoke (ETS).

**Q: You mentioned research regarding biomarkers. Can you explain this research for the Court?**

A: Biomarkers are chemical substances that can be detected in the body as a result of the consumption of tobacco. Often times the biomarkers are more easily measured than the actual amount of nicotine in the body because they persist for a longer period of time and are present in higher concentrations. Thus, we have studied biomarkers as an indicator of the amount of nicotine intake for smokers.

**Q: Finally please describe your administrative responsibilities.**

A: Administration includes activities related to running the Division of Clinical Pharmacology and the Clinical Pharmacology Postdoctoral Training Fellowship Program, which I head. I am also the program leader for the Tobacco Control Group of the University of

California San Francisco Comprehensive Cancer Center. Furthermore, I serve as chairperson of the Pharmacy and Therapeutics Committee at San Francisco General Hospital and the Pharmacy Council for the San Francisco Department of Public Health.

**Q: In your years as a physician, health researcher, and dedicated public-health professional, have you received any awards?**

A: Yes. I have received the Ove Ferno Award.

**Q: Who was Ove Ferno?**

A: Ove Ferno was a Swedish scientist who invented nicotine gum. Ferno's research was conducted to help sailors who were not permitted to smoke in submarines to deal with nicotine withdrawal symptoms.

**Q: What is this award?**

A: This is an award given every three years for outstanding accomplishments in the area of nicotine, tobacco, and health. I received this award in 1996.

**Q: Did you receive this award for your research?**

A: Yes.

**Q: Any research in particular?**

A: Yes. I received this award for my work on the human pharmacology of nicotine and nicotine addiction.

**Q: Any other awards?**

A: I received the Alton Ochsner Award in 1996.

**Q: Who was Alton Ochsner?**

A: Alton Oschsner was a New Orleans surgeon who was one of the first doctors to note the association between smoking and lung cancer.

**Q: What is this award?**

A: This is an award that is given by the American College of Chest Physicians to honor individuals who have made outstanding contributions to studying tobacco and health.

**Q: Why did you receive that award?**

A: I received this award to acknowledge my contributions in the area of studying nicotine addiction.

**Q: Any other awards you would like to mention?**

A: I have received the Rawls Palmer Award and the American Thoracic Society Presidential Commendation. I also was selected as the 2002 annual faculty clinical research lecturer at the University of California San Francisco.

**Q: What is the Rawls Palmer Award?**

A: This is an annual award given by the American Society for Clinical Pharmacology and Therapeutics to acknowledge outstanding contributions to medical research. The American Society for Clinical Pharmacology and Therapeutics is the major society for clinical pharmacologists in the world.

**Q: Why did you receive this award?**

A: This award was given to honor my research on the human pharmacology of nicotine and its role in tobacco addiction.

**Q: Any research in particular?**

A: Studies of the effects of nicotine in people, including addiction, nicotine metabolism (including racial differences), the low-yield cigarette and other harm-reduction strategies, and the cardiovascular effects of tobacco use and nicotine.

**Q: You also mentioned being selected as your school's annual clinical research lecturer. What was the subject of your lecture?**

A: The subject of my lecture was the human pharmacology of nicotine, including nicotine addiction, and the implication of addiction in understanding the risks of smoking low-tar cigarettes, as well as issues of nicotine related to cardiovascular disease.

**Q: Have you ever published any of your research results?**

A: Yes.

**Q: Approximately how many articles have you published?**

A: I have published approximately 350 articles.

**Q: Were these peer-reviewed articles?**

A: Approximately 250 were peer-reviewed articles.

**Q: Did these articles address your original research?**

A: Most of these articles have addressed my original research, but I have also published numerous scientific review articles, three of which specifically involve the pharmacology of nicotine and its addiction processes.

**Q: Of these articles, how many dealt with the issue of smoking and health?**

A: Approximately 80 to 90 percent dealt with smoking and health issues.

**Q: How many articles dealt with nicotine addiction?**

A: Approximately 70 percent have dealt with nicotine and/or addiction.

**Q: In what journals did these articles appear?**

A: I have published my work in a great many different journals. Some of these include the *New England Journal of Medicine*, the *Journal of the American Medical Association*, the *Journal of the National Cancer Institute*, the *American Journal of Public Health*, *Clinical Pharmacology and Therapeutics*, the *Journal of Pharmacology and Experimental Therapeutics*, the *Journal of the American College of Cardiology*, *Circulation,* and many others.

**Q: In addition to the numerous articles you have published, have you written any other published work?**

A: Yes. I have authored approximately 70 book chapters on subjects including pharmacology, toxicology, and substance abuse, most of which deal with the pharmacology of nicotine and nicotine addiction.

**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: I have consulted with the Surgeon General's Office, the National Cancer Institute, the Occupational Safety and Health Administration, the Food and Drug Administration, the Environmental Protection Agency, and the World Health Organization.

**Q: What was your involvement with the Surgeon General's Office?**

A: I was a senior scientific editor of the 1988 Surgeon General's Report on nicotine addiction. I have also contributed written material to the 1986 Surgeon General's Report on the Effects of Involuntary Smoking (also known Environmental Tobacco Smoke), the 1986 Surgeon General's Report on Smokeless Tobacco, the 1998 Surgeon General's Report on Tobacco Use Among Racial and Ethnic Minorities, and the 2001 Surgeon General's Report on Smoking and Women. I was also a peer reviewer for the 1994 Surgeon General's Report on Smoking and Youth.

**Q: With regard to the 1988 Report, what did you do as senior scientific editor?**

A: I was one of four senior editors who were responsible for deciding which topics should be reviewed in the report, selecting experts to draft written material on various topics, editing these comments into a single document, sending the document to other experts for review, and incorporating review comments into a final document.

**Q: What did the planning involve?**

A: The planning involved determining the important scientific areas that would address the questions relating to tobacco addiction. As noted previously, we then identified scientific experts who could write monographs on various topics.

**Q: For which areas did you take major responsibility?**

A: My specialty areas included nicotine pharmacokinetics and metabolism and nicotine toxicology.

**Q: What are nicotine pharmacokinetics and metabolism?**

A: Pharmacokinetics is the study of the concourse of the drug in the body and how it distributes to various body tissues or body organs. Nicotine metabolism refers to how nicotine is broken down and excreted from the body.

**Q: How was the report received in the medical and scientific communities?**

A: This Report is considered to be a landmark Report. This Report was a comprehensive review of the scientific evidence that nicotine is the addictive principal of tobacco.

**Q: Does this mean that prior to this report, the addictiveness of nicotine was not appreciated?**

A: That is not correct. It was well known even at the time of the first Surgeon General's Report on Smoking and Health in 1964 that people smoked cigarettes for nicotine and that it was extremely difficult to quit smoking. This is the crux of addiction. The 1988 report synthesized the existing scientific literature on the subject.

**Q: You also mentioned that you worked on a 1994 Surgeon General's Report. What was the nature of your participation for that Report?**

A: The 1994 Report was a report on Smoking and Youth. I served as an expert peer reviewer.

**Q: What conclusions did the 1994 Surgeon General's Report on Smoking and Youth reach?**

A: The 1994 Report concluded, among other things, that most adolescent smokers are addicted to nicotine and want to quit, and that adolescent smokers experience relapse rates and withdrawal symptoms similar to those of adults.

**Q: How was the 1994 Surgeon General's Report on Smoking and Youth received in the medical and scientific community?**

A: Like the 1988 Report, the 1994 Report is the product of numerous renowned scientists and extensive peer review. The reports of the Surgeon General are considered to be authoritative sources in the scientific and medical communities.

**Q: You also mentioned other Surgeon General's Reports. What was your role with respect to these Reports?**

A: In 1986, the Surgeon General issued a Report on the Health Effects of Involuntary Smoking. My role in that Report was to draft material on quantification of human exposure to secondhand smoke. I was also involved that year in preparing materials for the Surgeon General's Report on Smokeless Tobacco. In the Smokeless Tobacco Report, I prepared materials on nicotine kinetics, nicotine metabolism and human exposure in the chapter on addiction to smokeless tobacco. In the Reports in 1998 and 2001, I wrote sections on addiction for the reports related to smoking among minorities and women.

**Q: With respect to your consulting work with the National Cancer Institute, please explain to the Court what you did?**

A: I served as co-editor and chapter author for Monograph 13, which focused on the health consequences of low-tar cigarettes.

**Q: What was the subject of your chapter?**

A: My chapter was focused on compensation.

**Q: Briefly, what is compensation?**

A: Compensation refers to the behavior of smoking cigarettes of different nominal machine measured nicotine yields in a manner to achieve a particular level of intake of nicotine.

**Q: Have you performed any other work for the National Cancer Institute?**

A: I also worked on Monograph 7, which was another document on the low-tar cigarette.

**Q: What was your role with respect to Monograph 7?**

A: This monograph was based on the proceedings of the President's Cancer Panel to discuss the Federal Trade Commission method for testing cigarettes and whether there was any health benefit to switching to low-yield cigarettes. I presented a paper at the committee meeting, and I prepared a monograph chapter on the topic of compensatory smoking.

**Q: Have you performed any other work for the National Cancer Institute?**

A: Yes. I have served on a number of National Cancer Institute grant-review committees.

**Q: What is the Institute of Medicine?**

A: The Institute of Medicine, or IOM, is a division of the National Academy of Sciences, which is composed of prominent scientists from the United States and around the world. The National Academy of Sciences serves to consider scientific issues that have potential public impact. The Institute of Medicine focuses on health-related issues.

**Q: What involvement have you had with the Institute of Medicine?**

A: I have served as a member of two IOM committees, and as a permanent consultant for a third committee. The 1994 committee was focused on how to prevent and/or reduce smoking among adolescents.

**Q: Did the 1994 IOM committee issue a report?**

A: Yes. The 1994 IOM committee report was called *Growing Up Tobacco Free: Preventing Nicotine Addiction in Children and Youths*.

**Q: What was your involvement with the 1994 IOM report?**

A: I served on the committee that reviewed the problem of smoking in adolescents, and developed recommendations for how to prevent and reduce the prevalence of smoking in adolescents. I also participated in drafting the chapter on nicotine addiction in adolescents.

**Q: Can you explain to the Court how the *Growing Up Tobacco Free* report was prepared?**

A: The committee reviewed numerous scientific documents and heard live testimony from a number of outside experts. This material was then synthesized into draft chapters for discussion and review at committee meetings. An initial draft of the IOM report was then sent to selected scientific experts for review, and then the reviewers' comments were incorporated into a revised document, which was then published.

**Q: Were the findings in the chapter you drafted for the report related to youth addiction?**

A: Yes. The entire chapter was focused on the issue of whether youths become addicted to nicotine.

**Q: What were the key findings in your chapter?**

A: The key findings were that youth are exposed to substantial levels of nicotine from cigarette smoking and do become addicted to nicotine in adolescence. Adolescent smokers make numerous quit attempts, and have as much difficulty quitting smoking as do adults. The IOM report found that over 89 percent of adult daily smokers began using cigarettes by or at age 18, and that 71 percent of adult daily smokers began smoking daily by or at age 18.

**Q: Were the findings from the 1994 Growing Up Tobacco Free report accepted by the medical and scientific community?**

A: Yes, this report was taken as an authoritative paper on how to address the smoking problem among adolescents.

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

A: Yes. I have testified or given a deposition several times.

**Q: Have you ever been disqualified as an expert?**

A: No.

**Q: Have you spent the majority of your research and medical careers studying the effects of nicotine on the human body?**

A: Yes.

**Q: Are you well acquainted with the ways in which nicotine enters the human body?**

A: Yes.

**Q: And how nicotine travels through the human body?**

A: Yes.

**Q: What happens when a person takes a puff on a cigarette?**

A: The person inhales cigarette smoke, which consists of an aerosol of particles and gases. The particles consist of water, nicotine, and tar.

**Q: What is tar?**

A: Tar is what remains of cigarette smoke particles after one takes away water and nicotine. Tar is composed of thousands of chemicals, many of which are known to be cancer-causing chemicals, or carcinogens. Tobacco tar is very similar to the black gummy substance that one sees in a barbecue pit.

