Published in final edited form as:

Psychopharmacology (Berl). 2016 December ; 233(23-24): 3829–3848. doi:10.1007/s00213-016-4441-4.

Nicotine self-administration research: the legacy of Steven R. Goldberg and implications for regulation, health policy, and research

Jack E. Henningfield^{1,2}, Tracy T. Smith^{3,4}, Bethea A. Kleykamp¹, Reginald V. Fant¹, and Eric C. Donny⁵

¹Pinney Associates, 4800 Montgomery Lane, Suite 400, Bethesda, MD 20814, USA

²Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

³University of Pittsburgh Cancer Institute, 4120 Sennott Square, 210 S. Bouquet Street, Pittsburgh, PA 15260, USA

⁴Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 4120 Sennott Square, 210 S. Bouquet Street, Pittsburgh, PA 15260, USA

⁵Department of Psychology, University of Pittsburgh, 210 S. Bouquet Street, Pittsburgh, PA 15260, USA

Abstract

Background and rationale—Steven R. Goldberg was a pioneering behavioral pharmacologist whose intravenous drug self-administration studies advanced the understanding of conditioned stimuli and schedules of reinforcement as determinants of pattern and persistence of drug-seeking behavior, and in particular, the importance of nicotine in tobacco use. His passing in 2014 led to invitations to contribute articles to psychopharmacology dedicated to his work.

Objectives—The objectives of this review are to summarize and put into historical perspective Goldberg's contributions to elucidate the reinforcing effects of nicotine and to summarize the implications of his research for medication development, tobacco regulation, and potential tobacco control policy options. This includes a review of intravenous nicotine self-administration research from the 1960s to 2016.

Results—Goldberg's application of behavioral pharmacology methods to investigate nicotine reinforcement and the influence of schedule of reinforcement and conditioned stimuli on nicotine administration contributed to the conclusions of the US National Institute on Drug Abuse, and the Surgeon General, that nicotine met the criteria as a dependence-producing drug and cigarette

Correspondence to: Jack E. Henningfield.

Conflicts of interest Through Pinney Associates, Drs. Fant, Henningfield, and Kleykamp have consulted or are presently consulting to GlaxoSmithKline on smoking cessation, NJOY on electronic cigarettes, Reynolds American Vapor Products, and to pharmaceutical companies on substance abuse-related regulatory issues on drug products under development. Henningfield shares interest in a patent for a new nicotine gum for smoking cessation that is under license to Nicovum, which is a smoking cessation product subsidiary of Reynolds American, Inc.

Drs. Smith and Donny have no conflicts of interest to report.

smoking as a prototypic drug dependency or “addiction.” Equally important, this work has been systematically extended to other species and applied to address a range of factors relevant to tobacco use, medication development, regulation, and public health policy.

Conclusions—Steven R. Goldberg was a pioneering scientist whose systematic application of the science of behavioral pharmacology advanced the understanding of tobacco and nicotine use and contributed to the scientific foundation for tobacco product regulation and potential public health tobacco control policy development.

Keywords

Behavioral pharmacology; Self-administration; Intravenous; Nicotine; Tobacco; Sensory; Second-order schedule; Reinforcement; Punishment; Antagonists

Introduction

In 1981, Steven R. Goldberg and colleagues published their pioneering primate intravenous (IV) nicotine self-administration (SA) paper that contributed to an escalation in nicotine research by the National Institute on Drug Abuse (NIDA) and NIDA director William Pollin’s testimony to the US Congress that nicotine met all the criteria as a dependence-producing drug (Goldberg et al. 1981; US Department of Health and Human Services (DHHS) 1984a; Henningfield 2004, 2011). More than three decades of perspective suggests that the paper’s concluding sentence was a considerable understatement of the actual impact of their work: “*Second-order schedules of nicotine injection may therefore provide a useful experimental technique for examining environmental and pharmacological factors that contribute to the maintenance of tobacco use by humans*” (Goldberg et al. 1981, p. 575). In fact, they had elucidated keys to nicotine’s potential powerful reinforcing effects: a combination of small, rapidly delivered doses, in the context of discrete environmental stimuli, under intermittent schedules of reinforcement. This was the first robust laboratory model for cigarette-delivered nicotine.

When Goldberg began researching nicotine in the late 1970s, it was not considered an addictive drug by the US Surgeon General or NIDA (Henningfield 2011; U.S. DHHS 1988, 2014). Nor did either the American Psychiatric Association (APA) or World Health Organization (WHO) recognize tobacco/nicotine dependence as a disease in their diagnostic manuals. Today, the cigarette is considered among the most addictive manufactured products on the planet and tobacco control among the major global public health challenges (WHO 2016a). Goldberg would have been the first to acknowledge that many other scientists and scientific approaches contributed to understanding the role of nicotine in tobacco use, but this commentary and review is focused on his impact.

