Psychopharmacology (1992) 108:397–407

Psychopharmacology

Review

The role of nicotine in tobacco use

John H. Robinson and Walter S. Pritchard

Biobehavioral R&D, R.J. Reynolds Tobacco Company, Bowman Gray Technical Center, Reynolds Boulevard, Winston-Salem, NC 27102, USA

Received November 26, 1991 / Final version January 14, 1992

Abstract. The 1988 US Surgeon General's Report titled "Nicotine Addiction", is cited frequently in the literature as having established the "fact" that nicotine derived from cigarette smoke is addictive in the same sense as "classic" addicting drugs such as heroin and cocaine. This manuscripts critically evaluates key research findings used in support of this claim and identifies shortcomings in the data that seriously question the logic of labeling nicotine as "addictive". In addition, the manuscript argues that the role of nicotine in tobacco use is not like the role of cocaine in coca leaf use as argued by the 1988 Surgeon General's Report, but is, in fact, more like the role of caffeine in coffee drinking as concluded in the 1964 US Surgeon General's Report.

Key words: Tobacco use – Nicotine – Addiction

Historically, tobacco and its primary active pharmacologic ingredient, nicotine, have been the focus of more scientific study than perhaps any other product consumed by humans. Since the publication by Langley and Dickinson (1889) on the effects of nicotine on peripheral ganglia, scientists have studied its effects on various biological tissues and, in particular, the central nervous system (CNS). A review of reports published by the US Surgeon General and the National Institute of Drug Abuse (NIDA) indicates that the physiological, pharmacological, medical, psychological, and sociological aspects of nicotine and cigarette smoking have been the subject of literally thousands of scientific articles. Despite this huge literature, however, the question "Why do people smoke?" is still asked and, as behavioral scientists, we believe that it is to a great extent still unanswered.

One approach to answering this question is to ask a large number of smokers why they smoke. In general, two broad categories of responses have emerged, one related to pharmacological aspects of smoking and the other related to non-pharmacological factors (Spielberger 1986). The pharmacological effects produced by cigarette smoking have been attributed, for the most part, to nicotine absorbed by the smoker from inhaled mainstream smoke. We will use the term "smoking/nicotine" to refer to this determinant of the pharmacological effects.

The non-pharmacological aspects of smoking include the "taste" of the cigarette smoke, sensory responses in the throat and upper airway, manipulation of the cigarette itself as well as the smoke it produces, and the social aspects of cigarette smoking. A demonstration of the importance of non-pharmacological factors in smoking motivation can be seen in the findings reported by Rose and colleagues (Rose et al. 1984) that anesthetization of the mouth, throat, and upper airway significantly reduced self-reported desire to smoke in a group of regular smokers.

The "nicotine paradox"

The responses related to smoking's pharmacological effects can be categorized on two predominant dimensions. The peripheral effects of smoking/nicotine are largely stimulatory (e.g., increased heart rate, most noticeable for the initial cigarette of the day; Benowitz 1987). Indeed, a large segment of smokers report that increased mental alertness produced by smoking/nicotine is an important aspect of their smoking motivation.

However, an even larger segment of smokers report that smoking/nicotine helps them to function in the face of environmental stress by having a calming effect on their mood, and that this effect comprises a major aspect of their smoking motivation. For example, Frith (1971) reported that over 80% of 2000 smokers questioned listed "pleasurable relaxation" as an important smoking motive. These two seemingly contradictory motives (smoking for purposes of mental stimulation and smoking for purposes of mental relaxation) form the so-called

Correspondence to: J.H. Robinson

"nicotine paradox" (see Gilbert 1979). Coupled with the non-pharmacological motives, this paradox provides some insight into the difficulty in answering the seemingly simple question "Why do people smoke?".

One hypothesis relating to the question of why people smoke, which was formalized in the 1988 Surgeon General's Report (SGR; US DHHS 1988), is that people smoke because they are "addicted", either to cigarettes or to nicotine. A study by Eiser (1990) reported that for a sample of British smokers many (but by no means all) endorsed the "addiction" hypothesis by agreeing with statements such as "I'm not going to be able to give up smoking unless someone helps me" and disagreeing with statements such as "If I really wanted to, I could give up smoking"[1]. However, Gallup Poll data indicate that, in the US, smokers often hold dissonant views, with 61% answering "Yes" to the statement "Do you consider yourself addicted to cigarettes or not?" while 78% of this same sample of 1240 adult smokers answered "Yes" to the question "Do you feel you would be able to quit smoking if you made the decision to do so or not?" (Gallup Poll National Survey Data, July 1990; Public Opinion On-Line Database). Moreover, Spielberger and Jacobs (see Spielberger 1986) factor analyzed responses from 1029 smokers to a large number of smoking motivation questions representing, psychometrically, the "best" questions from a number of previous smoking motivation scales. An addiction-like factor labeled "Automatic/Habitual" accounted for less variance than would be predicted based on the number of questions loading on the factor, whereas a factor labeled "Negative Affect Control" (cf previous paragraph) accounted for more.

We believe that a more reasonable hypothesis concerning why people smoke, a hypothesis that is consistent with the smoking motivation literature, is that smokers use cigarettes primarily as a "tool" or "resource" that provides them with needed psychological benefits (increased mental alertness; anxiety reduction, coping with stress). This "resource" hypothesis (Wesnes and Warburton 1984a; Warburton 1988a, b; Warburton et al. 1988; see also Pritchard 1991a) stands as a major alternative to the addiction hypothesis, and we argue that the resource hypothesis passes a "common-sense" test that the addiction hypothesis fails. In addition, the comparison of nicotine to heroin and cocaine (US DHHS 1988) contrasts sharply with the findings of the 1964 SGR (US DHEW 1964) which compares the role of nicotine in tobacco to the role of caffeine in coffee. We will briefly review several lines of research leading to the conclusion that the 1964 SGR was, in many ways, more accurate in classifying nicotine as "habituating" rather than "addicting" and will argue that classifying nicotine as habituating represents a more balanced perspective than classifying nicotine as addicting.

[1] Eiser has proposed that some smokers endorse the "addiction" hypothesis in an attempt to explain their smoking behavior in a way that removes any personal responsibility in making a choice that is viewed by others as unsound or even irrational. After all, if a smoker is "addicted", he can argue that he has no control over his smoking behavior and can use this helplessness as a "shield" for the criticism he receives for engaging in this behavior. In addition, Eiser has identified another group of smokers who ascribe to an "illness" definition of addiction, even to the extent of blaming others for their failure to "cure" this "illness" (see Eiser 1990 for discussion). In essence, by expressing the belief that he is addicted, a smoker can use this as an excuse for not making the commitment required to accomplish a permanent behavioral change in a habit that is often viewed by others as "wicked" (see Davies 1990).