**Q: What is nicotine?**

A: Nicotine is a chemical that is found primarily in tobacco plants, but also in small amounts in other plants. Nicotine has a structure that is similar to a chemical in the body called acetylcholine. Acetylcholine is a neurotransmitter. That is, it is a chemical that provides the pathway of communication from one nerve cell to another. In high concentrations, nicotine

competes with and blocks the effects of acetylcholine in the body, and can be quite toxic. It is thought that nicotine is present in tobacco plants because it serves as a natural insecticide, poisoning any insects that try to eat the plant.

**Q: Can you explain for the Court how nicotine travels through the body after being inhaled by the smoker?**

A: When a person puffs on a cigarette, tobacco smoke is inhaled deeply into the lungs. Nicotine particles impact on the small airways or breathing tubes in the lungs and nicotine is rapidly absorbed into the blood stream. It then rapidly moves into the heart and from there through the arterial blood vessels to the rest of the body, including to the brain and other body organs.

**Q: From the time that a person takes a puff of a cigarette, how quickly does nicotine travel to the brain?**

A: It takes 15-20 seconds for nicotine to pass from a puff on a cigarette to entering the brain.

**Q: Once nicotine reaches the brain, what does it do?**

A: As I briefly explained previously, nicotine binds to receptors that are intended to bind to the body's own neuro-transmitter, acetylcholine. A receptor is a protein with a structure such that it specifically binds to another particular chemical or drug. The receptor and the chemical or drug act like a lock and key mechanism. The receptor, or "lock," uniquely fits with the chemical that binds to it and acts as the "key." A receptor that binds nicotine and acetylcholine is called the nicotinic cholinergic receptor. When nicotine binds to this receptor, it causes the release of a number of other brain hormones, which then affect mood and behavior.

**Q: Can you explain in more detail what acetylcholine is?**

A: Acetylcholine is a chemical that is released by nerves and then acts on other nerves. The release of acetylcholine is the main mechanism by which one nerve cell communicates with another nerve cell. Thus, acetylcholine is responsible for communication of information from

one nerve to the next.

**Q: How is nicotine related to acetylcholine?**

A: The three-dimensional structure of nicotine is similar to that of acetylcholine. There is a significant similarity in the structure of nicotine and acetylcholine. Therefore the receptor, which is intended to recognize acetylcholine and to bind it, will also recognize and bind nicotine.

**Q: You said that when nicotine binds with the brain's receptors it causes a release of brain hormones. Could you explain this?**

A: Yes. When nicotine binds to receptors, it results in a change in the nerve cell membrane, allowing calcium and/or sodium ions to enter the cell. The entry of calcium or sodium then causes the release of various hormones depending on the particular brain cells.

**Q: What other hormones are activated by the nicotine from a cigarette?**

A: A number of hormones are released. The most important of these with respect to nicotine addiction is dopamine. Other hormones that are released include noreprinephrine, serotonin, GABA (gamma hydroxybutric acid), endorphins, and glutamate.

**Q: What effects do these hormones have on the body?**

A: Each hormone has different effects, which can vary according to what the individual is doing. For instance, dopamine is involved in pleasure. Whenever a person is doing something that is pleasurable it is preceded by or associated with the release of dopamine. All drugs that are abused and are addicting release dopamine. Norepinephrine is involved in arousal and may reduce appetite. Serotonin is involved in mood modulation, as well as appetite control. GABA produces a calming or anti-anxiety effect. Endorphins are the body's own opiates, and they have a role in reducing anxiety and reducing the perception of pain. Glutamate is involved in learning and memory enhancement.

**Q: Is the brain naturally exposed to nicotine?**

A: No. In non-smokers the brain is not naturally exposed to nicotine.

**Q: What is the consequence of nicotine on the natural functioning of the brain?**

A: Nicotine artificially stimulates the acetylcholine system, and the release of the hormones described above. That is, instead of having a natural event in the body activate the system, it is artificially activated by the consumption of nicotine.

**Q: Does nicotine affect any other parts of the body in addition to the brain?**

A: Nicotine has effects on virtually every body organ. For example, nicotine increases the rate and force of contraction of the heart, constricts blood vessels, affects the rate at which the stomach empties, and affects kidney function as well.

**Q: How much nicotine does a person generally absorb when he or she smokes a cigarette?**

A: On average, the smoker takes in 1 to 1.5 milligrams per cigarette.

**Q: How long does nicotine continue to affect the body?**

A: The half-life of nicotine, which is the time it takes for the nicotine level to decline by 50 percent, averages two hours. Nicotine persists in the body for eight to twelve hours.

**Q: What happens when someone smokes more than one cigarette in the eight to twelve hour window?**

A: There is an accumulation of nicotine in the body.

**Q: You said earlier that it takes 15 to 20 seconds for nicotine to travel from a puff to the smoker's brain. What is the significance of the speed with which nicotine moves through the bloodstream to the brain?**

A: The rapidity with which a drug has its effects is an important determinant of the addictiveness of the drug. Rapidity of delivery to the brain is important for several reasons. First, the more quickly a drug gets absorbed and goes to the brain, the higher will be the concentrations and the greater the effects. Second, the more rapidly a drug effect occurs with respect to taking a drug, the more reinforcing the drug-taking process becomes. When a drug is

more reinforcing it is more likely to produce addictive behavior. Third, the fact that one takes a drug and gets an effect from that drug quickly allows the individual to titrate or adjust the dose to get the optimal effects. Thus a person can take bigger or smaller puffs, or more or fewer puffs in order to get just the amount of nicotine that they desire.

**Q: How would you describe the high concentration in which nicotine enters the brain from smoking?**

A: This has been described as an arterial spike. In other words, there is a very rapid rise in the nicotine concentration in the arterial blood which supplies the brain, as well as other body organs.

**Q: What is the consequence of the rapid delivery of nicotine to the brain with respect to its reinforcing qualities?**

A: The fact that nicotine is absorbed very quickly and results in high arterial blood levels, makes nicotine obtained from cigarette smoke highly reinforcing and addicting. This phenomenon is sometimes called rapid reinforcement.

**Q: Is there any other significance to the speed with which nicotine enters the brain?**

A: Rapid absorption results in arterial levels of nicotine that are high enough to overcome, at least in part, the tolerance the body has developed to the drug.

**Q: What is the significance of smoking nicotine in the form of a cigarette, instead of ingesting it in some other form?**

A: Smoking nicotine provides the fastest rate of absorption and highest blood levels of nicotine. When nicotine is taken in from a patch, blood levels rise gradually over four to six hours, and the intensity of effect on the brain is quite low. When someone takes nicotine from gum or a lozenge, blood levels rise over about 30 minutes, with much less intense stimulation than with smoking. Even with nicotine nasal spray, which is the fastest delivery system aside from smoking, it takes about five minutes before one sees maximal nicotine levels, compared to

15 to 20 seconds with smoking.

**Q: As a comparison, how long does it take medicine in the form of a pill to enter and affect the body?**

A: Drugs taken in the form of a pill reach their peak concentrations from 30 minutes to two hours, depending upon the drug and the characteristics of the pill.

**Q: Why the large difference in the amount of time?**

A: When a drug is taken by mouth, the pill has to dissolve and the drug has to pass through the stomach to the small intestine, from which it is absorbed.

**Q: How does the rate at which nicotine is delivered from a cigarette compare to the amount of time it takes alcohol to affect the body after someone takes a drink of alcohol?**

A: Alcohol is absorbed much more slowly, with peak concentrations seen at 30 minutes or later. Thus, the rate of rise of alcohol levels in the bloodstream and in the brain is much, much slower than that of nicotine after smoking.

**Q: In terms of its effects on the body, how does chewing nicotine gum compare to obtaining nicotine through a cigarette?**

A: When a person chews a two milligram piece of nicotine gum, the overall absorption is about one milligram, similar to that of a cigarette. However, when chewing nicotine gum, blood levels rise gradually over thirty minutes, reaching peak levels of 5 to 7 nanograms per milliliter. In contrast, smoking a cigarette delivers the same one milligram over approximately eight minutes, with peak arterial nicotine levels in the range of 50 nanograms per milliliter or higher.

**Q: In terms of its effects on the body, how does use of a nicotine patch compare to obtaining nicotine through a cigarette?**

A: When nicotine is absorbed from a patch, it moves slowly through the skin, and peak levels are achieved in four to six hours. Nicotine levels rise so slowly that most individuals are not aware of the psychoactive effects of the nicotine they are absorbing.

**Q: Are nicotine patches addictive?**

A: No.

**Q: Why is a cigarette addictive and the patch not?**

A: The difference is due to the rate of absorption. As noted previously, each cigarette results in a high peak arterial nicotine level and rapid and intense effects on the brain. In contrast, a patch produces a gradual and slowly rising nicotine level, which has relatively little psycho-activity.

**Q: Some people have compared caffeine with nicotine in its effects on the body. What do you think of that comparison?**

A: Both caffeine and nicotine are drugs that work on receptors and have stimulant effects. However, caffeine, like alcohol, is absorbed slowly, with peak levels seen in about 30 minutes. The resultant effects on mental functioning are more subtle. Most people feel a gradual alertness and brightness, but generally do not feel the rapid stimulation that one feels after smoking a cigarette.

**Q: Can caffeine be addictive?**

A: Yes.

**Q: Is addiction to caffeine common?**

A: Use of caffeine in a compulsive manner indicative of addiction is not common and occurs in only about 10 percent of coffee drinkers.

**Q: How does the pattern of caffeine use compare to the pattern of nicotine use through cigarette smoking?**

A: Smokers repeatedly self-administer throughout the day. Coffee drinkers, on the other hand, typically administer only once or twice and usually only during the morning hours.

**Q: Is there anything else of significance about the cigarette as the delivery system for nicotine?**

A: The cigarette can be viewed as a nicotine delivery device. Each puff of a cigarette is analogous to a small injection of nicotine into the blood stream. Each cigarette can be conceived as providing approximately eight doses of nicotine. Thus, a pack of cigarettes is an easy way to carry around a day's supply of nicotine that will produce about 160 individual doses of the drug.

**Q: How does an individual perceive the effects of nicotine on the body?**

A: Smokers perceive different effects of nicotine at different times of day and according to their mood and what they are doing. For example, the first cigarette in the morning usually has a stimulating or alerting effect. Later on in the day when a smoker is feeling fatigued or having difficulty concentrating, a cigarette will make them feel more alert and allow them to focus better on their job. At the same time, if a person is feeling stressed or anxious or depressed, nicotine may reduce stress, relieve anxiety and depression, and make a person feel better. Nicotine can also be used at night for relaxation prior to sleep.

**Q: What is the importance to the individual smoker of the physiological effects of nicotine on the body?**

A: The smoker comes to use nicotine as a way to cope with daily stresses. Nicotine is used to modulate arousal, producing either stimulation or relaxation according to what the person desires. Smoking is also used to modulate mood, particularly to deal with stress, anxiety, and depression.

**Q: How does nicotine modulate mood?**

A: The effects of nicotine occur in two ways. First, there are some primary effects of nicotine on the brain that smokers may find desirable. These are called positive reinforcements. I discussed these previously. However, smokers develop tolerance to many of the primary effects of nicotine. In a regular smoker, when nicotine is not available, such as in periods of time when a smoker cannot smoke a cigarette, withdrawal symptoms emerge. Withdrawal symptoms are the opposite of the primary symptoms. Withdrawal symptoms include irritability, difficulty

concentrating, lethargy, anxiety and depression. When a person is experiencing nicotine withdrawal symptoms, taking nicotine reverses these effects. This reversal of unpleasant withdrawal effects, which is called negative reinforcement, is perceived by the smoker as having beneficial effects on mood and arousal.

**Q: How does nicotine affect the brain over time?**

A: A regular smoker exposes his or her brain to nicotine 24 hours per day. As occurs with the use of all psychoactive drugs, the brain attempts to adapt to the persistent presence of nicotine. This adaptation, called neuroadaptation, or tolerance, includes changes in brain structure, such as an increase in the number of nicotinic receptors. Over time, the brain becomes tolerant to the effects of nicotine and needs greater amounts of nicotine to produce the same effects on hormones as it once did before the development of tolerance.

