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Subject: Oversight hearing on tobacco products

WITNESSES

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WRITTEN STATEMENT OF VICTOR JOHN DeNOBLE, Ph.D

April 27,1994

Mr. Chairman and members of the committee, I am Dr. Victor John DeNoble, a behavioral psychologist and I am Senior Behavior Analyst for the Community Mental Retardation Program for the State of Delaware. I am grateful to have this opportunity to discuss my research at this hearing on tobacco.

From 1980 to 1984, I was employed at the Philip Morris Research Center in Richmond, Virginia as an Associate Senior Scientist. My responsibilities were to establish and direct a behavioral pharmacology laboratory to study the behavioral and physiological effects of nicotine and other smoke components in rats. Our initial goal was to identify the behavioral effects of nicotine on the central nervous system and to establish structure activity relationships among organically synthesized nicotine analogues. The purpose of the nicotine analogue program was to develop an analogue that would retain physiological and behavioral effects in the brain and be devoid of any pharmacological effects in other organs, specifically, the cardiovascular system. In order to accomplish this goal, a characterization of the behavioral effects of nicotine in rats using a variety of operant conditioning procedures needed to be developed.

With regard to the nicotine analogue program, our primary behavioral test was a nicotine drug discrimination procedure. Rats were trained to identify whether they had been injected with nicotine or saline. Using nicotinic-cholinergic antagonists, we demonstrated that the rats ability to discriminate (identify) whether it was injected with nicotine or saline was mediated by nicotine's effect in the brain not by nicotine's effect on the peripheral nicotinic receptors.

This test procedure was used to identify nicotine analogues that would mimic the effects of nicotine in this discrimination procedure. This behavioral data was then combined with nicotinic receptor binding data, as well as, peripheral pharmacology data generated outside Philip Morris Research Center to develop structure-activity relationships among these analogues. The goal of this program was to identify a nicotine analogue that would have central nervous system effects without effects on the cardiovascular system.

In our self-administration studies we demonstrated that, (1) nicotine functioned as a intravenously delivered reinforcer for rats, (2) that rats would press levers several times for a single injection, (3) that nicotine self-administration was controlled, at least in part, by nicotine levels in blood or tissue,

(4) that the reinforcing effects were mediated by central nicotinic-cholinergic receptors, (5) that endogenous opioid receptors did not mediate nicotine's reinforcing effects and, finally, (6) that termination of chronic self-administration of nicotine over several weeks did not result in observable behavioral signs of a physiological dependence.

With regard to this last observation, we extended our findings by examining the effects of nicotine self-administration on concurrent lever pressing maintained by food. Concurrent nicotine self-administration was shown not to interfere with lever pressing for food and that discontinuing access to nicotine self-administration did not alter the rate or pattern of food intake. In a related experiment, we examined the effects of pharmacological antagonism of chronic nicotine administration on lever pressing maintained by food. The results showed that antagonism of chronically administered nicotine also did not result in a disruption of schedule-controlled behavior.

Termination or antagonism of chronic nicotine administration did not result in a disruption of lever pressing for food suggesting that chronic administration of nicotine did not result in a physiological dependence in these tests

Studies on the development and loss of tolerance to chronic nicotine exposure revealed that tolerance to the behavioral effects of nicotine developed following chronic administration of nicotine. The study design allowed us to demonstrate that both physiological and behavioral tolerance develops to chronic nicotine administration. Following tolerance development, higher doses of nicotine were required to produce effects that were both quantitatively and qualitatively similar to those observed before tolerance had developed.

Our laboratory also conducted a series of studies on the behavioral effects of nicotine when injected directly into the ventricles of the brain, as well as, when nicotine is injected into different brain sites. This research was directed at identifying the neuroanatomical substrates mediating the behavioral effects of nicotine. These test procedures also became a primary screening tool for the nicotine analogue program since the behavioral effects of nicotine were shown to be controlled by nicotine's effect on the brain, not on peripheral systems.

The above mentioned studies summarizes major research efforts with nicotine and nicotine analogues. There were several other experiments which provided support for these major research programs.

Almost all of the research that that occurred between 1980 and 1984 has subsequently been replicated, confirmed and extended by other investigators around the world.

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

In our search to identify other molecules in tobacco smoke that may have reinforcing properties, we identified acetaldehyde as a major component of gas phase smoke. Tobacco itself does not contain acetaldehyde, but, as a product of pyrolysis, large amounts of acetaldehyde are formed and delivered in the gas phase of smoking. Interest in this molecule began in the mid 1960's when it was demonstrated that another aldehyde, formaldehyde, was shown to condense with endogenous catecholamines to form compounds called tetrahydroisoquinolines (TIQs). In the mid 1970's, it was demonstrated that acetaldehyde, a major metabolite of alcohol could also form TIQs. TIQs have been hypothesized to act as "false neurotransmitters" in catecholamine-containing neurons. The fact that acetaldehyde is in high concentration in smoke, is delivered to brain in seconds, and is highly reactive with

catecholamines led us to hypothesize that, (1) acetaldehyde may function as an intravenously delivered reinforcer for rats, (2) that the reinforcing effect would be mediated by the formation of TIQs, and that, (3) interactions with nicotine's reinforcing effects would be possible.

Our research confirmed that acetaldehyde was, (1) a reinforcer when delivered intravenously, (2) that rats would press levers several times for a single injection, and (3) that termination of acetaldehyde access did not result in observable signs of a physiological dependence. In a related series of experiments, we further demonstrated that the reinforcing properties of nicotine and acetaldehyde would interact behaviorally producing additive effects in rats.

These results formed the basis for the hypothesis that both nicotine and acetaldehyde are reinforcing agents in cigarette smoke and that their interaction would result in an enhanced reinforcing effect in humans.

I would like to thank you for allowing me to place my statement in the record.