The nicotine addiction hypothesis

The 1988 SGR titled *The Health Consequences of Smoking – Nicotine Addiction* (US DHHS 1988) resolved, for many people, the question of why people smoke. Quite simply, the report stated that people smoke because they are addicted to nicotine. To ensure that this impression would not be missed by anyone, including the popular press, the report highlighted three major conclusions: (1) cigarettes and other forms of tobacco are addicting; (2) nicotine is the substance in tobacco that causes addiction; and (3) the fundamental processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Verification that these conclusions have been widely accepted by the medical and scientific community requires only a quick review of the recent literature, where it is invariably asserted that the "addictiveness" or "abuse potential" of nicotine equals (or even exceeds) that of substances such as cocaine, opiate narcotics (e.g., heroin), barbiturates, benzodiazepines, and alcohol (e.g., Jasinski and Henningfield 1988; Goldstein and Kalant 1990; Henningfield et al. 1990, 1991; Russell 1990; Stolerman 1990a, b). Yet, the conclusion that cigarette smoking is the same as heroin or cocaine addiction seems fundamentally flawed from a common-sense point of view, and is diametrically opposed to the conclusions stated in the 1964 SGR that nicotine was definitely *not* an addicting drug. How persuasive *is* the evidence presented in the 1988 SGR supporting the conclusion that smoking/nicotine is the same as addiction to heroin or cocaine?

Habituation versus addiction

There is currently no universally accepted scientific definition of addiction. While the term "dependence" has been given a somewhat more precise definition [e.g., World Health Organization (WHO) 1981] and on that basis is more acceptable from a scientific standpoint (as acknowledged in the 1988 SGR), the 1988 SGR consistently uses the word "addiction" interchangeably with the word "dependence" on the grounds that the former provides "information at a more general level" (p 7). In other words, the word "addiction" is familiar to the average layperson, even if her/his conception of what addiction typically means is based on common misperceptions and lacks scientific foundation. To the average layperson, the word "addiction" carries affective

connotations of a strongly negative nature (Davies 1990), a ploy "not lost sight of by the Surgeon General's Office" according to Pandina and Huber in their review of the nicotine addiction question (1990, p 55).

In addition, as noted above, the conclusions drawn in the 1988 SGR are in sharp contrast to those of the 1964 SGR (*Smoking and Health – Report of the Advisory Committee to the Surgeon General of the Public Health Service*, US DHEW 1964). When a universally accepted scientific definition of addiction did exist, the 1964 SGR concluded "In medical and scientific terminology the practice [smoking] should be labeled *habituation* to distinguish it clearly from *addiction*, since the biological effects of tobacco, like coffee and other caffeine-containing beverages, ... are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs" (p 350, emphasis in original).

The basis for the distinction developed in the 1964 SGR was the established WHO definitions of addiction and habituation as outlined on p 351 of the 1964 SGR. *Addiction* was defined as "a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;

2) a tendency to increase the dose; 3) a psychic (psychological) and generally a physical dependence on the effects of the drug; 4) detrimental effect on the individual and on society." We may also note that this definition probably comes close to what the average layperson has in mind when using the term "addiction".

In contrast, *habituation* was defined as "a condition resulting from the repeated consumption of a drug. Its characteristics include: 1) a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders; 2) little or no tendency to increase the dose; 3) some degree of psychic dependence on the effect of the drug, but absence of physical dependence and hence of an abstinence syndrome; 4) detrimental effects, if any, primarily on the individual [rather than society]".

The 1988 SGR acknowledged the dramatic change in position regarding nicotine "addiction" relative to the 1964 SGR. According to the 1988 SGR, the reclassification of nicotine as addictive rather than habituating is supported by two key arguments:

1) The WHO no longer used the terms "addiction" and "habituation", dropping this distinction in favor of a single new entity, *drug dependence*. (This action by the WHO was perhaps motivated by the trivialization of the term "addiction" in the popular media, where it was used to refer to any behavior that people regularly engaged in: sex, watching TV, exercise, video games, eating chocolate, etc.);

2) Reports appearing in the scientific literature since the publication of the 1964 SGR reportedly demonstrated that nicotine shared many features with prototypic drugs of abuse and had now been shown to fulfill the three primary criteria (as defined by the Surgeon General for the first time in the 1988 SGR) of an addicting drug. These criteria were: (a) *highly controlled or compulsive use*; (b) *psychoactive effects*; and (c) *drug-reinforced behavior*. The 1988 SGR also asserted that the recent scientific literature had demonstrated that nicotine passed several of the "additional criteria" listed as "useful" in defining addictiveness. These included *use despite harmful effects*, *relapse following abstinence*, *recurrent drug cravings*, *tolerance*, *physical dependence*, and *euphoric effects*. We will examine both of these claims used by the Surgeon General in support of his reclassification of nicotine as addicting rather than habituating.

While it is true that the WHO dropped the semantic distinction between "habituation" and "addiction", replacing its concept of addiction with the term "dependence" (as stated in the 1988 SGR), a key concept from the original WHO definition of addiction was *not* dropped (as implied by the 1988 SGR) when the term dependence was adopted by the WHO, namely, the concept of *intoxication*.

Intoxication

A critical attribute stressed in the original WHO definition of *addiction* was "a state of periodic or chronic intoxication produced by the repated consumption of a drug" (1964 SGR, p 351). Since this phrase was not included in the definition of habituation, it served as a key point of distinction between addicting and habituating drugs. This definition of addiction also implied that someone under the influence of an addicting drug not only had a diminished capacity to decide whether to continue taking the drug, but also suffered impaired cognitive performance. One consequence of the latter was the potential for adverse impact on others (e.g., workplace accidents, impaired driving ability leading to vehicular accidents).

In 1978 the WHO reiterated the importance of the concept of intoxication, stating that "psychotropic" substances considered for control by the international community must be capable of producing both a state of "dependence" *and* "central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behavior or perception or mood" (WHO, Technical Report Series, No. 618, 1978, p 8). The concept of "intoxication" (negative disturbances in psychological or motor function) is viewed by many as critical in determining if a drug is addictive.

In 1984, NIDA presented the First Triennial Report to Congress from the Secretary of Health and Human Services (US DHHS Publication No. ADM 85-1372). The report presented the state of drug abuse and drug abuse research as determined by NIDA. In describing the effects of psychoactive drugs (psychoactivity now being a primary criterion in the new definition of addiction), the report states:

A predictable effect of the use of almost any psychoactive drug is a distortion of the perception of time, space, and the location of objects within space. A corollary

effect is a dose-related reduction in physical coordination or psychomotor functioning. Normally easy tasks like placing a top on a jar or walking become difficult to perform. The ability to visually locate objects in space, judge their distance and track them is impaired. (pp 19–20).

In short, the NIDA report states that psychoactive drugs produce intoxication, and that psychoactivity is a primary criterion for addiction. The concept that addictive drugs produce disturbances in psychological and/or motor functions was thus forcefully stated. It should be noted however, that the concept of a psychoactive drug producing intoxication does not appear in the 1988 SGR, perhaps because the literature demonstrates that it simply does not apply to nicotine, as discussed below. The same NIDA report (1984) did conclude, however, that compulsive tobacco use

... is a form of drug abuse, or drug addiction, in which nicotine is critical. Specifically, it is evident that the role of nicotine in cigarette smoking is similar to the role of cocaine in coca use, of THC [delta-9-tetrahydrocanibinol] in marijuana smoking, and of ethanol in alcoholic beverage consumption (p 113).

The NIDA report comes to this conclusion with regard to nicotine, but makes no mention of nicotine producing psychological or motor disruption. This is in sharp contrast to the other substances to which nicotine was compared, and, in fact, the NIDA report contains extensive documentation regarding disturbances in psychomotor, behavioral, and cognitive functions of people and animals under the influence of (or experiencing withdrawal from) these other substances, including THC (marijuana), alcohol, amphetamines, cocaine, narcotics, barbiturates, and hallucinogens.