**Q: The brain structure actually changes with the presence of nicotine?**

A: Yes.

**Q: What is the evidence of these structural changes?**

A: In studies of animals that were given nicotine over long periods of time, autopsies reveal increases in the number of nicotine receptors in the brain. Also, studies of human brains at autopsy show an increase in nicotine receptors in smokers as compared to non-smokers.

**Q: How does this change in the brain's structure affect its functioning?**

A: Neuroadaptation occurs in order to maintain normal brain functioning. However, the consequence of neuroadaption is that the brain becomes dependent on nicotine to function normally. When a smoker does not have nicotine, the brain functions abnormally and the individual experiences withdrawal symptoms.

**Q: What are these withdrawal symptoms?**

A: Withdrawal symptoms include irritability, restlessness, difficulty in getting along with family and friends, sleeplessness, anxiety, depression, hunger, and weight gain.

**Q: How long does it take for someone to experience withdrawal symptoms after stopping smoking cigarettes?**

A: Most of the symptoms of withdrawal are experienced in greatest intensity over the first seven to ten days after quitting smoking. However, there are delayed withdrawal symptoms such as reduced energy, a bad mood, and low level depression. This latter syndrome can last for many months.

**Q: Typically when do withdrawal symptoms begin?**

A: Withdrawal symptoms begin to occur as soon as nicotine levels in the body start to decline.

**Q: Define positive reinforcement for the Court.**

A: Positive reinforcement refers to the experience of the direct enhancing effects of the drug.

**Q: Define negative reinforcement for the Court.**

A: Negative reinforcement is the reversal of the adverse effects of withdrawal.

**Q: Can nicotine serve as both a positive and negative reinforcement?**

A: Yes. A beginning smoker generally will experience positive reinforcement. However, over time as an individual continues to smoke, the reinforcement shifts to negative reinforcement.

**Q: What effect does tolerance have on an individual's smoking behavior?**

A: As tolerance develops, the smoker gets fewer positive reinforcements from each cigarette, and smokes more and more to avoid withdrawal symptoms.

**Q: How quickly does tolerance build?**

A: Tolerance can be considered in two different time frames. One time frame considers the transition from a beginner smoker to a regular smoker. It takes on average seven years to reach a plateau level of cigarette consumption. Tolerance to many effects of nicotine develop over this period of time. A second time frame is the daily smoking cycle. The first cigarette of the day

after the smoker wakes in the morning produces the greatest intensity of effect. As smoking continues throughout the day, each cigarette has less and less of an effect. Eventually, a smoker is smoking just to prevent withdrawal symptoms.

**Q: What happens when the daily smoker sleeps, and correspondingly does not smoke for several hours?**

A: When a person sleeps, the levels of nicotine in the body and in the brain decline. During this period of time, there is some loss of tolerance and the brain becomes more sensitive to the effects of cigarettes. This explains why the first cigarette in the morning has the greatest effect and is perceived as being the most satisfying.

**Q: How does a daily smoker respond to this cycle?**

A: The smoker experiences the greatest pleasure from the first cigarette of the day. The pleasure of satisfaction tends to decrease with each cigarette later on in the day and the smoker continues to smoke mostly to prevent withdrawal symptoms.

**Q: How does tolerance affect the number of cigarettes that an individual smokes from year to year?**

A: After the time frame from beginner smoker to regular smoker, in which daily consumption slowly increases, the daily smoking cycle is such that the smoker tends to take in the same amount of nicotine day to day and from year to year.

**Q: How do we know this?**

A: This is shown by data on cigarette consumption and studies of blood cotinine levels measured in the same smoker at different times.

**Q: Wouldn't it follow from the fact that people develop tolerance that smokers would over the years continually increase the number of cigarettes they smoke each day?**

A: As mentioned previously, there is some increase in the first few years of smoking. However, over time, the number of cigarettes smoked per day stabilizes. This occurs in the

context of the daily smoking cycle where there is a balance of development of tolerance and loss of tolerance.

**Q: What does the term "drug addiction" or "drug dependence" mean?**

A: The key concept in understanding drug addiction is loss of control of drug-taking behavior. This means that once a person is addicted to a drug, it is difficult to stop using it, even when there are compelling reasons to do so.

**Q: Is there a distinction between the term "drug addiction" versus "drug dependence"?**

A: I use those terms interchangeably, as was suggested in the 1988 Surgeon General's report on nicotine addiction.

**Q: Do the scientific and public health communities generally recognize these terms as synonymous?**

A: Yes.

**Q: Have these terms always been considered synonymous?**

A: No.

**Q: Why not?**

A: In 1964, nicotine was classified by the Surgeon General as an habituating drug and not an addicting drug. The reason for that classification was that, at that time, drug addiction was used to describe drugs that produced marked intoxication with concomitant impairment of performance and severe physical dependence, meaning severe symptoms of withdrawal when use of the drug was discontinued. Drug addiction also meant damage not only to the individual, but to society (for example, association with anti-social behavior and criminality). The prototypic drug with these characteristics was heroin. A drug habit, on the other hand, was considered to be a psychological dependence with no physical dependence and/or no damage to society. Examples of drugs in this habit class, under the Surgeon General's 1964 classification, would include cocaine and nicotine. The distinction between drug dependence and drug habit

was dropped in 1964, subsequent to the issuance of that year's Surgeon General's Report, when the World Health Organization revised its definition of drug dependence.

**Q: What are the scientific authorities that define drug addiction?**

A: Drug addiction or dependence has been defined by the World Health Organization, the U.S. Surgeon General, and the American Psychiatric Association.

**Q: How do these authorities define drug addiction or drug dependence?**

A: The World Health Organization defines drug dependence as "a behavioral pattern in which the use of a given psychoactive drug is given a sharply higher priority over other behaviors which once had a significantly higher value." The U.S. Surgeon General defines drug addiction by three primary criteria: (1) highly controlled or compulsive use, (2) psychoactive affects, and (3) drug-reinforced behavior. The American Psychiatric Association defines drug dependence in the DSM-IV as requiring three or more of a possible seven characteristics of drug use.

**Q: These authorities appear to employ slightly varying definitions of drug addiction. Is there a common concept among these definitions?**

A: The common concept is loss of control of drug-taking behavior.

**Q: How does the concept of loss of control over use of the drug factor into the Surgeon General's definition of drug addiction?**

A: Loss of control is indicated by the requirement for highly controlled or compulsive use in the Surgeon General's definition.

**Q: Can you further define the meaning of the Surgeon General's first criterion, highly controlled or compulsive use?**

A: This simply means that when a person tries to stop use of the drug, it is very difficult to do so, and individuals are often unsuccessful. Compulsive use refers to drug-seeking and drug-

taking behavior that is driven by strong, often irresistible urges, and such use persists despite a desire to quit and repeated attempts to do so.

**Q: Is highly controlled or compulsive use different from habitual behaviors, such as overeating or exercising?**

A: Yes. While drug addiction as well as overeating and exercising all can be compulsive behaviors, drug addiction differs from those other compulsive behaviors in that drug addiction occurs only after a person is exposed repeatedly over a period of time to a drug. A drug is defined as a chemical substance, other than food, that affects body structure or function. One cannot avoid food, and one cannot avoid exercise. In contrast, however, one never needs to be exposed to a drug such as nicotine, which can cause addiction.

**Q: In your opinion was the Surgeon General's 1988 definition of addiction intended to include compulsive behaviors that do not involve use of a drug?**

A: No. The use of a drug is inherent in the Surgeon General's definition.

**Q: And regarding the Surgeon General's second criterion, what does it mean for a drug to have a psychoactive effect?**

A: A drug that is psychoactive is one that affects a user's mood or behavior.

**Q: Can you further define the Surgeon General's third criterion: drug reinforced behavior?**

A: Yes. Drug reinforced behavior means that a person is taking the drug to experience the specific effects of the drug. The drug functions as a reinforcer that can directly strengthen behavior leading to further drug ingestion. For example, a person can be dependent on caffeine and can drink many cups of coffee per day to sustain caffeine dependence. One could not, however, diagnose caffeine dependence in a person who is compulsively drinking decaffeinated coffee.

**Q: Can you provide examples of the kinds of reinforcing effects of a drug that typically lead to further drug ingestion?**

A: Virtually all dependence-producing drugs are pleasurable. Many, such as nicotine, produce stimulation and arousal. Others, including nicotine, can produce calming, relaxation and reduction of stress. As explained above, nicotine use is reinforced both positively, i.e., smokers seeking to experience nicotine's pleasurable effects, and negatively, i.e., smokers seeking to avoid negative withdrawal symptoms.

**Q: Do the Surgeon General's three primary criteria for addiction apply to cigarette smokers?**

A: Yes.

**Q: How so?**

A: Smokers smoke cigarettes, often in large numbers every day, and have difficulty not smoking for prolonged periods of time. This represents highly controlled or compulsive use. Nicotine from cigarettes produces changes in mood and arousal level, including stimulation, attention, relaxation, calming, and reduction of stress. These are psychoactive effects. Smokers only smoke cigarettes containing nicotine. Very few people smoke cigarettes that do not contain nicotine. This reflects drug-reinforced behavior; that is, nicotine must be present for a cigarette to be rewarding (and therefore addicting).

**Q: You've referred to three "primary" criteria. Are there additional criteria identified by the Surgeon General that may be helpful in characterizing drug addiction?**

A: Yes. Although the three primary criteria are sufficient to define addiction, the Surgeon General recognizes additional criteria as helpful in characterizing drug addiction.

**Q: What are these additional criteria?**

A: These criteria include stereotypic patterns of use, use despite harmful effects, relapse following abstinence, recurrent drug cravings, tolerance, physical dependence, and pleasant (euphoric) effects.

**Q: Do these additional criteria apply to cigarette smokers?**

A: Behaviors meeting these additional criteria are exhibited by most smokers; however, they are not universal in all smokers.

**Q: Do you have an opinion as to whether – under these criteria established by the Surgeon General – nicotine is an addictive substance?**

A: Yes.

**Q: What is your opinion?**

A: My opinion is that nicotine fully meets these criteria.

**Q: Is nicotine delivered through cigarette smoke addictive?**

A: Absolutely.

**Q: From your experience studying and researching addiction and nicotine, are you aware of what historically the tobacco industry's position has been with respect to whether nicotine is addictive?**

A: Yes.

**Q: What is your understanding, generally, of the industry's historical position?**

A: The tobacco industry historically has characterized cigarette smoking as merely a habit. The industry has maintained that nicotine is not addictive because it does not cause intoxication. They argue that nicotine is different from other drugs that are considered addictive, such as alcohol, heroin, or cocaine, because nicotine does not produce a state of intoxication that renders a smoker unable to function or perform normal, everyday tasks. And, the industry has repeatedly failed to acknowledge that smoking is a drug reinforced behavior driven by the drug nicotine.

**Q: Based on your experience in the field, do you have an opinion on the argument that nicotine is not addictive because it is not intoxicating?**

A: Yes.

**Q: What is your opinion?**

A: My opinion is that intoxication as a requirement for addiction is based on a conception of addiction which currently is not generally accepted in the medical and scientific community. Most authorities consider the loss of control of drug use as the relevant defining factor for addiction. Intoxication as a standard for evaluating nicotine addiction has been rejected by leading scientific and public-health authorities.

**Q: Historically, has intoxication ever been considered to be a relevant factor in evaluating drug addiction?**

A: Yes, it was identified as a relevant factor in the 1964 Surgeon General's Report. At that time, the prototypical addictive drug was heroin and, as stated above, addiction had a connotation of social deviance and criminal behavior. Under the standards described in the 1964 Report, nicotine was considered to be habituating rather than addicting. The distinction between habituating substances and addicting substances was based primarily on the link between addiction and socially deviant behaviors, states of intoxication, impaired performance, and medically severe withdrawal symptoms.

**Q: What has changed since the publication of the 1964 Surgeon General's report?**

A: A number of things have changed. Shortly after publication of the 1964 Surgeon General's report, the 1964 expert committee of the World Health Organization concluded that the historical definition of "addiction" was too narrow. The WHO criteria for dependence-inducing drugs were revised. Since that time, based on research and scientific advances, the scientific and public-health communities have gradually gained more knowledge and understanding of the addictive processes.

