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The following comments pertain to several reports (unpublished, published or in press) from the Philip Morris Research Center. They are as follows:

1. Unpublished manuscript: Brain Sites Involved in the Mediation of the Behavioral Effects of Intraventricularly Administered (-)- Nicotine.

This paper by DeNoble, et al. reports an attempt to isolate the predominant anatomical brain areas at which nicotine acts. The methodology involved injecting nicotine into various brain structures and measuring effects on lever pressing by rats (this lever pressing was maintained by food reinforcement).

The major finding was that the "[p]rimary site of central action of nicotine is the vestibular nucleus . . . ." Additional evidence was provided suggesting that the action of nicotine on the vestibular nucleus could be influenced by "blocking," with drugs, a different brain stucture.

The research reported in this DeNoble, et al. manu-

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script has no clear implications regarding smoking motivation. The authors make no speculation regarding cigarette smoking. The only troublesome aspect about the report (as is typical of all the papers in this packet) is that nicotine is treated as a drug, and as a drug affecting the central nervous system. Although nothing is said about this being related to smoking or a motivation for smoking, the fact that Philip Morris is even engaged in such research may be taken by some as indicating a particular view of the importance of nicotine in cigarette smoking.

2. Unpublished manuscript: Development of Behavioral Tolerance Following Chronic Nicotine Administration.

As is clear from the title, this Mele and DeNoble paper deals with tolerance to the effects of nicotine. It begins with the statement that it is "well documented that tolerance develops to many of the effects of nicotine following its repeated administration." The question for this study is to what extent the development of tolerance is mediated by behavioral/environmental factors versus physiological factors. The methodology is what is known as the "before/after" method. In this method, a behavioral task is employed -- in this specific case, a food reinforcement schedule in rats. Over a series of experimental sessions, one group receives nicotine injections before the experimental sessions (performance of the behavioral task). The other group receives the drug after the experimental sessions. The logic is that both groups receive equal exposure to the drug, therefore both have

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equal opportunity to experience physiological tolerance to the drug. However, the "before" group experiences exposure to the task under the conditions of the drug, and should or could also show a behavioral/environmental tolerance -- i.e., learning of a task particular to a particular situation. The test for tolerance involves, after a period of repeated administration, giving both groups nicotine before the experimental session. If the "before" group performs better than the "after" group, then this indicates that a behavioral tolerance is involved. A physiological tolerance can also be assessed by comparing effects of nicotine on performance following repeated administration in the "after" group to effects on performance in a baseline test before the chronic administration.

Using such a procedure, Mele and DeNoble reported that the "before" group showed less disruption of responding in the test for tolerance than the "after" group, thereby indicating behavioral tolerance. Also, they reported that the "after" group showed less disruption of responding than during an initial baseline test, thereby indicating some physiological tolerance.

The bottom line is that the authors are maintaining that there is tolerance to nicotine, which involves both behavioral and physiological factors.

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It is obvious that such a report has undesirable implications for smoking and health litigation. Tolerance is frequently cited as one of the hallmarks of addiction. It is the industry's

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position that one of the classic criteria for addiction is tolerance, and that such has not been demonstrated in the case of nicotine. While it is true that the Mele and DeNoble paper does not discuss smoking in particular or attempt to extrapolate their experimental findings beyond the laboratory, there is nevertheless the implication simply by the fact that Philip Morris is doing this research, that it is viewing the research as relevant to smoking behavior.

3. Published abstract: Antagonism of Chronic Nicotine Administration: Effects on Schedule-Controlled Behavior in Rats.

This study by DeNoble, et al. was of the effect of nicotine, and of the effect of the nicotine antagonist mecamylamine, on a particular pattern of food reinforced lever pressing in rats. Rats were given chronic nicotine injections during their performance of a food reinforcement schedule. Following this period of chronic administration of nicotine, the rats were challenged with the drug mecamylamine. This drug presumably blocks the central nervous system actions of nicotine. The logic is that if nicotine leads to physiological dependence, then mecamylamine should precipitate withdrawal and lead to a disruption of behavior in rats chronically exposed to nicotine. This disruption was not found.

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It should be noted that in this particular abstract, the authors did not state the implication of their research for

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physiological dependence involving nicotine. Nevertheless, in a subsequent paper they refer to this abstract and do make that implication explicit.

4. Published article: Behavioral Effects of Intraventricularly Administered (-)- Nicotine on Fixed Ratio Schedules of Food Presentation in Rats.

This was a study by DeNoble, et al. of the response suppressing effects of nicotine, and their elimination by administration of mecamylamine. The authors established a pattern of lever pressing in rats using food reinforcement, then administered nicotine into the ventricles of the brain. This resulted in suppression of responding, which was eliminated if the central nervous system nicotine antagonist mecamylamine was also administered. The response suppressing effects of nicotine were not blocked by the peripheral nervous system nicotine antagonist hexamethonium. According to the authors this indicated that nicotine was having its response suppressing effect due to its action in the central nervous system. 1005059925

There was no speculation made by the authors as to relevance of their results to human smoking behavior. Nevertheless, the authors do use drug terminology (e.g., dose, antagonism, site of action, etc.). This, in the context of research supported by a cigarette manufacturer, could leave implicit to some that

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the cigarette manufacturer views the research as relevant to cigarette smoking behavior. If so, then the emphasis of this study on central nervous system pharmacological actions is clearly at variance with positions which the industry takes in regard to nicotine and smoking.

5. "In press" manuscript: Nicotine as a Positive Reinforcer in Rats: Effects of Infusion Dose and Fixed Ratio Size.