We believe that the omission of any discussion regarding the effects of nicotine on psychological function was not simply an oversight by the author of the nicotine chapter of the NIDA report (Burling) or an indication that he disagreed with statements in the report concerning the adverse psychological and motor effects of the other substances discussed in the report. This seems evident from the footnote that accompanies the nicotine chapter, which states:

A concept central to many discussions of drug abuse is that the substance produces "damage" or "debilitation." This aspect of cigarette smoking will not be addressed here as there are extensive data indicating 1) the actual toxicity of tobacco, and 2) the widespread perception by smokers that their *habit* is harmful. (p 97, emphasis added).

In this NIDA report, Burling has subtly changed the meaning of "damage" or "debilitation" from the psychological domain to the health domain in an attempt to classify nicotine as an addicting drug. A person who has ingested nicotine in amounts characteristic of normal smoking does not suffer the "distortion of time, space and the location of objects within space" associated with the other substances reviewed in the report. A smoker does not find it difficult to perform "easy tasks like placing a top on a jar or walking" (ibid.), or driving a car. Indeed, nicotine in the majority of circumstances results in *improved* performance as well as other psychological benefits to the smoker (Wesnes and Warburton 1978, 1983, 1984a, b; Wesnes 1987; Warburton 1988a, b; Pritchard 1991b; Pritchard et al. 1991).

In addition, Hindmarch and colleagues have consistently reported distinct differences in the effects of nicotine and "classic" addicting drugs on performance tasks, including "driving" automobile simulators (see Hindmarch et al. 1991; Kerr et al. 1991). In these tests, smoking/nicotine clearly resulted in improved mental and motor performance in contrast with "classic" addicting drugs, which resulted in reduced mental and motor performance. The concept of "intoxication", central to the issue of whether or not a drug is addicting, simply does not apply to nicotine. Moreover, smoking/nicotine is clearly compatible with performing everyday tasks and is perceived by the smoker as providing psychological benefits.

To reiterate, the author of the nicotine chapter of the 1984 NIDA report, referenced the smoking and health literature and not the cognitive performance literature to illustrate the "debilitating" effects of nicotine. However, others (US DHHS 1988; Froggatt and Wald 1989; Roe 1989), have suggested that the smoker's increased risk of health-related problems is believed to be due primarily to the ingestion of the "tar" fraction of cigarette smoke, *not* to the ingestion of nicotine. While some may argue that this is a subtle distinction, and that nicotine and "tar" should not be separate issues, the distinction becomes important when attempting to compare nicotine with "classic" addicting drugs (whose intoxicating effects diminish cognitive performance as well as the capacity of the user to decide whether or not to use that drug). Increased risk of developing certain diseases in smokers has been principally ascribed to the "tar" fraction of cigarette smoke, and should remain a separate issue from that of the "addictiveness" of nicotine, especially given the potential availability of cigarettes yielding nicotine but having minimal biological activity (Russell 1991).

Thus, it is clear that nicotine lacks a feature many consider essential to the definition of an addictive drug. In our opinion, the fact that smoking/nicotine clearly does not result in "intoxication" (psychological debilitation) is consistently overlooked in the debate on nicotine "addiction". This obvious difference between nicotine and the "classic" addicting drugs has been ignored by the Surgeon General in changing the classification of nicotine from habituating to addicting. To this end, he cited evidence appearing in the scientific literature of certain commonalities between nicotine and "classic" addicting drugs (cocaine, heroin, alcohol, etc.). The underlying rationale for these studies has been termed the "analogy" argument (Warburton 1989). From the perspective of the Surgeon General, if studies demonstrated that two drugs share a certain number of features in common, then by analogy, those drugs may be considered to share other, perhaps untested, features.

The "analogy argument"

The "analogy argument" is seriously flawed from a scientific standpoint. As Warburton (1989) pointed out in his critique of the 1988 SGR, no matter how many features X has in common with Y, it takes only one feature of X not found in Y to make the analogy fallacious. We have already identified one key concept (intoxication) in the WHO definition of an addictive drug that nicotine does not share with "classic" drugs of abuse. Yet, the 1988 SGR goes to great lengths to establish commonalities between nicotine and other drugs in an attempt to prove that nicotine is addicting.

The shortcomings of this line of reasoning should be obvious. Imagine a researcher interested in studying pain. He chooses to use two stimuli, a bowling ball and a cinder block, and begins to identify the physical and behavioral traits these two objects have in common. Both objects weigh about the same. When dropped on a subject's foot, both objects accelerate at the same rate, inflict similar amounts of pain, produce similar physiological responses and result in similar verbal reports by the subject. The two objects appear to possess a number of common properties. It would, however, be inaccurate to conclude that the subject could achieve his usual bowling average using the cinder block.

The logic of this admittedly facetious example is not too far removed from that used to draw inferences in some of the studies cited in support of the conclusions reached in the 1988 SGR. We will now critically examine some of the key evidence used to support the 1988 SGR's conclusion that "the pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine" (p 9).

Nicotine and the three primary 1988 SGR

Criteria for defining addictive drugs

The 1988 SGR employed a definition of "addiction" that included three main criteria along with several "additional criteria". The list of additional criteria included such factors as tolerance, withdrawal/physical dependence, drug craving, relapse following abstinence, and stereotypic patterns of ingestion behavior. Warburton (1989) and Collins (1990) have addressed these issues and concluded that while nicotine may, under limited circumstances or to a limited degree, possess or result in some of these, the literature in general does not support the concept that nicotine is equivalent to cocaine, heroin, or other potent addicting drugs in terms of these additional criteria.

Since the task of adequately reviewing the literature regarding the "additional" criteria is beyond the scope of the present paper, the reader is referred to Warburton (1989) and Collins (1990) for summaries of these topics. Only the three primary criteria were deemed by the 1988 SGR to be *necessary* for defining addiction. We will focus our comments mainly on the three primary criteria as specified in the 1988 SGR. We will also examine the "euphoriant" model of nicotine addiction, since this model is often cited as an explanation of the reinforcing psychoactive effect of smoking/nicotine that contributes to the "addictive" nature of smoking (e.g., Henningfield 1984a; Carmody 1989; Bourne 1991).

Criterion 1: highly controlled or compulsive use

The concept of highly controlled or compulsive use has been included in many definitions of addiction (Warburton 1985) and fits extremely well with the layperson's idea of drug addiction, i.e., the addict who is unable to resist uncontrollable drug cravings (Davies 1990). However, as Warburton (1990) has noted, this criterion does not fit particularly well when one considers cigarette smoking, where extended periods of abstinence may be readily managed by many smokers. In today's restrictive environment, many smokers are prevented from smoking on planes, in public places, or at work, without significantly disrupting other aspects of their behavior or performance. Formal restrictions aside, some smokers may smoke only at work because their spouse objects to smoking in the home, and may abstain from smoking in specific social situations if others object. Others smoke on a regular basis throughout the day, and do develop strong habitual behaviors relative to when and where they smoke.

Since many smokers perceive smoking as providing benefits in terms of enhanced cognitive performance or stress reduction (Gilbert 1979; Warburton 1988a, b; Wesnes 1987; 1988 SGR), it is not surprising that regular patterns of use develop. By applying the 1988 SGR definition of compulsive use as a criterion for addiction, anything that a person ingests, enjoys, and therefore ingests again under regular circumstances fulfills this criterion for being "addicting". This would apply to such behaviors as the proverbial morning cup of coffee, regular use of aspirin or non-steroidal anti-inflammatory drugs for relief of arthritis pain, or obtaining psychoactive effects from sweets or a bedtime glass of milk due to alterations in brain levels of the neurotransmitter serotonin (Fernstrom 1983)[2].