**Q: Aside from nicotine, are there other drugs that would not have been considered addictive under the 1964 definition but are recognized as addictive today by the scientific and public-health communities?**

A: Yes. Cocaine would not have been considered addictive under the 1964 definition because it was not associated with medically severe withdrawal symptoms.

**Q: Has research been conducted comparing nicotine to other drugs, such as heroin, cocaine, or alcohol, in terms of its addictiveness?**

A: Yes. The 1988 Surgeon General's Report on nicotine addiction includes an extensive discussion, based on scientific research, of similarities in the addictive properties of these drugs.

**Q: What has that research demonstrated?**

A: This research demonstrates that, while there are some differences in the way in which these drugs affect the body, the addictiveness of nicotine is very similar to that of other drugs, such as heroin, cocaine, and alcohol. Nicotine is just as addictive, or more addictive, than these other drugs.

**Q: What are the similarities between the characteristics of nicotine addiction and addiction to other drugs?**

A: The addiction process is essentially the same for nicotine as it is for other drugs, such as heroin, cocaine, and alcohol. All of these drugs are associated with compulsive use. All of these drugs have psychoactive effects on the user. They are all associated with the development of tolerance. They are all associated with withdrawal symptoms when the user attempts to quit. They are all associated with similar high rates of relapse when users try to quit. Finally, in many cases, they show similarities in the use of agonists to treat them.

**Q: What is an agonist?**

A: An agonist is a drug that has the same types of effects as another drug, and, in this case, is used as a medical treatment to deal with withdrawal symptoms. Examples of this include the use of methadone to treat heroin withdrawal and the use of nicotine gum to treat nicotine withdrawal.

**Q: You identified a number of similarities. Starting with the factor of compulsive use, can you explain precisely how nicotine addiction is similar to heroin, cocaine, or alcohol addiction?**

A: Yes. Like users of cocaine, heroin, and alcohol, people addicted to nicotine exhibit compulsive use, meaning that they experience a need to use the drug repeatedly. Cigarette smokers rarely go more than a single day without nicotine. In work or public places where smoking is proscribed, smokers often take numerous breaks throughout the day to smoke. People who are addicted to heroin, cocaine, or alcohol also have difficulty refraining from drug use.

**Q: Is there any other evidence supporting this similarity in terms of compulsive use?**

A: Yes. Compulsive use is also indicated by a smoker's persistence in smoking cigarettes, that is, taking nicotine despite the harmful effects of cigarettes. In that regard, its use is similar to that for heroin, cocaine, and alcohol.

**Q: How might compulsive use be evident to a clinician treating individuals who use drugs of abuse?**

A: This is clearly evident to clinicians who treat alcoholics with chronic alcoholic liver disease or heroin addicts with infective endocarditis, which is an infection of the heart valves that occurs with the use of dirty needles by heroin addicts. In the case of cigarette smokers, many continue to smoke after having a lung removed because of lung cancer or having undergone a tracheotomy for throat cancer. Only 50 percent of smokers who suffer heart attacks quit smoking, despite a physician's advice to do so. The fact that individuals continue to use the

drug, even after suffering from life-threatening harmful effects, is a characteristic common to nicotine, heroin, and alcohol.

**Q: With respect to the factor of relapse after multiple attempts to quit, how is nicotine addiction similar to heroin or alcohol addiction?**

A: The relapse rates after abstinence are similar for tobacco, heroin, and alcohol. Approximately 60 percent of quitters relapse within three months, and 75 percent relapse within six months.

**Q: Where were these relapse rates observed?**

A: These relapse rates have been observed in clients in drug abuse or tobacco dependence treatment programs. The data on these relapse rates was extensively reviewed in the 1988 Surgeon General's Report.

**Q: With respect to relapse rates, is there any difference for people who quit without seeking medical assistance?**

A: It's been argued that the relapse rate for those who do not seek medical assistance, known as "spontaneous quitters," may be lower, but published data indicate otherwise. The relapse rates for smokers who have undergone minimal intervention treatment in a physician's office and who have successfully abstained for 24 hours are 25 percent at two days, 50 percent at one week, and 75 percent at two months. Two-thirds of smokers who quit on their own relapse within two days.

**Q: Are there any other similarities in the factor of relapse rates?**

A: Recurrent drug cravings have been described for cigarettes, heroin, cocaine, and alcohol. A study comparing the desire to use different drugs among individuals who use multiple drugs of abuse, most of whom smoke cigarettes, indicated that the desire to smoke cigarettes when cigarettes were unavailable was as strong as, and in most cases stronger than, the desire to use heroin, cocaine, or alcohol.

**Q: Can you explain how the tolerance factor in nicotine addiction is similar to that factor in addictions to other drugs?**

A: The development of tolerance is a characteristic that is common to nicotine, as well as other drug addictions. Although the time course varies, the development of tolerance to various drugs of abuse is well documented. Tolerance to many effects of nicotine develops quickly, within a day, and there is re-sensitization to many of the effects overnight. Tolerance to the effects of other drugs has likewise been demonstrated.

**Q: As for the factor of withdrawal, how is nicotine withdrawal similar to withdrawal experienced by people with addictions to other drugs?**

A: Physical dependence on the drug (that is, experiencing withdrawal symptoms during periods of abstinence) occurs in smokers as well as in other drug users. Although it is true that withdrawal from nicotine addiction does not produce seizures and delirium such as may be experienced during alcohol withdrawal, nicotine withdrawal can be extremely disruptive to personal life.

**Q: How is nicotine withdrawal disruptive to a smoker's personal life?**

A: Nicotine withdrawal is similar to withdrawal from other stimulants, such as cocaine. The withdrawal is not life-threatening, but profoundly affects mood and behavior and remains a strong impetus to recurrent drug use. During withdrawal, smokers are often irritable, anxious, feel they are in a bad mood, and have difficulty concentrating and/or performing their jobs.

**Q: Do all smokers experience withdrawal?**

A: No, most do, but some do not. Approximately 20 percent of smokers do not report withdrawal symptoms when they stop smoking. Why smokers differ in their experience of withdrawal symptoms is not known, but is suspected to relate to genetic differences.

**Q: Is that true for users of other drugs of abuse, that not all users experience symptoms of withdrawal?**

A: Yes. Not all heroin addicts or alcoholics experience severe withdrawal, and some are able to stop their drug use abruptly without experiencing any withdrawal symptoms.

**Q: Earlier you mentioned similarities between nicotine and other drugs with respect to treatment with agonists. How is nicotine addiction treated with agonists?**

A: Nicotine agonists, including nicotine gum, nicotine patches, nicotine nasal spray, and nicotine lozenges have been used with some success to alleviate withdrawal symptoms and to facilitate smoking cessation. Similarly, agonists such as methadone for heroin addiction and benzodiazepines for alcoholism have also been successfully employed.

**Q: In what ways, if any, is nicotine addiction dissimilar to addiction to other drugs?**

A: The main difference is in the nature of the psychoactive effects of the drugs. Cocaine and heroin produce high levels of euphoria, which may be disruptive for everyday activities. Nicotine's mood-altering effects, in contrast, are generally subtle and consistent with maintaining a normal level of cognitive performance. In other words, a person can smoke cigarettes and experience nicotine's psychoactive effects hundreds of times throughout the day, and still carry on a normal, everyday life. It is only when the addicted smoker stops smoking that he or she has difficulty performing their daily tasks. This quality allows nicotine to exert a very powerful effect on behavior over time.

**Q: Does this difference mean that nicotine addiction is fundamentally different than addiction to other drugs?**

A: The fact that nicotine’s psychoactive effects are generally more subtle than those of other drugs of abuse does not mean that the nature of addiction to nicotine is fundamentally different than the nature of addiction to other drugs.

**Q: In your opinion, are the effects of nicotine's addictiveness less harmful than addiction to other drugs?**

A: No. The strength of nicotine addiction is just as, or more, powerful than addiction to other drugs. In fact, the consequences of nicotine addiction are more pervasive, as tobacco use is the number-one preventable cause of illness and death in the United States. Individuals are able to use nicotine more frequently than other drugs of abuse because cigarettes are legal and because they do not produce the intoxication that disrupts the smoker's ability to perform everyday activities. In terms of the long-term health consequences, an individual is much more likely to die from health complications associated with smoking than those from the use of any other drug of abuse.

**Q: In your career, have you ever been involved with the issue of children and smoking?**

A: Yes.

**Q: Please describe the nature of that involvement.**

A: I participated in researching and writing the 1994 Institute of Medicine report on preventing nicotine addiction in children and youth. I also served as an expert peer reviewer for the 1994 United States Surgeon General's Report concerning the use of tobacco by young people.

**Q: Did these reports contain any findings concerning the addictiveness of smoking for youths?**

A: Yes.

**Q: Have these reports been well received in the public health community?**

A: Yes. Both of these reports have been widely used to guide the development of policy for the prevention of smoking in youth.

**Q: What was the purpose of the IOM's 1994 Committee on Preventing Nicotine Addiction in Children and Youths?**

A: The charge of the Committee was to study the prevention of nicotine dependence among children and youths. Specifically, the Committee was asked to review and evaluate the scientific literature on the epidemiology of nicotine dependence among children and youths; to review and

evaluate the scientific literature on primary and secondary prevention of nicotine dependence among children and youths; to review and evaluate the scientific base of knowledge about the causes of nicotine addiction; to review important grass roots programs on tobacco use and youths; and to outline a research agenda that will contribute to reducing nicotine dependence among children and youths.

**Q: Was this report widely publicized?**

A: Yes.

**Q: Were its results accepted by the public health community?**

A: Yes.

**Q: What was the nature of your involvement with the IOM report?**

A: I prepared the chapter concerning the nature of nicotine addiction. I also participated in research and writing of other portions of the report.

**Q: Were any of your findings in that chapter related to youth smoking?**

A: Yes.

**Q: Is smoking an important health issue for youth?**

A: Yes.

**Q: Why is smoking an important health issue for youth?**

A: Because youth smokers become the addicted adult smokers who seek treatment for smoking-related illnesses later in life and who suffer the health consequences of long term smoking, including premature death. In addition, some diseases, like infectious diseases, are substantially enhanced by smoking, even for youths.

**Q: Can you provide me an example of how the effects of infectious diseases are enhanced by smoking?**

A: Yes. Influenza and other respiratory infections have been shown to be worse for youths who smoke.

**Q: Is smoking prevalent among youth?**

A: Yes. Among high school seniors, the prevalence of daily smoking is about 20 percent.

**Q: When do most smokers begin to smoke?**

A: Most smokers begin to smoke in adolescence. Over 88 percent of adult daily smokers start smoking before the age of 18.

**Q: How do you know that?**

A: This has been the subject of a number of research studies which are summarized in the IOM report and the 1994 Surgeon General's report.

**Q: Do they provide any additional statistics on youth smoking?**

A: Yes. In addition, over 70 percent of adult daily smokers began daily smoking by age 18.

**Q: Have other studies been performed regarding smoking initiation by youth?**

A: Yes. This has been done in the Youth Risk Behavior survey.

**Q: Were the results of the Youth Risk Behavior survey peer-reviewed?**

A: Some presentations of the data from the survey have been peer-reviewed upon publication in medical journals. Other portions have been published in the Surgeon General's reports.

**Q: What did the survey report?**

A: The 1990 Youth Risk Behavior survey found that by age 13, 56 percent of youths had tried smoking and 9 percent were regular smokers (that is, they smoked on 5-15 days or more in the past 30 days). The percentage of youths trying a cigarette increased with each year of age, so that by age 17, 77 percent of youths had tried smoking and 25 percent were regular smokers.

**Q: Were there any other relevant findings in the Youth Risk Behavior survey?**

A: The Youth Risk Behavior survey and other surveys report that the percentage of youths trying cigarettes increases with each year of age during adolescence.