This was a study by DeNoble, et al. of lever pressing in rats, such that presses led to contingent nicotine infusion. This is the classical nicotine self-administration in animals paradigm. In this particular study, two levers were used, such that if the rat pressed one lever it would result in nicotine injection; if the rat pressed the other lever there was no effect other than for the response to be counted. Thus, one lever served as a control for any noncontingent stimulatory effects of nicotine. This particular control has been absent in most past research on nicotine self-administration in animals and has been a primary criticism of that research.

At any rate, the authors of this report claim to have shown the reinforcing properties of nicotine -- a believable claim based on their data. They state that their results "unequivocally" demonstrate that contingent nicotine infusions will maintain behavior.

There are two other pertinent aspects of their study. First, at one point in their study, they delivered, in addition to the response contingent nicotine injections, an additional series of spaced nicotine injections which were programmed regardless of the animals' behavior. They varied the interval between these noncontingent injections and sought to determine the effects of these on the animals responding for nicotine injections. They reported that as the interval between noncontingent nicotine injections increased, there was less of a suppressing effect on response contingent nicotine injections. What this implies is that the more the rat received nicotine noncontingently, the less it was motivated to respond to obtain nicotine injections. According to the authors, these results "suggest that under the present conditions the daily level of nicotine self-administration is at least in part under the control of some circulating blood level."

A second additional aspect of the study is that the investigators visually observed the rats during a control procedure where saline was substituted for nicotine. They visually noted no signs of withdrawal. They claim that based on this there was no evidence that nicotine injections were leading to physiological dependence.

Despite the authors' position regarding the apparent lack of physiological dependence, their overall results are

extremely unfavorable. The major reasons are: (1) Few people, if any, accept that demonstration of reinforcement capacities of a drug is sufficient to label that drug as addictive. However, many people do use that as a primary criterion for assessing the "abuse liability" of a drug. Even more people accept demonstration of reinforcement capacities in animals as at least one of several criteria for an addictive drug. Thus, research such as this strengthens the adverse case against nicotine as an addictive drug. (2) The addiction view of cigarette smoking posits that cigarette smoking is influenced by circulating levels of blood nicotine. The DeNoble, et al. study is consistent with this notion, since apparently the reinforcing capacity of nicotine injections was influenced by an experimentally manipulated blood nicotine level. (See earlier comments in regard to noncontingent nicotine infusions superimposed on primary response contingent nicotine procedure.) As with the previous point, this serves to strengthen the adverse case of cigarette smoking as an addiction. (3) It may be considered helpful that the authors speculated, based on their visual observation during a saline control procedure, that physiological dependence to nicotine had not developed. Nevertheless, their rather gross observational procedure, which provided the basis for their opinions of physiological dependence, is subject to strong criticisms. It is not a sophisticated test for physiological dependence and I think that the authors would be easily challengeable on this basis.

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In sum, there are at least two major reasons why this research is detrimental to the industry, and the one reason for which the research might be considered helpful is subject to strong challenge.

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The following discussion pertains to a letter from Leo Abood to Dr. Osdene in which Abood enclosed a paper by Bozarth and Wise entitled "Disassociation of the Rewarding and Physical Dependence-Producing Properties of Morphine."

The Bozarth and Wise paper reports an attempt to identify the anatomical brain areas responsible for the physical dependence producing aspect of morphine. According to the paper, previous research by this group had already anatomically localized the reward producing aspect of morphine.

The basic procedure was to inject morphine repeatedly into particular brain areas, then challenge the animals with the morphine antagonist naloxone. If the rats were physically dependent on morphine, such an injection should precipitate withdrawal symptoms. Bozarth and Wise reported that naloxone precipitated withdrawal symptoms only when the rats had been previously injected with morphine in the "periventricular gray" area of the brain. Morphine injected into other brain areas did not lead to physical

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dependence, as suggested by an absence of naloxone-induced withdrawal. Thus, they claim to have localized anatomically the physical dependence producing aspect of morphine.

The Bozarth and Wise results have little helpful bearing on the smoking and addiction issue. It is conceivable that someone might be thinking along the lines of trying to extrapolate the findings (i.e., that physiological dependence and reward properties are anatomically separable) for morphine to nicotine. The point would be to demonstrate that nicotine's actions were demonstrable in a reward area, but not a physiological dependence area, of the brain. The thinking might be that this would be one way to demonstrate clearly that nicotine did not act as an addictive drug analogous to morphine.

There are several difficulties with such thinking. First, it is highly speculative whether or not the Bozarth and Wise findings apply to nicotine. In particular, nicotine may have its own reward and dependency producing anatomical sites in the brain and they may differ totally from those identified for morphine. Second, even if it was possible to demonstrate that nicotine was active in a reward, but not a dependency producing, area of the brain, it seems doubtful that this would have much of an impact on our adversaries. Such a finding would probably be looked on as largely irrelevant and esoteric by those who emphasize behavioral conceptualizations of addiction. Third, it is not

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possible to predict with certainty how research such as this might turn out. (E.g., what if the results implied that nicotine's actions were tied to a dependency-producing area of the brain?)

Conclusion

Research engaged in, as well as some possibly under consideration, by Philip Morris has undesirable and dangerous implications for litigation positions the industry takes in regard to smoking behavior. The pharmacological nature of the research implies strongly a view of the importance of nicotine. What is worse, research reports under Philip Morris' sponsorship contain claims of physiological tolerance to nicotine, as well as claims of unequivocal demonstrations of reinforcement by nicotine in animals. This kind of research is a major tool of our adversaries on the addiction issue; the irony is that industry-sponsored research is honing that tool. In the final analysis, the performing and publishing of nicotine related research clearly seems ill-advised from a litigation point of view.