Criterion 2: psychoactivity

The second primary criterion proposed by the 1988 SGR for an addicting drug, psychoactivity, was characterized by Warburton (1990, p 166) as "trivial" when one considers nicotine. While it is true that nicotine is "psychoactive" which can be defined as *producing pharmacological effects in brain tissue that result in changes in nerve cell activity*, so are a number of other drugs that

[2] Nicotine gum has been reported *not* to relieve craving for cigarettes (Hughes et al. 1984; Schneider and Jarvik 1985) while administration of other sustances does, e.g., dextrose (West et al. 1990) or the antidepressant doxepin (Murphy et al. 1990). In fact, *telling* subjects that they are receiving nicotine gum during cessation has been reported to attenutate craving regardless of whether the gum in fact contains nicotine or not (Hughes et al. 1989).

are consumed every day by millions of people. Theophylline in tea, theobromine in cocoa products, and the most widely consumed drug in the world, caffeine (coffee, soft drinks) are all "psychoactive".

The fact that a drug is psychoactive (capable of producing central nervous system effects) cannot establish whether or not it is addicting. The determining factors should be the specific effects produced and the magnitudes of these effects. The vast majority of published research findings show that the subtle "psychoactive" effects of nicotine are clearly distinct from the mental and motoric disturbances produced by the "classic" addicting drugs.

In spite of these clear differences, some researchers have reported studies of nicotine-induced "euphoria" in an attempt to demonstrate similarity between nicotine and "classic" addicting drugs on the bases of specific psychoactive effects (Henningfield et al. 1983, 1985; Jasinski et al. 1984; see Henningfield 1984b; Jasinski and Henningfield 1988, and Henningfield et al. 1986 for reviews). In these studies, subjects (typically with histories of hard-core drug abuse) were allowed to self-administer (by lever pressing) injections of nicotine or physiological saline, or were given intravenous (IV) injections if nicotine. Henningfield stated that because of their drug histories, these subjects represent "a very discriminating population, like fine wine tasters" (Charlotte Observer, April 24, 1982). An extension of this logic would indicate that manufactures of fine wines and spirits waste huge sums of money for trained taste panelists when they could get better information from derelict "winos".

The subjective responses of these chronic, illicit drug-abusing subjects were measured using questionnaires designed to measure "liking" or "euphoria". The responses for nicotine were then compared to the ratings of "classic" drugs of abuse. Among the major weaknesses of these comparisons, it should be noted that the ratings were not necessarily from the same study or the same subjects, and the drugs were not administered via the same procedures. Nevertheless, Henningfield and his colleagues (Henningfield 1984b; Jasinski et al. 1984; Henningfield et al. 1985), concluded that high intravenous doses of nicotine (3 mg/kg administered in 10 s) resulted in significant elevations in "euphoria" or "liking-scores". They also claim that the effects of this very large, rapid injection of nicotine are frequently misidentified by these "discriminating" drug abusers as being similar to the effects of cocaine or amphetamine. For example, in the Henningfield et al. (1985) study six of these "experienced" addicts misidentified the high dose of nicotine as cocaine and one misidentified nicotine as amphetamine. However, as Clark (1990) correctly notes, the value of these data is highly questionable since four of the seven subjects that misidentified nicotine had no prior experience with stimulants!

Since hard-core drug addicts obviously represent a highly deviant group the logic of generalizing the results of these studies to the population at large can be questioned. We concur with Collins' (1990) observation that the conclusions drawn from these studies are of limited value because of the methodological reasons that have been noted. Consequently, in our opinion, the results of these studies cannot be readily extended to normal smokers without extensively testing subjects who are not drug addicts.

To illustrate another example, the results ("liking score" figure) of a single study (Jasinski et al. 1984) have been reported numerous times (Henningsfield 1984a, b, 1987; Burling 1984; Henningfield et al. 1985; Henningfield and Nemeth-Coslett 1988; Henningfield et al. 1987; NIH Publication No. 86-2874, Jasinski and Henningfield 1988; US DHHS 1988) to support establishing as "fact" that nicotine is a euphoriant just like cocaine. We believe that this study and others are seriously flawed and vastly over-interpreted by subsequent authors for the following reasons.

The results of several studies taken together (Henningfield et al. 1983; Jasinski et al. 1984; Henningfield et al. 1985)[3] indicated that hard-core drug addicts would lever-press to self-administer nicotine but not saline. However, these data can be readily explained without invoking the "nicotine addiction" hypothesis. In a boring or stressful laboratory session, subjects might achieve some benefit from nicotine's capacity to provide mental stimulation or reduce stress (see Gilbert 1979; Gilbert and Welser 1989). Drug addicts typically score high on Zuckerman's Sensation Seeking Scale (Zuckerman 1983, 1987), a measure including thrill- and adventure-seeking as important components, and have been reported to experience drug-like responses when presented with visual cues associated with drug taking apparatus or in response to placebo drug injections (O'Brien et al. 1978). Preference for the nicotine lever over the saline lever may merely reflect the subjects' preference for any pharmacological stimulus over no stimulus at all. In addition, heroin addicts have reported physiological responses following injections of inactive substances (sterile saline; O'Brien et al. 1978). This may simply be a conditioned response to the stimuli associated with drug taking behavior.

[3] Precisely identifying a single study where Henningfield and his colleagues determined that nicotine is a euphoriant similar to cocaine is difficult. The "liking score" figure that has appeared in the literature numerous times is from Jasinski et al. (1984). However, this paper is inadequate in describing the subjects and procedures used to make this determination. For example, the number of subjects in the nicotine group is not reported and no statement about the subjects misidentifying the nicotine injections is made. However, in this report the authors also published a figure (Fig. 3) illustrating cumulative lever pressing records for subject KU self-administering nicotine and saline. This figure was published with the note "Submitted for publication in *Pharmacology, Biochemistry and Behavior*" and indeed did appear in Henningfield et al. (1983) where the subjects were reported to have misidentified nicotine as "morphine or cocaine". Since data from subject KU appears in both reports and since data from subjects KU, SK and PE appear in both Henningfield et al. (1983) and Henningfield et al. (1985) (where subjects were also reported to have misidentified high IV doses of nicotine as cocaine) it is not known whether these subjects were tested in all three studies, or if all the data were collected in a single study and reported separately, or if subjects were asked to identify the drug they received in the Jasinski et al. (1984) study and the data were simply not reported.

These studies fall short on other methodological grounds as well. If a goal of these studies was to compare the effects of nicotine to cocaine, then cocaine should have been included in the experiment. Cocaine is generally accepted as one of the most addictive drugs known. Results of animal self-administration studies (see below) suggest that it is quite likely that, if given a choice, these drug addicts would have consistently chosen the cocaine lever over the nicotine lever. Apparently the authors were willing to accept the subjects at their word that IV nicotine felt like cocaine. This is despite indications that hard-core drug addicts typically have antisocial personality disorders, including histories of pathological lying in order to cover their drug abuse (Schuckit 1973; Lewis et al. 1983) and that some of the subjects who mis-identified nicotine as cocaine had apparently never used cocaine (Clark 1990). Other important questions can be raised. What kind of informed consent did the subjects sign? Were they led to believe that some of the injections they received during the test might be cocaine? Did the subjects therefore experience some expectancy bias? Did they tell the experimenters what they thought the experimenters wanted to hear in hopes of participating in other sessions where they might in fact receive injections of cocaine?[3]. Clark (1990) is again correct when he notes that the authors did not conduct the proper test to support their conclusions.