**Q: Are there other relevant findings from other authoritative literature?**

A: Yes. the 1994 Surgeon General's Report indicates that older children are more likely to be daily smokers and to smoke more cigarettes than younger children. For example, the data demonstrate that at ages 12-13, 16.5 percent of adolescent smokers were daily smokers while in comparison, 47.5 percent of smokers ages 16-18 were daily smokers.

**Q: Has anyone ever estimated how many youth under the age of 18 smoke cigarettes?**

A: Yes. The 1994 Surgeon General's Report indicates that over three million youths under age 18 smoke cigarettes.

**Q: Why is the age at which someone starts smoking so significant?**

A: The earlier a person starts smoking cigarettes, the more highly dependent they will be as an adult, and the more difficult it will be for them to quit. In addition, the earlier someone starts smoking, the higher that person's smoking rate is later on in life.

**Q: What does this information show?**

A: The 1994 Surgeon General's Report cited to a study that found that 67 percent of children who started smoking in sixth grade became daily adult smokers compared with 46 percent of teenagers who began smoking in eleventh grade.

**Q: How long does it take a youth smoker to become a daily smoker?**

A: On average, it takes three years from experimentation to becoming a daily smoker.

**Q: Why does it take this period of time?**

A: Initially, youth smoke for psychosocial and environmental reasons. However, over time, smokers begin to experience the pharmacologic effects of nicotine. The transition takes a period of time, during which the brain is exposed to the effects of nicotine and there is development of physical dependence. On average, this process takes about three years.

**Q: Are youth smokers' smoking patterns the same as those of adult smokers?**

A: No.

**Q: How are they different?**

A: Youth smokers do not smoke as many cigarettes.

**Q: Why is that?**

A: Youth often have limited financial resources to purchase cigarettes, may have restricted access to cigarettes, have many restrictions on where they are allowed to smoke, and are often not as free as adult smokers to smoke cigarettes in their homes. For example, students are not allowed to smoke in schools, on school grounds, and in many cases are not allowed to smoke in their homes.

**Q: How does the difference in smoking patterns affect a youth smoker's ability to become addicted to nicotine from cigarette smoking?**

A: This pattern means that a youth is not exposed to as much nicotine in a day as an adult is. However, there is adequate exposure to nicotine for an addiction to develop, as discussed previously.

**Q: Getting back to the sensitivity of youth to nicotine, has any research demonstrated its existence?**

A: Yes. Animal research was performed.

**Q: What type of animal research was performed?**

A: Nicotine has been administered to rodents (rats and mice), comparing the effects in adolescent rodents to those in adult animals. Nicotine produced changes in brain chemistry in adolescent rodents and changes in rodent behavior that were long-lasting or permanent, whereas nicotine-induced changes in adult rodents were fully reversible. This suggests that the adolescent rodent is more vulnerable than the adult rodent to long-term effects of nicotine.

**Q: Can you explain for the Court the development of addiction in youths?**

A: Yes. The development of nicotine addiction in youth has five stages. The five stages are: (1) preparatory stage; (2) initial trying stage; (3) experimentation; (4) regular use; and (5) nicotine addiction.

**Q: I'd like to go through the five stages one by one. First, what is the preparatory stage?**

A: The preparatory stage includes formation of knowledge, beliefs and expectations about smoking.

**Q: What is the initial trying stage?**

A: Initial trying refers to trials with the first two or three cigarettes.

**Q: What is the experimentation stage?**

A: The experimentation stage refers to repeated irregular use over an extended period of time. Such smoking may be situation specific, for example, smoking at parties.

**Q: What is the regular use stage?**

A: Regular smoking by youths mean smoking every weekend or in certain parts of each day, such as after school with friends.

**Q: Finally, what is the nicotine addiction stage?**

A: Nicotine addiction refers to regular smoking, usually every day, with an internally regulated need for nicotine.

**Q: What are the signs that typify the nicotine addiction stage?**

A: Addicted youths consume substantial levels of nicotine, experience pharmacologic effects from smoking, experience withdrawal symptoms when they're not able to smoke, and often have difficulty in quitting tobacco use.

**Q: How does the addiction process work?**

A: There is a progression from initiation to the development of pharmacologic effects.

**Q: What are these pharmacologic effects?**

A: As noted previously, pharmacologic effects of nicotine may include pleasure, stimulation, arousal, relaxation, calming, and management of stress.

**Q: Do youth manifest symptoms of dependence?**

A: Yes, they do.

**Q: How has this been demonstrated?**

A: The McNeill study of seventh graders, described in more detail below, reported that 22 percent of seventh-grade smokers had at least one symptom of nicotine dependence within four weeks of beginning to smoke. Sixty-two percent of these seventh graders reported their first withdrawal symptoms before becoming a daily smoker.

**Q: What withdrawal symptoms did they report?**

A: They reported feeling like they really needed a cigarette, a strong urge to smoke, a strong craving to smoke, feeling nervous, restless or anxious, feeling irritable, difficulty concentrating, feeling addicted, found it hard to refrain from smoking where it is not permitted, and feeling sad, blue or depressed.

**Q: How do the biological processes, such as pharmacological effects and withdrawal symptoms, compare between adults and youth smokers?**

A: The 1994 Surgeon General's report concludes that basic biological processes underlying nicotine addiction appear to be similar in youths and adults.

**Q: How are they similar?**

A: The process of nicotine addiction includes absorption of nicotine into the bloodstream, from which it goes to the brain; and activation of nicotinic receptors in the brain resulting in the modulation of levels of hormones, such as dopamine. The release of hormones then results in behavioral and mood changes. Over time, neuro-adaptation develops with a change in the number of nicotinic receptors and a decreased responsiveness to effects of nicotine. After neuro-adaptation has occurred, one sees tolerance to effects of nicotine and the development of physical dependence. Physical dependence refers to developing withdrawal symptoms when the use of the substance stops. These processes occur in youth as they do in adults.

**Q: How do youth smoke as compared to adults?**

A: Studies have indicated that even when youth smoke only a few cigarettes per day, they inhale tobacco smoke effectively and take in as much nicotine per cigarette as adults who smoke more cigarettes per day.

**Q: What evidence exists to demonstrate that nicotine dependence has become established in youth smokers?**

A: There are four lines of evidence: (1) youth consume substantial levels of nicotine; (2) youth smokers experience the pharmacologic effects of nicotine from tobacco smoke; (3) youth smokers experience withdrawal symptoms when they quit smoking; and (4) youth smokers experience difficulty when attempting to quit smoking.

**Q: What is the evidence for the first point about the levels of nicotine consumed by youths?**

A: Nicotine intake in adolescence has been studied by measuring levels of its metabolite, cotinine, in the saliva of adolescents. In studies of adolescents, the saliva cotinine levels are similar to those in adult smokers who smoked the same number of cigarettes per day.

**Q: What does this lead you to conclude?**

A: The fact that cotinine levels were similar means that just as much nicotine is taken in by adolescents as by adults from each cigarette.

**Q: What is cotinine?**

A: Cotinine is the breakdown product from nicotine. Cotinine is present in higher concentrations and persists for a longer period of time than nicotine, and has been widely used as an indicator of nicotine intake.

**Q: How did the cotinine levels compare between youths and adults?**

A: Cotinine levels in adolescents who smoked cigarettes were comparable to those of adults who smoked the same number of cigarettes.

**Q: What happens to youth consumption and cotinine levels over time?**

A: They generally go up because youth are on an upward addiction trajectory. For example, one study of adolescent girls who smoked at the time of three yearly surveys, including those who were occasional smokers or non-smokers at the time of the first survey but who subsequently became daily smokers, showed increases in both cigarette consumption and saliva cotinine levels over time.

**Q: What other evidence exists to demonstrate that nicotine dependence does become established in youth smokers?**

A: Youth smokers have been found to experience the pharmacologic effects of nicotine from tobacco smoke.

**Q: What evidence is there of the pharmacologic effects of nicotine on youths?**

A: In the study of adolescent girls described previously, daily smokers reported pharmacologic effects such as feeling calmer after smoking cigarettes more frequently than did occasional smokers. This was part of a study where 170 English school girls ages 11 to 17 were asked about five possible effects of smoking: dizziness/lightheadedness, nausea, feeling high, increased alertness, and feeling calmer. As noted above, the majority of smokers reported feeling calmer after smoking cigarettes, and this was seen more frequently in daily smokers compared to occasional smokers.

**Q: What does feeling calmer represent?**

A: The feelings of calmness or relaxation are pharmacologic effects of nicotine. These effects are an important component of the development of nicotine addiction.

**Q: What other evidence demonstrates that nicotine dependence is established in youth smokers?**

A: Youth smokers experience withdrawal symptoms when they attempt to quit smoking. In the study of English school girls ages 11 to 17 who were current cigarette smokers, the study

participants were asked how they felt when they tried to quit smoking. The study found that many of the girls experienced withdrawal symptoms when they were not able to smoke.

**Q: What withdrawal symptoms did the school girls experience?**

A: The most prominent symptoms were a strong need to smoke, feeling more irritable and feeling restless. Smokers also reported feeling unable to concentrate, feeling hungry, and feeling miserable.

**Q: Did the study find any correlation between the number of withdrawal symptoms and the participant's smoking level?**

A: Yes. Those who were daily smokers were significantly more likely to report a strong need to smoke, more irritability and restlessness compared to occasional smokers.

**Q: What does this study demonstrate?**

A: This study demonstrates that physical dependence to nicotine develops during adolescence.

**Q: Is there any other evidence demonstrating nicotine dependence in youths?**

A: Yes. An important line of evidence is that while many youths wish to quit smoking, many have great difficulty doing so

**Q: What is the basis for this conclusion?**

A: A number of studies have shown that youth smokers have difficulty quitting. For example, one study by researchers Stone and Cristeller of tenth-grade students in suburban Massachusetts revealed that 14 percent of the surveyed students were daily smokers, and of that percentage, 28 percent reported that they continued to smoke because they were addicted.

**Q: What other studies do you rely upon for this conclusion?**

A: The Monitoring the Future project, which studied high school seniors in the United States from 1985 to 1989, asked the participants about their interest in quitting and their prior attempts to quit smoking. Of smokers who have smoked at all in the past 30 days, 42.5 percent reported

they desired to stop smoking. Of this group, and of the subgroup who smoked daily, 28 percent and 39 percent respectively, stated that they have tried to stop in the past and could not.

**Q: Why do you think that youths have so much difficulty quitting smoking?**

A: The main reason is that they are addicted to nicotine. Certain other factors also work against them.

**Q: What factors?**

A: One important aspect of youth smoking is underestimation of addictiveness. Most youths understand that cigarette smoking is potentially hazardous to their health and do not intend to be lifelong smokers. Most think they can smoke only for a few years then quit, but later they find that they have become addicted and cannot quit. Most youths underestimate the power of nicotine addiction and their personal risk of addiction.

**Q: Why is underestimation of addictiveness significant?**

A: This is an important factor as to why it is impossible for youths to make a reasoned decision to smoke. Making such a decision implies understanding the risks, and youths consistently underestimate the risks of addiction.

**Q: What is the basis for your conclusion that youth underestimate the addictiveness of smoking?**

A: The Monitoring the Future project studied 1976 through 1986 senior classes. Seniors in high school were asked, "Do you think you will be smoking cigarettes five years from now?" Among the respondents who were occasional smokers (less than one cigarette per day), 85 percent stated that they probably or definitely would not be smoking in five years, as did 32 percent of those who smoked one pack per day or more. However, at follow-up five to six years later, of those who smoked occasionally, 28 percent had actually increased their cigarette consumption and only 58 percent had quit as compared to their own projections that 85 percent would be able to quit.

Of those who had smoked one pack or more per day, only 13 percent had quit and 70 percent still smoked one pack or more per day. Smokers in the other studied categories of 1 to 5 cigarettes per day and of about 10 cigarettes per day at the time of the initial questionnaire also were less likely to quit than they had predicted, and on average escalated their smoking over the subsequent five years.

**Q: What does this study demonstrate?**

A: Consistent with the concept of addiction, youth smokers' expectations of future smoking behavior showed little relationship to their actual behavior. That is, youths think they will be able to quit but underestimate the power of their addiction. Even those who smoke only a few cigarettes per day during high school have a high risk of becoming heavy smokers as adults.