In addition, while the nicotine "liking" graph originally taken from Jasinski et al. (1984) has been published numerous times in the studies listed above, we have never seen this graph published with accompanying (standard) error (of the mean) bars. This leaves unknown the nature of the individual differences that were found between responses to the nicotine injections and the "classic" addicting drugs that were tested. Furthermore, it is apparent that not all subjects experience "euphoria" following IV injections of nicotine. In this context, two important points that are often omitted or ignored in subsequent discussions of nicotine "euphoria" are provided by two earlier studies (Henningfield and Goldberg 1983a; Henningfield et al. 1983): 1) nicotine does not necessarily maintain a *sustained* rate of lever pressing that is higher than placebo (saline), and 2) the subjective responses that follow a *rapid* (10 s) *very high* (3 mg) IV dose of nicotine typically include respiratory problems, tightness in the chest, and a lightheaded (faint) sensation lasting approximately 15–20 s. Especially interesting is one subject's report that he "would be willing to (pay) seventy-five dollars" *not* to receive another nicotine injection. In addition, the "liking" score for nicotine is significantly different from the placebo "liking" score only at the 3 mg dose of nicotine. This amount of nicotine (administered in a very short period of time, 10 s) is much greater than is typically achieved during smoking.

Another important question to be considered when critically evaluating the results of the Henningfield group is the method of nicotine administration. How do the effects of these bolus (rapidly-administered, single administration) IV injections of a large dose of nicotine (3 mg in 10 s) compare to smoking a 0.5–1.5 mg cigarette over a 5–10 min period? The key datum here is the comparison of the degree of liking/euphoria that people experience when they smoke a cigarette versus the liking/euphoria subsequent to an IV injection of nicotine. The "liking" of a smoker who has just enjoyed a cigarette is obviously not the same as the "liking" of a heroin or cocaine addict in response to drug taking (often described as the ultimate pleasure or in sexual terms; Warburton 1990). In fact, Benowitz and Jacob (1990) have shown that when nicotine is infused at a slower rate (2 μg/kg/min for 30 min), smokers cannot tell the difference between nicotine and saline.

The authors of two reports (Henningfield 1984b; Henningfield and Nemeth-Coslett 1988) attempted to address the important distinction between rapid, bolus administration of nicotine and rates that would better approximate the absorption of nicotine during normal cigarette smoking. These authors presented graphs (again without error bars, also note that the relevant graph in the second reference is published with the wrong legend) illustrating subjects' feelings following administration of nicotine (IV and cigarette smoking), *d*-amphetamine, morphine, diazepam, ethanol, pentobarbital, marijuana, and "simulated gambling". At first glance, the results appear to support the authors' contention that both IV nicotine and tobacco smoking produce similar euphoric feelings of the same magnitude as those seen with known addicting drugs. It should be noted however, that the graphs are plotted on quite differently scaled y-axes.

The Henningfield graphs give the (casual) reader the *impression* that tobacco smoking and nicotine are similar to known drugs of abuse, but the data clearly do not support the conclusion that nicotine is a euphoriant similar to morphine or *d*-amphetamine. Cocaine is not directly compared with nicotine or smoking, despite the repeated references to the similarity of nicotine to cocaine. When Warburton (1988) re-plotted the euphoria data as difference scores between drug and placebo using identically-scaled y-axes for each compound tested (Fig. 1), smoking and IV nicotine (again 3 mg in 10 s) had the lowest difference scores, with the difference between cigarette smoking and placebo being the smallest of all (even lower than "simulated gambling").

Subsequent research by Henningfield's group (Henningfield et al. 1985) has expressly failed to find a difference between cigarette smoking and placebo with regard to self-reported euphoria, even using a very high-yield (2.9 mg nicotine, FTC yield) cigarette. Nicotine gum also fails to produce euphoria (Snyder et al. 1989). In fact, Nemeth-Coslett et al. (1987) reported that 4 mg nicotine gum produced lower "euphoria" scores than placebo. Warburton (1988) presented data on the pleasure-stimulation and pleasure-relaxation effects of nicotine and other substances. Nicotine was rated as less stimulating than alcohol, amphetamine, cocaine, heroin, marijuana and sex and approximately equal to caffeine and chocolate. Finally, when McNeill et al. (1987) queried a sample of 104 regular smokers, not one reported that "feeling high" was an effect that they experienced following smoking. The predominant effect (64% of the sample)

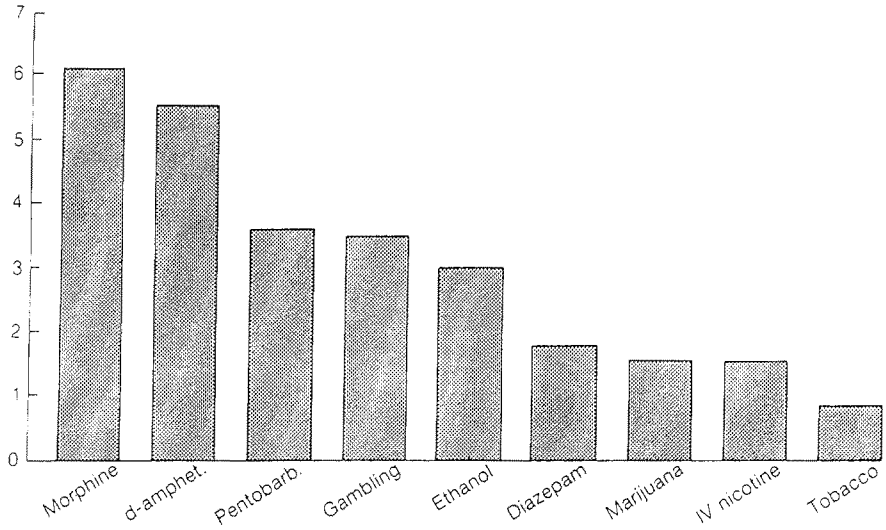

Fig. 1. When Warburton (1988) re-plotted Henningfield's (1984b) "euphoria" data as a differential from baseline (placebo) score, he concluded that "nicotine is, at best, a weak euphoriant and ... it is not like morphine in opium use." From "The Psychopharmacology of Addiction" (1988) Lader MH (ed) by permission of Oxford University Press

was feeling calmer. In our opinion the data do not support the contention that nicotine is a euphoriant and are presented in a misleading fashion to give the impression that nicotine is similar to "classic" addicting drugs when, in fact, it is not.

In summary, Henningfield and his colleagues have drawn conclusions without conducting a proper drug discrimination study (see Clark 1990). However, the data from these and other studies, coupled with the determination that nicotine (under limited contingencies) can serve as a reinforcer in animal self-administration paradigms are used to support the contention that nicotine possesses all the properties of "a prototypic drug of abuse" (Henningfield 1984a, p 197). In our opinion the data clearly do not support such a contention, but this conclusion and these data have, nevertheless, been widely publicized.

A variation of the "euphoria model" of smoking has been argued by Pomerleau (see Pomerleau and Pomerleau 1984). The results of this study have been widely interpreted as evidence that *nicotine obtained from smoking* has the capacity to cause the release of the endogenous opioid beta-endorphin. This research has also been used to support the notion that smoking is addictive by implying that "euphoria" produced by smoking results from increases in circulating levels of beta-endorphin (Bourne 1991). The Pomerleau model also proposes that changes in the circulating levels of beta-endorphin or other hormones and neuromodulators [e.g., cortisol, adrenocorticotrophic hormone (ACTH)] are responsible for the psychological effects of smoking. However, this model is also inadequate.

The neurohumoral changes (especially beta-endorphin) that were reported by Pomerleau, were seen only in subjects who achieved extremely high plasma concentrations of nicotine (>60 ng/ml). These unusually high plasma nicotine concentrations were achieved as a result of smoking two very high-yield cigarettes (2.87 mg nicotine versus 1.1 mg for leading, filtered, "non-light" cigarettes) in an extremely short period of time. Research has shown that this smoking paradigm in all likelihood resulted in symptoms of acute nicotine toxicity (primarily nausea; see Gilbert and Welser 1989; Gilbert et al. 1992). The cigarettes and smoking paradigm (2 cigarettes 5 min apart) used in this study are unrelated to the real-life smoking patterns of the vast majority of smokers. Furthermore, although often overlooked in subsequent reports of these data, these neurohumoral effects were *not* observed when the subjects smoked two "low" nicotine (0.48 mg, FTC yield) cigarettes in succession. What has been *assumed* to be a specific rewarding effect of nicotine in humans was, in all probability, a non-specific response to the stress of nausea and malaise brought about by toxic levels of nicotine. Pomerleau has stated that "Because the hormonal profile associated with nicotine-induced nausea resembles that of nausea produced by other manipulations (motion sickness, administration of other drugs), it is likely that the observed hormonal pattern at this level of stimulation is characteristic of nausea and not unique to nicotine" (Majchrzak et al. 1987). However, this "qualification" of the original report is not generally cited when these data are referenced. In sum, the studies purporting to demonstrate that smoking/nicotine is a euphoriant similar to cocaine and heroin are seriously flawed from a number of perspectives. A critical review of this literature leads to the conclusion that nicotine absorbed from cigarette smoke is simply *not* a euphoriant in humans.

Criterion 3: drug reinforced behavior

The few extant human studies of the self-administration of nicotine also indiate that nicotine is not a particularly good reinforcer. Although the primary focus of this review is on human studies, we will briefly examine literature regarding nicotine self-administration in animals. NIDA has established such studies as an important test of a drug's "abuse potential" and the 1988 SGR relies heavily on these studies to support the third major criterion of an addicting drug.

Animal self-administration

The 1988 SGR provided a table (pp 183–188) summarizing nicotine self-administration studies. Much of this table had appeared verbatim in a report by Henningfield and Goldberg (1983 b) in which they concluded that "... nicotine shares many salient features of other drugs of abuse. However, nicotine *differs* from other drugs in that the range of environmental conditions under which it serves as a reinforcer appears to be more restricted" (p 991, emphasis added). Yet, the 1988 SGR concluded that the "... pharmacologic and behavioral processes that determine tobacco addiction are *similar* to those that determine addiction to drugs such as heroin and cocaine" (p 9, emphasis added). This conclusion is based in large part on nicotine's ability to serve as a primary reinforcer in animal self-administration studies.

A review of the studies outlined in the 1988 SGR supports the original conclusion of Henningfield and Goldberg (1983 b) that the range of environmental conditions under which nicotine reinforces behavior appears to be more restricted than "classic" addicting drugs, in particular heroin and cocaine. There are clear-cut differences between the self-administration behavior of animals for drugs such as cocaine and heroin versus nicotine and caffeine (which has also been shown to be self-administered relative to saline; Griffiths et al. 1979). For example, animals given unlimited access to cocaine and heroin often ignore food and water, self-administering the drug until death (Bozarth and Wise 1985).

Environmental stimuli play a much more important role in the self-administration of nicotine than heroin or cocaine self-stimulation (see Bozarth 1990). With the exception of some reports by Henningfield and Goldberg (cf 1988 SGR), studies that directly compare the reinforcing efficacy of nicotine and cocaine generally find nicotine to be a much weaker reinforcer than cocaine (see US DHHS 1988, Table 4, pp 183–188).

We should also note that self-administration behavior does not prove that the reinforcing stimulus is producing euphoria nor should that stimulus be considered "addictive". Given the proper schedule of reinforcement, monkeys have been trained to self-administer painful electric shocks to themselves (Morse et al. 1967). In one study (McKearney 1968), three monkeys lever-pressed over 800000 times to receive some 3000 painful electric shocks. One would hardly argue that electric shocks produce euphoria or that they are addicting.

Thus, while IV nicotine can serve as a reinforcer in self-administration paradigms (as caffeine can), the circumstances under which nicotine is reinforcing are much more limited than the "classic" addicting drugs such as cocaine, heroin, and amphetamine (see Bozarth 1990). Specifically, even IV nicotine is a much *weaker* reinforcer (Dworkin et al. 1991) than these other substances and in all likelihood is much closer to caffeine on a hypothetical "reinforcement continuum" than it is to cocaine or heroin. It seems clear that the role of nicotine in cigarette smoking is similar to the role of caffeine in coffee or cola drinking as concluded in the 1964 SGR. The pursuit of the goal of "creating" a smoke-free society by the year 2000 has led the authors of the 1988 SGR to rely on data that do not often support the conclusions they have drawn.

Summary and conclusion

The goal of this paper was to critically evaluate evidence used to support the conclusions expressed in the 1988 SGR that have been popularly reported as proving the claim that nicotine is addicting, just like heroin and cocaine. Much of the data offered as evidence for this conclusion simply do not stand up under critical review. If this paper provokes a spirited and open discussion of these data, it will have served an important goal.

In our opinion, it is political zeal rather than scientific merit that supports the conclusion of the 1988 SGR that the "pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine". We recognize that nicotine plays an important role in smoking behavior for many people. Of hundreds of vegetable materials that could readily be put in pipes or rolled in cigars or cigarettes and smoked, people have chosen to smoke nicotine-containing tobaccos.

We also recognize that these people enjoy whatever pharmacological and psychological effects they achieve from smoking, and that this enjoyment can positively reinforce the smoking habit. Most importantly, however, common sense tells us that nicotine *is not* like heroin, cocaine or any other "classic" addicting drug in its physiological and behavioral effects. One does not have to be a trained behavioral scientist to come to this conclusion. Simply ask and honestly answer the question as to how many people would board a plane piloted by someone who had just consumed an addicting drug (alcohol, heroin, cocaine, barbiturates) versus a plane piloted by someone who had just had a cup of coffee and smoked a cigarette. Interestingly, this latter pilot would be classified as a "poly-drug" abuser by NIDA since, like nicotine, caffeine produces "euphoria" (Henningfield 1986) and possesses "all the cardinal features of a prototypic drug of abuse (Griffiths et al. 1986, p 416; see also Griffiths and Woodson 1988; Holtzman 1990).

If nicotine is not an *addicting* drug as the 1988 SGR has painted it to be, the next question that arises is: what motivates the continued use of tobacco products by humans? We believe that Warburton (1990) has developed a balanced, functional theory of nicotine use that recognizes the beneficial psychological effects of nicotine. This "resource" or "psychological tool" hypothesis holds that people smoke cigarettes primarily for purposes of enjoyment, performance enhancement and/or anxiety reduction. This theory also passes the commonsense test of why people smoke. They smoke, not because they are addicted to nicotine, but because they achieve some benefits from smoking, enjoy these benefits which are totally compatible with everyday tasks and stresses, and choose to continue to enjoy these benefits. While this manuscript cannot "prove" the resource hypothesis,

we note that this hypothesis still stands, using the same data, after the addiction hypothesis has fallen.