**Q: How does the number of smokers who quit smoking each year compare to the rate of youth who begin smoking?**

A: In the United States, approximately 1.2 million smokers quit smoking every year. However, this number is countered by the approximately 3,000 youths who become regular smokers every day. Statistics show that approximately 75 percent of adolescents who are daily smokers become regular smokers as adults. Furthermore, once they become daily smokers, adolescents' quit rates are low.

**Q: How low are adolescent quitting rates?**

A: Among adolescent smokers who smoke one to nine cigarettes per day, the quit rate is 12 percent. Among those adolescent smokers who smoke ten or more cigarettes per day, the quit rate is only 6.8 percent. These rates remain low despite the fact that 70 percent of adolescent smokers attempt to quit smoking. Thus, the issue of youth smoking remains a key one for the tobacco industry's ability to maintain a supply of future adult smokers.

**Q: Have you considered the issue of what level of smoking intensity represents addiction in youth smokers?**

A: Yes.

**Q: Have you formed an opinion based upon a reasonable degree of scientific certainty as to whether youth smoke cigarettes because they are addicted to nicotine.**

A: Yes.

**Q: What is that opinion?**

A: There is very strong evidence that youth do become addicted to nicotine, and have difficulty quitting smoking because of nicotine addiction.

**Q: What level of smoking intensity is indicative of addiction for youth?**

A: It is my opinion that youths who smoke at least one cigarette every day have a high likelihood of being addicted.

**Q: Is there authoritative literature that supports your conclusion?**

A: Yes. The 1994 Surgeon General's report on Smoking and Youth indicates that smoking one to five cigarettes per day among teenagers is a strong predictor of continued smoking and dependence.

**Q: What are the bases for your conclusion that youth who smoke daily are addicted to nicotine?**

A: The bases include the following: First, nicotine is absorbed into the bloodstream to achieve levels in youth that are similar to those observed in adult smokers. Second, youth report pharmacologic effects of nicotine from cigarettes similar to those of adults, and report similar withdrawal symptoms when they are unable to smoke. Third, youth have difficulty quitting smoking. Their relapse rates when trying to quit are as high or higher than those of adults. In that addiction refers to loss of control of drug use, it's clear that many youth smokers have difficulty controlling their use of nicotine from tobacco.

**Q: What do you mean by the statement that youth that are daily smokers experience pharmacologic effects?**

A: Youth who are daily smokers experience effects such as feeling calmer when smoking cigarettes as compared to those who do not smoke daily. The calming effect is an important motivation for smoking in many smokers. This is an example of positive reinforcement, which I testified about earlier. Youth also experience negative reinforcements, the negative symptoms related to withdrawal when they do not smoke.

**Q: What are the bases for your conclusion that youth who are daily smokers are smoking for the pharmacologic reason of positive reinforcement?**

A: Positive reinforcement refers to the use of a substance to obtain direct effects from that substance. For nicotine, it means that someone is obtaining direct pharmacologic effects of nicotine that they find pleasant or satisfying or useful. Youth have been known to smoke for the calming effect of nicotine, this is an example of positive reinforcement.

**Q: What proof do you have for that statement?**

A: Researchers led by Anne McNeill prepared a smoking questionnaire for a group of 170 British schoolgirls which focused on the subjective effects of smoking. These effects included dizziness, feeling sick, feeling "high," increased alertness and increased calmness.

**Q: What did the results reveal?**

A: Only a few of the respondents reported feeling "high" or more alert. In contrast, feeling calmer was the most common effect reported in the study. In addition, this feeling of increased calmness was more likely to be reported by daily smokers than by occasional smokers.

**Q: What are the bases for your conclusion that youth who are daily smokers are smoking for the pharmacologic reason of negative reinforcement?**

A: Negative reinforcement means taking a drug to prevent or moderate withdrawal symptoms that occur when one has become physically dependent on the drug. Youth who are daily smokers report symptoms such as a strong need to smoke, irritability and restlessness when

they are not able to smoke their cigarettes. When they smoke a cigarette and these symptoms resolve, they are smoking for the reason of negative reinforcement.

**Q: What proof do you have for that statement?**

A: McNeill also conducted a study with 191 subjects ages 11-17, current cigarette smokers were asked about how they felt when they tried to quit smoking. Seventy-one percent of the daily smokers and 72 percent of the occasional smokers had made at lest one failed attempt at quitting. In addition, 74 percent of the daily smokers and 47 percent of the occasional smokers experienced at least one symptom of nicotine withdrawal; including a strong need to smoke, increased irritability, and inability to concentrate, hunger, restlessness, and feeling miserable.

**Q: In addition to the fact that youth smoke for pharmacologic reasons, are there other bases for your conclusion that the overwhelming majority of youth smoking daily are addicted?**

A: Addiction refers to loss of control of drug use. Most youths when questioned indicate that they do not intend to smoke cigarettes as adults. That is, they are smoking because it is a social thing to do, and plan to quit when they get older. However, when the same individuals are surveyed five years later, most are not able to quit and, in fact, most are smoking more cigarettes per day then they were originally. The fact that daily smoking as a youth predicts addictive smoking as an adult, supports the idea that addiction begins in youth.

**Q: What are the bases for this conclusion that youth who smoke daily will continue to smoke as adults, and in most instances will smoke in even greater quantities?**

A: This conclusion comes from the "Monitoring the Future" project conducted by the University of Michigan. This project interviewed high school seniors regarding their smoking status, and asked them to predict whether or not they would be smoking in five years. The researchers then contacted the smokers five years later, and confirmed that most who were

smoking daily in high school had become daily adult smokers and were smoking more than they were in high school.

**Q: How do youth smoking intensity levels compare to adult smoking intensity levels?**

A: In adults, smoking five to ten cigarettes a day is considered to be an addictive level of smoking. Youth, however, are in an escalating phase of addiction, and youth smoking intensity is generally lower than that of adults.

**Q: What is the reason why youth smoking intensity is generally lower than adult smoking intensity levels?**

A: It takes about seven years from the beginning of daily smoking until a smoker reaches a plateau level of cigarette consumption. When an adolescent begins to smoke cigarettes on a daily basis and alone, this usually means they are smoking for pharmacological reasons, which represents an early stage of addiction. The reason for this gradual escalation phase is two-fold. First, in most cases youth simply are not provided the same opportunities to smoke as adults. For example many youth cannot smoke at home. Second, as smokers begin and continue smoking, the smoking intensity increases as the brain adapts and the smoker becomes tolerant. Since most smokers start smoking in their teens and since it takes seven years to reach a stable level of cigarette consumption, teenagers are in the escalating phase of the smoking trajectory.

**Q: Do you have an opinion to a reasonable degree of scientific and medical certainty regarding whether there is a difference in the level of smoking intensity that would represent a strong predictor of addiction to nicotine among youths as compared to adults?**

A: Yes.

**Q: What is that opinion?**

A: My opinion is that youth who are daily smokers are likely to be addicted at levels of cigarette consumption below those that typically characterize addiction in adult smokers.

**Q: Does the American Psychiatric Association have a method for diagnosing addiction?**

A: Yes. It's called the DSM-IV, otherwise known as the Diagnostic Statistical Manual.

**Q: Do you consider the DSM-IV to be the best tool for identifying addiction among youth smokers?**

A: No.

**Q: Can you explain why the DSM-IV is not the most useful tool for identifying nicotine addiction in general?**

A: The DSM-IV was not developed to assess nicotine dependence. Rather, it was designed primarily for adults using drugs of abuse other than nicotine. Some of the questions are not clearly relevant to tobacco use.

**Q: Can you provide an example of how the DSM-IV fails as a diagnostic tool for nicotine addiction?**

A: The DSM-IV evaluates seven drug dependence criteria using a series of questions. Criterion one of the DSM-IV addresses the evidence of tolerance. The question asks about needing greater amounts of a drug to get the same effect. Most smokers who smoke a consistent number of cigarettes from day to day would respond 'no' to such a question. Yet all smokers who have smoked more than a few cigarettes have developed tolerance to the noxious effects of nicotine, and tolerance to many other effects of individual cigarettes develops every day during cigarette smoking, with a loss of tolerance overnight. If the question were posed appropriately, virtually all daily smokers would have to say "Yes" to tolerance. Likewise, criterion five indicates that a great deal of time is spent to obtain the substance. This is marginally related to cigarette smokers, because access to cigarettes is so easy. Careful questioning of many dependent smokers, however, reveals that they are obsessive about whether they have adequate supplies of cigarettes, and are careful not to run out, even if it means going out at night to buy cigarettes so that they have them when they awake the next morning. Finally, criterion six refers to negative social, occupational, and recreational consequences, which is much less of a problem

with smoking compared with other drugs of dependence, the latter of which are associated with intoxication and impaired performance.

**Q: You also indicated that in addition to not generally being the most useful diagnostic tool for addiction, the DSM-IV is particularly unhelpful as an indicator of nicotine addiction among youth. Can you explain why that is?**

A: Some of the criteria of the DSM-IV, as well as other questionnaires, may inquire about the time or the number of cigarettes smoked per day, the time of awakening to smoking the first cigarette, as well as some of the criteria described in my previous answer. Because youth have limited resources to purchase cigarettes, may have restricted access to cigarettes, have many restrictions on where they can smoke, and are often not as free as adult smokers to smoke their cigarette immediately when they wake, most dependence questionnaires are not very helpful as indicators of addiction in youth.

**Q: In your opinion, is the use of more than five cigarettes per day at the age of 21 a reasonable indicator of addiction?**

A: Yes. I think this is a conservative estimate. Most likely, youth who are smoking even fewer than five cigarettes per day on a daily basis are addicted.

**Q: Is the standard of smoking more than five cigarettes a day at the age of 21 supported by the relevant scientific studies and literature?**

A: Yes. As set forth in several of my previous answers, a standard as low as one cigarette per day – and certainly more than five cigarettes per day at the age of 21 – as a reasonable indicator of addiction is fully supported by medical and scientific findings.

**Q: Are you familiar with the FTC smoking method?**

A: Yes, I am.

**Q: What is the FTC smoking method?**

A: The FTC method consists of placing a cigarette into a syringe-like device which withdraws exactly 35 milliliters of smoke over two seconds, once every sixty seconds, until the cigarette is smoked to a given distance above the filter, or the filter over-wrap.

**Q: What is machine measured yield?**

A: This is the amount of nicotine, tar, carbon monoxide, or other chemicals that are generated in the smoke of a cigarette that is smoked in a standardized fashion. The standard machine measured yields of tar and nicotine measured using the FTC method are reported in cigarette advertising.

**Q: Are you familiar with the concept called compensation?**

A: Yes.

**Q: Have you performed research concerning compensation?**

A: Yes.

**Q: Have you published articles on this subject?**

A: Yes.

**Q: Is this an area of expertise for you?**

A: Yes.

**Q: What is compensation?**

A: Compensation refers to the behavior of smoking cigarettes of different machine measured yields more or less intensively, and/or smoking more or fewer cigarettes to achieve a particular level of intake of nicotine. Compensatory smoking behavior implies that there has been a change in smoking behavior in response to a change in the nominal nicotine delivery of the cigarette that is being smoked.

**Q: Are you familiar with a smoking concept called titration?**

A: Yes, I am. Titration essentially is maintaining the desired level of nicotine intake and refers to the phenomenon of taking in similar levels of nicotine from day to day. This reflects

the observation that smokers have particular desired levels of nicotine intake throughout the day that appear to result in optimal functioning.

**Q: What happens if a smoker achieves perfect titration?**

A: Perfect titration means that the level of nicotine intake is exactly the same no matter what cigarette brand or type or what nominal machine measured nicotine yield is smoked.

**Q: What is individual smoker variation?**

A: Individual smoker variation refers to the fact that one smoker may smoke cigarettes – either regular or low tar – differently than another smoker, and that the same person may smoke the same cigarette differently on different occasions. No standardized testing procedure can account for these types of variations, such as the speed a particular individual smokes a cigarette, whether a person is engaging in other activity -- like talking or listening or reading -- while smoking, or the emotional state of a person while he or she is smoking.

**Q: So, if I was to tell you that no two people smoke in the same way, is that compensation?**

A: No, individual variability in how a cigarette is smoked does not address the compensation issue.

**Q: Why not?**

A: Individual smoker variability relates to the fact that cigarettes are smoked differently by different individuals. This type of variability is separate and distinct from the issue of compensation, which relates to the phenomenon of smokers smoking purportedly low-delivery cigarettes more intensely in order to achieve their particular desired level of nicotine intake.

**Q: Is it fair to say that compensation occurs primarily due to nicotine?**

A: Yes. Compensatory smoking behavior is a manifestation of nicotine addiction.

**Q: What evidence supports that?**

A: The evidence for compensation for purposes of titrating nicotine is described in NCI Monograph 13. The most important finding is that, comparing smokers of brands with machine measured nicotine yields ranging from low to high, the average intake of nicotine, indicated by measuring a blood, saliva or urine cotinine level, is almost the same.

**Q: What is the consensus in the medical and scientific fields with respect to compensation?**

A: The concept of smoking to obtain desired levels of nicotine and the concept of nicotine titration with associated compensation is widely accepted by the scientific and public health communities.

**Q: What happens when a smoker switches from a regular to a low tar or light cigarette?**

A: In general, the smoker will engage in compensatory smoking behavior in order to increase his or her intake of smoke to compensate for the reduced delivery of nicotine. This is done by either taking in more smoke per cigarette or smoking more cigarettes per day.

**Q: Is switching cigarette products or categories necessary for compensation to occur?**

A: This depends on whether one is looking at individual behavior or population behavior. To assess compensation in the individual, one does need to look at effects of switching cigarettes. However, if one looks at compensatory behavior for a population, one can compare nicotine intake for different smokers across the range of cigarettes with different machine measured yields. If nicotine intake is similar across machine measured yields, then one can assume that, compared to any standard yield cigarettes, the population has compensated for differences in nicotine yield.

**Q: Please explain the compensation mechanisms with a little more detail.**

A: A person can take in more smoke per cigarette by several means. One is by taking bigger puffs, another is by taking more frequent puffs from the cigarette. Yet another way to increase

smoke intake is to block the ventilation holes in the filter. Ventilation holes are small perforations in the filter that are difficult for a smoker to see, but which when blocked by the fingers or lips improve the draw characteristics of the cigarette and increase the resultant nicotine yield. It should be noted that most smokers are not aware of the ventilation holes, but come to learn by trial and error that holding the cigarette in a certain way in their hands or in their mouth results in better smoke characteristics. Ventilation holes are not blocked, on the other hand, when a cigarette is smoked by a machine according to the FTC method.

**Q: Are these conscious acts on the part of the smoker?**

A: No, these compensatory smoking behaviors are not conscious acts by the smoker.

**Q: How do you know this?**

A: There is evidence from observational studies and studies of looking at the tar pattern in filters that smokers block ventilation holes. There is also evidence in talking to smokers that they are unaware that ventilation holes exist.

**Q: What is the specific evidence that smokers block ventilation holes?**

A: The fact that many smokers block ventilation holes has been demonstrated in published peer-review research. For example, Kozlowski, *et al*. by using stain pattern, an unobtrusive indicator of vent blocking, found that 58 percent of the 135 filters from various ultra-light brands (4 milligrams of tar or less) had evidence of vent blocking. In another study, Kozlowski, *et al*., using similar research tactics as the previous study, found evidence of vent blocking in 53 percent of the 158 filters from various light brands.

**Q: You mentioned an indicator of vent blocking called stain pattern. What exactly is stain pattern?**

A: With the stain pattern technique, trained raters look at the mouth ends of cigarettes and determine if vent blocking has occurred by looking at the extent of the stain on the cigarettes' filters. A more uniform stain on the filter indicates that vent blocking has occurred.

**Q: What is the specific evidence that smokers are unaware that ventilation holes exist?**

A: Research performed by Kozlowski and colleagues found that the majority of smokers were unaware of the presence of vents in general or even on their own brands. Kozlowski, *et al*. found that the filter vents are often placed just millimeters from the smoker's lips or fingers and are thus often not noticed by smokers.

**Q: Do you have an opinion to a reasonable degree of medical or scientific certainty as to what percentage of smokers engage in compensation?**

A: The vast majority of smokers engage in compensation. If one looks at the broad population of smokers, there is a high degree of compensation that is seen from the range of machine-determined nicotine yields of about 0.3 milligram to 1.5 milligrams of nicotine. Across this range, there is only about a ten percent difference in nicotine intake from the lowest to the highest yield cigarette. When one switches to the ultra-low yield cigarettes with machine measured yields of 0.1 or 0.2 milligram of nicotine, then there is an approximately thirty percent reduction of nicotine exposure. It is more difficult for smokers to fully compensate for ultra-low yield cigarettes. However, very few smokers (less than 5 percent) smoke ultra-low yield cigarettes. This is most likely because they cannot adequately compensate and do not get enough nicotine for these cigarettes to be satisfying.

**Q: Are you familiar with the concept of complete or full compensation?**

A: Yes.

**Q: What is complete compensation?**

A: Complete compensation is where a person adjusts his or her smoking to take in exactly the same level of nicotine from one cigarette as they had from their original cigarette of different nominal machine measured yield.

**Q: What happens if there is a slight reduction in the nicotine intake level?**

A: This represents incomplete compensation. The importance of incomplete compensation depends on the extent to which exposure to various tobacco toxins is actually reduced.

**Q: In earlier testimony you mentioned that you have previously written on the topic of compensation. Have you written for any government publications?**

A: I prepared a chapter entitled "Compensatory Smoking of Low Yield Cigarettes" for NCI Monograph 13. I also wrote a chapter entitled "Biomarkers of Cigarette Smoking," which discussed some of the same issues, for NCI Monograph Seven.

**Q: What was the purpose of Monograph 13?**

A: The purpose was to review the evidence on the Federal Trade Commission (FTC) method for measuring tar and nicotine yields, and to determine whether smoking cigarettes with low machine measured yields was associated with any reduction in smoking induced disease risk.

**Q: Why had this issue arisen?**

A: A large percentage of smokers in the United States are currently smoking light cigarettes. Many of these smokers believe that light cigarettes are "safer" or "less harmful" than are regular cigarettes.

**Q: Do you have evidence for this statement?**

A: Yes, I do. In 1987, the National Health Interview Survey found that 45.7 percent of Ultra-Light smokers, 32.2 percent of light smokers, and 29.4 percent of Regular smokers believed that low tar cigarettes reduced the risk of cancer. In another national survey, reported by Kozlowski, *et al*., approximately 60 percent of ultra-light smokers and 40 percent of Light smokers responded that they smoked reduced-tar cigarettes in order “to reduce the risks of smoking without having to give up smoking.”

**Q: Do these light and ultra-light cigarettes actually reduce the risks of smoking?**

A: No. Experimental studies, which I will discuss further in this testimony, have suggested that smokers compensate quite well, and are exposed to similar levels of tobacco smoke toxins

when smoking cigarettes with low versus high machine measured yields. Thus, it was important from a public health perspective to review the evidence on whether low yield cigarettes have any impact on smoking disease risks.

**Q: Which diseases were examined in Monograph 13?**

A: Lung cancer, cardiovascular disease and chronic respiratory disease.

**Q: Did Monograph 13 involve comparisons between regular and light cigarettes?**

A: Yes.

**Q: Did you study the concept of compensation as part of your work on Monograph 13?**

A: Yes.

**Q: Why?**

A: Compensation explains why smoking of light cigarettes has not been associated with a reduction of smoking-induced disease risks. One would think, looking at the FTC yield data, that toxic exposures would be substantially reduced if one switches to light cigarettes; however, because of compensation, resulting toxic exposures are similar for light and regular cigarettes.

**Q: Were the authors of the Monograph able to reach conclusions about whether smoking low machine measured yield cigarettes was associated with any reduction in smoking-induced disease risk?**

A: Yes.

**Q: What were those conclusions?**

A: The conclusions were: (1) epidemiological and other scientific evidence does not indicate a benefit to public health from changes in cigarette design and manufacturing over the last fifty years; (2) for spontaneous brand switchers there appears to be complete compensation for nicotine delivery, reflecting more intensive smoking of low-yield cigarettes; (3) widespread adoption of lower yield cigarettes in the United States has not prevented the sustained increase in lung cancer among older smokers; (4) many smokers switched to lower yield cigarettes out of

concern for their health, believing these cigarettes to be less risky; (5) advertising and marketing of lower yield cigarettes may promote initiation and impede cessation, the latter of which is critically important in preventing smoking-related diseases; and (6) measurements of tar and nicotine yields using FTC methods do not offer smokers meaningful information on the amount of tar and nicotine they will receive from a cigarette.

**Q: What were the conclusions of your chapter of Monograph 13?**

A: The conclusions to my chapter were: (1) smokers regulate their intake of nicotine to obtain the amount of nicotine that they need to sustain their addiction; (2) spontaneous brand switching studies suggest that there is no reduction in smoke intake per cigarette, and that any reductions that are seen in brand switchers depend on whether or not those individuals also reduced their cigarette consumption; and (3) studies of smokers smoking self-selected brands showed a weak relationship between machine measured nicotine yield and a smoker's nicotine, carbon monoxide or thiocyanate exposure.

**Q: What are the different kinds of studies that are generally used to conduct research on compensation?**

A: There are three kinds of studies: spontaneous brand switching studies, cross-sectional studies, and forced brand switching studies.

**Q: Did Monograph 13 include an evaluation of the results of each of these types of studies?**

A: Yes.

**Q: What is a spontaneous brand switching study?**

A: A spontaneous brand switching study is a longitudinal study of individuals who switched from one brand to another brand of cigarettes.

**Q: What form of measurement do such studies attempt to collect?**

A: An attempt is made to collect information on intake of nicotine and other potential tobacco smoke toxins. For example, nicotine intake is estimated by measuring levels of its breakdown product, cotinine, in blood, saliva or urine. Exposure can also be quantitated by measuring carbon monoxide levels in exhaled air.

**Q: What is a cotinine level?**

A: Cotinine is the major breakdown product of nicotine. Nicotine is metabolized to cotinine by the liver, and 80 percent of nicotine is converted to cotinine. Cotinine persists in the body for a much longer period of time, and its concentrations in blood and other biological fluids are higher than those of nicotine. For this reason, cotinine has become the accepted marker for looking at nicotine exposure measurement from tobacco products.

**Q: Why is such a measurement more desirable for researchers than say, a measurement of the amount of smoke that enters a smoker's mouth or is going through a cigarette?**

A: Smokers inhale smoke from cigarettes in different ways, keep it in their lungs for different periods of time, and may absorb different amounts of nicotine and other chemicals from smoke. For example, some smokers take in tobacco smoke along with a very small amount of room air, while others take large puffs with a small amount of smoke and a large amount of room air. One cannot predict the absorption of nicotine and other chemicals from levels of these chemicals in the smoke that enters the mouth, or that which is emitted from the cigarette. The best marker of exposure is to actually measure levels of the chemicals in question in the body of the smoker.

**Q: Can you discuss the advantages of spontaneous brand switching studies?**

A: Spontaneous brand switching studies are studies of smokers who have chosen to switch to higher or lower machine-determined yield cigarettes, or vice versa. As a result, the advantage of these studies is that the brand of cigarette has been selected by the smoker and not by the

researchers. Such studies are more informative of smokers' exposure in the real world when switching from higher to lower yield cigarettes.

**Q: Are there any disadvantages to spontaneous brand switching studies?**

A: One disadvantage for these studies is that it is not clear why smokers have switched. In one study, for example, people who switched to light cigarettes also smoked many fewer cigarettes, and were presumably in the process of trying to quit cigarettes. In addition, these studies are also difficult to perform.

**Q: Why are they difficult to perform?**

A: Spontaneous brand switching studies require characterizing smoking behaviors of individuals and then following the same people over a number of years, with repeated measurements of their chemical exposures when switching to different cigarettes. Since most individuals tend to smoke the same cigarette over time, finding adequate numbers of spontaneous switchers requires very large numbers of research volunteers to be followed for many years.