We believe the distinctions are clear and cannot be stated more clearly than what was said in the 1964 SGR: "the practice [smoking] should be labeled *habituation* to distinguish it clearly from *addiction*, since the biological effects of tobacco, like coffee and other caffeine-containing beverages, ... are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs" (p 350, emphasis in original). If we lose this common-sense perspective of the role of nicotine in tobacco use, those of us who enjoy the "lift" we receive from that first cup of coffee in the morning or that cola drink in the late afternoon may find that a few years from now a small group of researchers have equated our coffee/cola-drinking behavior to that of a hard-core crack or heroin addict.

Acknowledgements. The authors wish to thank Drs. Charles D. Spielberger and John H. Reynolds, IV for comments on an earlier draft of this manuscript.

References

Benowitz NL (1987) The human pharmacology of nicotine. In: Cappell HD et al (eds) Research advances in alcohol and drug problems, vol 9. Plenum Press, New York, pp 1–52

Benowitz NL, Jacob P (1990) Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. J Pharmacol Exp Ther 254:1000–1005

Bourne SJ (1991) Towards a neuro-endocrine explanation of tobacco addiction. J Smoking-Related Disord 2:105–110

Bozarth MA (1990) Drug addiction as a psychobiological process. In: Warburton D (ed) Addiction controversies. Harwood, London, pp 112–134

Bozarth MA, Wise RA (1985) Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. JAMA 254:81–83

Burling TA (1984) Tobacco. In: Department of Health and Human Services Publication No. (ADM) 85-1372. US Government Printing Office, Washington DC, pp 85–104

Carmody TP (1989) Affect regulation, nicotine addiction, and smoking cessation. J Psychoact Drugs 21:331–342

Clark D (1990) Discriminative properties of drugs of abuse. In: Warburton D (ed) Addiction controversies. Harwood, London, pp 185–200

Collins AC (1990) An analysis of the addiction liability of nicotine. In: Erickson CK, Javors M, Morgan WW (eds) Addiction potential of abused drugs and drug classes. Haworth Press, New York, pp 83–101

Davies JB (1990) Life stress and the use of illicit drugs, alcohol, and tobacco: Empirical findings, methodological problems and attributions. In: Warburton D (ed) Addiction controversies. Harwood, London, pp 283–295

Dworkin SI, Broadbent J, Guarino R, Robinson JH (1991) Environmental determinants of the relative reinforcing efficacy of nicotine. Soc Neurosci Abstr 17:425

Eiser R (1990) Social cognition and comparative substance use. In: Warburton D (ed) Addiction controversies. Harwood, London, pp 271–282

Fernstrom JD (1983) Role of precursor availability in the control of monamine biosynthesis in brain. Physiol Rev 63:484–496

Frith CD (1971) Smoking behaviour and its relation to the smoker's immediate experience. Br J Soc Clin Psychol 10:73–78

Froggatt P, Wald NJ (1989) The role of nicotine in the tar reduction programme. In: Wald NJ, Froggatt P (eds) Nicotine, smoking and the low tar programme. Oxford University Press, Oxford, pp 229–236

Gilbert DG (1979) Paradoxical tranquilizing and emotion-reducing effects of nicotine. Psychol Bull 86:643–661

Gilbert DG, Welser R (1989) Emotion, anxiety and smoking. In: Ney T, Gale A (eds) Smoking and human behavior. Wiley, New York, pp 171–196

Gilbert DG, Meliska CJ, Williams CL, Jensen RA (1992) Subjective correlates of smoking-induced elevations of plasma beta-endorphin and cortisol. Psychopharmacology 106:275–281

Goldstein A, Kalant H (1990) Drug policy: Striking the right balance. Science 249:1513–1521

Griffiths RR, Woodson PP (1988) Reinforcing effects of caffeine in humans. J Pharmacol Exp Ther 246:21–29

Griffiths RR, Brady JV, Bradford LD (1979) Predicting the abuse liability of drugs with animal self-administration procedures: Psychomotor stimulants and hallucinogens. In: Thompson T, Dews PB (eds) Advances in behavioral pharmacology, vol 2. Academic Press, New York, pp 163–208

Griffiths RR, Bigelow GE, Liebson IA (1986) Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. J Pharmacol Exp Ther 239:416–425

Henningfield JE (1984a) Behavioral pharmacology of cigarette smoking. In: Thompson T, Dews PB, Barrett JE (eds) Advances in behavioral pharmacology, vol 4. Academic Press, New York, pp 131–210

Henningfield JE (1984b) Pharmacological basis and treatment of cigarette smoking. J Clin Psychiatry 45:24–34

Henningfield JE (1986) Nicotine: An old-fashioned addiction. In: Snyder S (ed) The encyclopedia of psychoactive drugs. Chelsea House Publishers, New York

Henningfield JE (1987) Nicotine. In: The second triennial report to congress; Department of Health and Human Services Publication No. (ADM)87-1486. US Government Printing Office, Washington DC, pp 93–119

Henningfield JE, Goldberg SR (1983a) Control of behavior by intravenous nicotine injections in human subjects. Pharmacol Biochem Behav 19:1021–1026

Henningfield JE, Goldberg SR (1983b) Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19:989–992

Henningfield JE, Nemeth-Coslett R (1988) Nicotine dependence: interface between tobacco and tobacco-related disease. Chest 93:37S–55S

Henningfield JE, Miyasato K, Jasinski DR (1983) Cigarette smokers self-administer intravenous nicotine. Pharmacol Biochem Behav 19:887–890

Henningfield JE, Miyasato K, Jasinski DR (1985) Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther 234:1–12

Henningfield JE, Lucas SE, Bigelow GE (1986) Human studies of drugs as reinforcers. In: Goldberg SR, Stolerman IP (eds) Behavioral analysis of drug dependence. Academic Press, New York, pp 69–122

Henningfield JE, London ED, Jaffe JH (1987) Nicotine reward: Studies of abuse liability and physical dependence potential. In: Engel J, Oreland L (eds) Brain reward systems and abuse. Raven Press, New York, pp 147–164

Henningfield JE, Clayton R, Pollin W (1990) Involvement of tobacco in alcoholism and illicit drug use. Br J Addict 85:279–292

Henningfield JE, Cohen C, Slade JD (1991) Is nicotine more addictive than cocaine? Br J Addict 86:565–570

Hindmarch I, Kerr JS, Sherwood N (1991) The comparative psychopharmacology of nicotine. In: Adlkofer F, Thurau K (eds) Effects of nicotine on biological systems. Birkhauser, Basel, pp 509–519

Holtzman SG (1990) Caffeine as a model drug of abuse. TIPS 11:355–356

Hughes JR, Hatsukami DK, Pickens RW, Krahn D, Malin S, Luknic A (1984) Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology 83:82–87