**Q: Do spontaneous brand switching studies support the existence of compensation?**

A: Yes, spontaneous brand switching studies generally show that there is no reduction in smoke intake per cigarette.

**Q: What evidence do you have for this statement?**

A: My own study demonstrated this.

**Q: Can you describe your study please?**

A: In my study, on which I reported in 1987, we studied 197 smokers who were smoking self-selected brands of cigarettes. Of these smokers, 104 smoked cigarettes of the same or similar machine-determined yields, 62 switched to lower yield cigarettes, and 31 switched to higher yield cigarettes. We had measurements of plasma cotinine and blood carbon monoxide levels on two occasions six years apart.

**Q: What were the results of this study?**

A: Smokers who did not change the nicotine yields showed a slight decrease in the number of cigarettes they smoked each day. However, there was no change in cotinine or carbon monoxide levels. For smokers who switched to lower yield cigarettes, the analysis of cotinine concentration or carbon monoxide per cigarette showed no change despite the reduction in nominal machine measured yield. Therefore, these smokers obtained the same dose of nicotine and carbon monoxide from each cigarette even though the machine measured yield was lower. For these smokers, there was a reduction in daily exposure to tobacco smoke. However, this reduction occurred because these smokers reduced their consumption of cigarettes by almost 20 percent.

**Q: What about the smokers of higher machine measured yield cigarettes?**

A: While these smokers did take in more nicotine and carbon monoxide per cigarette, the amount was much less than that predicted by the increase in the cigarettes' machine measured yield.

**Q: In summary, what does your study demonstrate about compensation?**

A: For spontaneous brand switchers, there is complete compensation for each cigarette smoked. As a result, for these smokers, switching from higher to lower yield cigarettes is not likely to reduce the risk of disease from smoking.

**Q: In the end, what do spontaneous brand switching studies show with respect to compensation?**

A: The spontaneous brand switching studies show a high degree of compensation per cigarette.

**Q: Can you be more specific?**

A: In the studies that I was involved with, smokers took the same amount of nicotine per cigarette from lower yield and higher yield cigarettes. Another study showed that nicotine intake as estimated by measurement of nicotine in metabolites in the urine were no different in

individuals who switched from higher to low machine measured yield cigarettes compared to those who had not switched.

**Q: Why is the per cigarette figure more important?**

A: The per cigarette figure shows what an individual can take in from a particular cigarette. Thus, it provides information on the delivery characteristics of the product.

**Q: How do these studies fit into your opinion regarding compensation?**

A: These studies support the concept of compensation and help explain why low yield cigarettes do not reduce the hazards of smoking.

**Q: What are cross-sectional studies?**

A: Cross-sectional studies involve sampling smokers in the general population who are smoking their own chosen brand of cigarettes.

**Q: What type of exposure markers are used in cross-sectional studies?**

A: Measurements are made in biological fluids or expired air of nicotine, cotinine, carbon monoxide and/or thiocyanate. Thiocyanate is used because that is a marker of human exposure to hydrogen cyanide, which is present in tobacco smoke.

**Q: What do the researchers do after they collect the marker samples?**

A: The concentrations of the various markers in individuals are compared with the machine measured yields of their own brand of cigarettes.

**Q: Do cross-sectional studies have any advantages?**

A: Cross-sectional studies are studies of chemical exposures in smokers who have selected the brand of cigarette that they find satisfying. As a result, data from this type of study provides the best estimate to chemical exposure in smokers smoking different brands of cigarettes. Because the brand of cigarette in these studies is selected by the smoker rather than by the researcher, such studies are more informative of smoker's exposure in the real world than when they are experimentally switching from higher to lower yield cigarettes.

**Q: Are there disadvantages to cross-sectional studies?**

A: The main disadvantage is that one does not know the smoker's smoking history. Therefore, one cannot tell if the smoker had started with a particular brand, or had switched to that brand from another type of cigarette.

**Q: And what have the results of such a study typically shown?**

A: Such studies show that there is very little difference in tobacco smoke exposure in people smoking cigarettes of different machine-determined yields. For the general population of smokers who select their own brand of cigarettes, the extent of nicotine compensation appears to be almost complete.

**Q: What is your evidence for this statement?**

A: There have been many cross-sectional studies performed, and overall they demonstrate that while there are some differences in nicotine exposure when high- and low-yield cigarette brands are compared, these differences are quite small. The differences do not equal and are much less than the change in nominal machine measured yield. For example, I conducted a cross-sectional study in 1983 of smokers seeking smoking cessation therapy. The study demonstrated that the cotinine blood levels of 273 U.S. smokers was similar across the range of FTC machine measured yields. Many other cross-sectional studies are discussed in Monograph 13.

**Q: Is this true for all types of cigarettes?**

A: This appears to be true of cigarettes with machine-determined yields of 0.3 milligram nicotine and higher. For the ultra-low yield cigarettes with yields of 0.2 milligram nicotine or less, there is on average a thirty percent reduction of exposure to cotinine.

**Q: What is your evidence for this statement?**

A: Gori and Lynch measured the plasma cotinine levels of 288 smokers of two brands of ultra-low-yield cigarettes (1 milligram tar). They found that the smokers of one brand of the

ultra-low-yield cigarettes had cotinine concentrations similar to the smoker population average of 300 mg/ml, while the smokers of the other ultra-low-yield brand had concentrations that were about 30 percent lower.

**Q: In the end, what do cross-sectional studies show with regard to compensation?**

A: Cross-sectional studies show nearly 100 percent compensation.

**Q: How do forced brand switching studies work?**

A: These are experimental studies where smokers are asked to switch from high to low yield cigarettes for a period of time, during which their exposure to various tobacco smoke toxins is measured and their general smoking behaviors are observed.

**Q: What are the advantages of forced brand switching studies?**

A: Because forced brand switching studies examine smokers who have switched to brands with higher or lower machine-determined yield compared to their usual brand, these studies are particularly useful in that smoking behavior and exposure can be assessed under close observation.

**Q: Are there disadvantages associated with forced brand switching studies?**

A: Yes. The limitations of such studies include the fact that smokers are switched only for the purpose of the research. Motivation and cigarette acceptability differ from the natural situation of brand switching. These studies are performed over periods of time that may not provide an adequate duration to adjust to the novel taste or puffing characteristics of the new cigarettes. Many of these short-term studies have been performed in laboratories or on research wards, environments in which individuals may not smoke cigarettes as they normally do.

**Q: What is your overall opinion of such studies?**

A: Such studies are particularly useful in providing information on the mechanisms and extent of compensation that can occur.

**Q: And, do these studies support the existence of compensation?**

A: Yes.

**Q: Do these studies also show differences between the machine measured nicotine yield of a cigarette brand and a smoker's actual nicotine exposure level?**

A: Yes.

**Q: What evidence do you have to support these statements?**

A: Many studies, involving both short and long-term switching periods, support these statements. For example, I have conducted studies involving short term forced brand switching. In one, I studied 11 smokers in a research ward. These 11 smokers were smoking their own brands (average yield: 16.3 mg tar, 1.1 mg nicotine) and were switched to either Camel (15.4 mg tar, 1.0 mg nicotine) or True (4.6 mg tar, 0.4 mg nicotine). I then measured nicotine intake by measuring blood nicotine levels throughout the day.

**Q: What were the results?**

A: When the smokers were switched from their usual brand to either Camel or True, their nicotine exposure did decrease by one-third. However, the smokers' intake of nicotine and carbon monoxide comparing Camel and True were the same. Thus, the degree of compensation for True, when compared to Camel, was 100 percent.

**Q: You mentioned long-term forced brand switching studies. How long do such studies last?**

A: To be considered long-term, they must last for more than a few weeks.

**Q: Do long-term forced brand switching studies support your earlier statements?**

A: Yes, they do. For example, Frost, *et al*. conducted a study wherein they studied 434 smokers of high-yield cigarettes who were switched to cigarettes with an approximately 50 percent lower machine measured yield. One group was switched immediately and the other was switched gradually over several months. A third group was switched to cigarettes that possessed a 10 percent lower machine measured yield.

**Q: Could the participants choose their own cigarettes?**

A: Yes, they were able to choose the brand they would smoke as long as it was within their prescribed yield.

**Q: Did the researchers follow-up on the subjects?**

A: Yes, they did. Follow-up was conducted six months later.

**Q: What were the results?**

A: In the fast-switching yield group, serum cotinine levels declined by approximately 11 percent and carbon monoxide levels declined by approximately 14 percent. For the slow-switching yield group, cotinine levels decreased by approximately 6 percent and carbon monoxide levels declined by approximately 16 percent.

**Q: In terms of compensation, what did these results mean?**

A: The extent of compensation was estimated to be 79 percent based on cotinine and 65 percent based on carbon monoxide. There was no difference in compensation based on the speed of the switch. More importantly, the high degree of compensation held even though the participants were smoking less cigarettes.

**Q: Why is that so important?**

A: It is important because it demonstrates that actual cigarette yields taken in by a smoker are substantially increased by smoking lower yield cigarettes more intensely.

**Q: In the end what do forced brand switching studies show with respect to compensation?**

A: The forced brand switching studies show on average about eighty percent compensation.

**Q: Why only eighty percent compensation?**

**A:** Presumably compensation is not complete because the smokers have been switched to cigarettes that were not of their own choosing.

**Q: How long does compensation exist for a smoker?**

A: So far as we know, compensation is permanent.

**Q: How do we know this?**

A: Cross-sectional studies include smokers who have smoked their chosen brand of cigarettes for many years. As these studies show evidence of nearly complete compensation, it appears that compensation is permanent. Additionally, in forced brand switching studies, the degree of compensation appears to be similar in studies lasting less than one month and studies lasting several months.

**Q: Which studies?**

A: This has been demonstrated in a number of cross-sectional and forced brand switching studies as discussed in my chapter for Monograph 13 and earlier in this testimony.

**Q: Defendants have previously argued, in other cases in which you have testified, that in a 1994 article you stated that to the extent that compensation occurs it is partial and temporary. Did you say that?**

A: This is not quite correct.

**Q: How is that not correct?**

A: This 1994 paper at issue was talking about the issue of over-compensation.

**Q: What is over-compensation?**

A: Over-compensation refers to a smoker taking in greater amounts of tobacco smoke toxins than they had originally. As a result, the smoker would be exposed to greater levels of toxins, namely tar and carbon monoxide which might increase the risk of tobacco disease.

**Q: Who prepared this paper?**

A: This paper was written by myself and Dr. Jack Henningfield.

**Q: Is Dr. Henningfield a nicotine researcher?**

A: Yes, he is. Dr. Henningfield is an internationally recognized nicotine researcher.

**Q: Getting back to the paper, did it include a proposal that caused concern among those who reviewed it?**

A: Yes. Our proposal was to reduce the nicotine content of cigarettes over time, to make them less addictive. The concern was that the reduction in the nicotine content of tobacco would cause people to over-compensate in their effort to obtain the necessary amount of nicotine.

**Q: What have studies revealed about over-compensation?**

A: As discussed earlier in Monograph 13, long term forced-switching studies have not revealed evidence of over-compensation.

**Q: Were there any other conclusions presented by you in your Monograph 13 chapter?**

A: Yes. Considering the overall exposure data for individuals selecting their own brand, there is little reason to expect that smokers of cigarettes with low machine measured yields will have a lower risk of disease than those who smoke higher yield cigarettes.

**Q: Why?**

A: Because of the high degree of compensation as discussed earlier.

**Q: When did you write your chapter for Monograph 13?**

A: I believe this chapter was prepared sometime in the year 2000, and revised and finalized in 2001.

**Q: Do you still hold these opinions to a reasonable degree of medial and scientific certainty?**

A: Yes.

**Q: How have the medical and scientific communities viewed these opinions?**

A: Most authorities are now convinced that there is little if any benefit with respect to health risk to smoking low yield versus regular cigarettes. The suggestion that smokers who cannot quit switch to light cigarettes is no longer considered to be beneficial health-related advice.

**Q: Thank you, Dr. Benowitz.**