Hughes JR, Gulliver SB, Amori G, Mireault GC, Fenwick JF (1989) Effect of instructions and nicotine on smoking cessation,

withdrawal symptoms and self-administration of nicotine gum. Psychopharmacology 99:486–491
Jasinski DR, Henningfield JE (1988) Conceptual basis of replacement therapies for chemical dependence. In: Pomerleau OF, Pomerleau CS (eds) Nicotine replacement, a critical evaluation. Liss, New York, pp 13–34
Jasinski DR, Johnson RE, Henningfield JE (1984) Abuse liability assessment in human subjects. TIPS 5:196–200
Kerr JS, Sherwood N, Hindmarch I (1991) Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacology 104:113–119
Langley JN, Dickinson WL (1889) On the local paralysis of peripheral ganglia, and on the connexion of different classes of nerve fibers with them. Proc R Soc London (Biol) 46:423–431
Lewis CE, Rice J, Helzer JE (1983) Diagnostic interactions: alcoholism and antisocial personality. J Nerv Ment Dis 171:105–113
Majchrzak MJ, Pomerleau OF, Pomerleau CS (1987) Nausea, cigarette smoking, nicotine, and pituitary hormone release. In: Martin WR, van Loon GR, Iwamoto ET, Davis DL (eds) Tobacco smoke and nicotine: a neurobiologic approach. Plenum Press, New York, pp 501–502
McKearney JW (1968) Maintenance of responding under a fixed-interval schedule of electric shock presentation. Science 160:249–251
McNeill AD, Jarvis M, West R (1987) Subjective effects of cigarette smoking in adolescents. Psychopharmacology 92:115–117
Morse WH, Mead RN, Kelleher RT (1967) Modulation of elicited behavior by a fixed-interval schedule of electric shock presentation. Science 157:215–217
Murphy JK, Edwards NB, Downs AD, Ackerman BJ, Rosenthal TL (1990) Effects of doxepin on withdrawal symptoms in smoking cessation. Am J Psychiatry 147:1353–1357
Nemeth-Coslett R, Henningfield JE, O'Keeffe MK, Griffiths RR (1987) Nicotine gum: dose-related effects on cigarette smoking and subjective ratings. Psychopharmacology 92:424–430
O'Brien CP, Testa T, Ternes J, Greenstein R (1978) Behavioral tolerance: Research and treatment implications. US Public Health Service, Department of Health, Education and Welfare Publication No. (ADM)78-551. US Government Printing Office, Washington DC, pp 67–71
Pandina RJ, Huber GL (1990) Tobacco, nicotine, and the question of addiction: What to do about a difficult problem? Sem Respir Med 11:50–68
Pomerleau OF, Pomerleau CS (1984) Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation. Neurosci Biobehav Rev 8:503–513
Pritchard WS (1991a) The link between smoking and P: A serotonergic hypothesis. Person Individ Diff 12:1187–1204
Pritchard WS (1991b) Electroencephalographic effects of cigarette smoking. Psychopharmacology 104:485–490
Pritchard WS, Robinson JH, de Bethizy JD, Davis RA (1991) Effect of smoking and caffeine on EEG, heart rate, performance, and anxiety/mental alertness/muscular tension. Psychophysiology 28:S44
Roe FJC (1989) The toxicity of nicotine: cancer. In: Wald NJ, Froggatt P (eds) Nicotine, smoking and the low tar programme. Oxford University Press, Oxford, pp 41–52
Rose JE, Zinser MC, Tashkin DP, Newcomb R, Ertle A (1984) Subjective response to cigarette smoking following airway anesthetization. Addict Behav 9:211–215
Russell MAH (1990) The nicotine addiction trap: a 40-year sentence for four cigarettes. Br J Addict 85:293–300
Russell MAH (1991) The future of nicotine replacement. Br J Addict 86:653–658
Schneider NG, Jarvik ME (1985) Nicotine gum vs placebo gum: Comparisons of withdrawal symptoms and success rates. In: Grabowski J, Hall SM (eds) Pharmacological adjuncts in smoking cessation; National Institute of Drug Abuse Research Monograph 53. US Government Printing Office, Washington DC, pp 83–101
Schuckit MA (1973) Alcoholism and sociopathy – diagnostic confusion. J Stud Alcohol 34:157–164
Snyder FR, Davis FC, Henningfield JE (1989) The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 23:259–266
Spielberger CD (1986) Psychological determinants of smoking behavior. In: Tollison RD (ed) Smoking and society: toward a more balanced assessment. DC Heath, Lexington MA, pp 89–134
Stolerman IP (1990a) Behavioral pharmacology of nicotine in animals. In: Wonnacott S, Russell MAH, Stolerman IP (eds) Nicotine psychopharmacology. Molecular, cellular and behavioral aspects. Oxford University Press, Oxford, pp 278–306
Stolerman IP (1990b) Nicotine on the brain. New Scientist 3:33–35
US Department of Health and Human Services (1988) The health consequences of smoking: Nicotine addiction. A report of the Surgeon General. US Government Printing Office, Washington DC
US Department of Health, Education, and Welfare (1964) Smoking and health. Report of the advisory committee to the Surgeon General of the Public Health Service. US Government Printing Office, Washington DC
Warburton DM (1985) Addiction, dependence and habitual substance use. Bull Br Psychol Soc 38:285–288
Warburton DM (1988a) The functional use of nicotine. In: Wald NJ, Froggatt P (eds) Nicotine, smoking, and the low tar programme. Oxford University Press, Oxford, pp 182–199
Warburton DM (1988b) The puzzle of nicotine use. In: Lader M (ed) The psychopharmacology of addiction. Oxford University Press, Oxford, pp 27–49
Warburton DM (1989) Is nicotine use an addiction? Bull Br Psychol Soc 4:166–170
Warburton DM (1990) Heroin, cocaine and now nicotine. In: Warburton D (ed) Addiction controversies. Harwood, London, pp 21–35
Warburton DM, Revell A, Walters AC (1988) Nicotine as a resource. In: Rand M, Thurau K (eds) The pharmacology of nicotine. IRL Press, London, pp 359–373
Wesnes K (1987) Nicotine increases mental efficiency, but how? In: Martin WR, van Loon GR, Iwamoto ET, Davis DL (eds) Tobacco smoke and nicotine: a neurobiologic approach. Plenum Press, New York, pp 63–80
Wesnes K, Warburton DM (1978) The effects of cigarette smoking and nicotine tablets upon human attention. In: Thornton RE (ed) Smoking behavior: physiological and psychological influences. Churchill Livingstone, New York, pp 131–147
Wesnes K, Warburton DM (1983) Effects of smoking on rapid information processing performance. Neuropsychobiology 9:223–229
Wesnes K, Warburton DM (1984a) Smoking, nicotine, and human performance. In: Balfour DJK (ed) Nicotine and the tobacco smoking habit. Pergamon Press, Oxford, pp 133–152
Wesnes K, Warburton DM (1984b) The effects of cigarettes of varying yield on rapid information processing performance. Psychopharmacology 82:338–342
West R, Hajek P, Burrows S (1990) Effect of glucose tablets on craving for cigarettes. Psychopharmacology 101:555–559
World Health Organization (1981) Nomenclature and classification of drug- and alcohol-related problems: a WHO memorandum. Bull WHO 90:225–242
Zuckerman M (1983) Sensation seeking: the initial motive for drug abuse. In: Gottheil E, Druley KA, Skoloda TE, Waxman HM (eds) Etiological aspects of alcohol and drug abuse. Charles C. Thomas, Springfield, IL, pp 202–220
Zuckerman M (1987) Is sensation seeking a predisposing trait for alcoholism? In: Gottheil E, Druley KA, Pasko S, Weinstein SP (eds) Stress and addictions. Brunner/Mazel, New York, pp 283–301