History and context at the dawn of nicotine self-administration research

In the 1970s, psychiatrists and scientists such as Michael Russell in London, Murray Jarvik and Charles Schuster in the USA, and leadership at NIDA began to seriously consider the possibility that cigarette smoking could be a form of drug dependence and that nicotine might meet the accepted criteria as a dependence-producing drug (Henningfield 2011). The first NIDA director, Robert DuPont, and the next director, William Pollin, convened

conferences that led to NIDA monographs that discussed nicotine as potentially meeting the criteria as an “abusable” and “dependence-producing drug” and that cigarette smoking could be considered a form of drug dependence (Jarvik et al. 1979; Krasnegor 1978, 1979a, 1979b; Pinney 1979). Conference participants included leading tobacco and nicotine researchers Jarvik and Russell; psychiatrist Jerome Jaffe; and psychologists and behavioral pharmacologists including Ellen Gritz, Schuster, and Norman Krasnegor. The conferences contributed to the inclusion of dependence and withdrawal in the American Psychiatric Association (APA) Diagnostic and Statistical Manual (APA 1980). The conferences also identified key gaps in knowledge that prevented the Surgeon General’s reports from concluding that nicotine met the criteria as an addicting drug (US Department of Health, Education, and Welfare (HEW) 1964, 1979).

The absence of a definitive conclusion on nicotine in 1979 prompted the Secretary of Health and Human Services, Joseph Califano, to direct Office on Smoking and Health Director John Pinney to meet with NIDA director Pollin to request that NIDA determine if nicotine met the criteria as an addictive drug and if cigarette smoking should be considered a form of drug dependence. A related practical policy and consumer issue was whether cigarette package warning labels should include an addiction warning as had been suggested by some (Brandt 1982; Pollin 1982). At that time, the quickest way to accomplish this was through NIDA’s Intramural Research Program (IRP), the Addiction Research Center (ARC), which had a history of rapidly exploring and characterizing the pharmacological basis of substance use and abuse (see Tables 1 and 2).

At approximately the same time, Goldberg, who was recognized as one of the nation’s premiere preclinical (animal) drug SA researchers, had turned his attention to nicotine in the Laboratory of Psychobiology at Harvard Medical School. Preclinical drug SA studies were among the most well-validated tools for predicting the liability of a drug for abuse and/or addiction (Ator and Griffiths 2003; FDA 2010a; Griffiths et al. 1980). The director of the NIDA ARC, Donald Jasinski, invited Goldberg to give a seminar on his initial findings. Jasinski then recruited Goldberg to the ARC preclinical program Lexington, Kentucky in 1979 while maintaining his collaboration with Roger Spealman at Harvard. Goldberg’s wife, Donna Goldberg, was an active collaborator.

Shortly thereafter, Jasinski recruited Jack Henningfield in 1980 to lead the clinical and human behavioral pharmacology research, then Edythe London in 1981, to lead the neuropharmacology research on nicotine. Meanwhile, the ARC was relocating from Lexington, Kentucky to The Johns Hopkins Bayview Campus in Baltimore, starting in 1979–1980 (Campbell 2007, 2009). Goldberg and other ARC preclinical researchers were reestablished on the Bayview campus beginning in 1981, and collaborations among Goldberg, Henningfield, and London developed quickly.

By 1982, the ARC research supported the joint testimony of the Secretary of DHHS, William Brandt, Surgeon General C. Everett Koop, and NIDA Director William Pollin in a March 11, 1982 congressional hearing on the proposed Comprehensive Smoking Prevention Education Act (Brandt 2007; Kluger 1996; Proctor 2012; US House of Representatives, 1982). They testified that cigarettes were addictive, that cigarette smoking could be a drug

addiction, and that cigarette packages should warn that cigarettes are addictive. Secretary Brandt stated "... on the basis of research conducted by the National Institute on Drug Abuse, it is our view [that] cigarette smoking represents a prototypic dependence process and in fact is the most widespread example of drug dependence in this country" (Brandt 1982). Pollin's testimony was expanded into the 1983 US Public Health Service educational publication, "Why People Smoke Cigarettes," which concluded that "smoking can be more than just a 'bad habit', that it can be a drug dependence and addictive behavior" (DHHS 2014).

The recommendation that cigarettes should include an addiction warning in 1982 was met with strong opposition by the tobacco industry and its supporters in the Congress (Brandt 2007; Kluger 1996; Proctor 2012). In negotiations leading to the 1984 Comprehensive Smoking Education Act by the US Congress, the potential addiction warning was essentially traded for the warning that "cigarette smoke contains carbon monoxide" (Kluger 1996; pp. 543–549; see also Brandt 2007; Proctor 2012).

The importance of nicotine and tobacco behavioral pharmacology research had been established, and NIDA's extramural research funding on tobacco increased rapidly over the 1980s. This included research on the molecular genetics of nicotine, the behavioral economics of tobacco use, and the treatment innovations. Research on the reinforcing effects of nicotine and other tobacco and nicotine research supported Surgeon General Koop's call to develop a report on addiction in 1987, resulting in the 1988 Surgeon General's report: nicotine addiction (US DHHS 1988).

Steven R. Goldberg's approach to nicotine self-administration research

What was it about Goldberg's approach that helped NIDA to move so quickly and definitively? He was not the first to demonstrate nicotine SA. He was, however, the first to bring together the pharmacologic and environmental factors in a way that generated the robust behavior typical of cigarette smoking and other drug dependencies in a model that was validated with several control approaches. This was no accident. When Goldberg turned his attention to nicotine, initially in collaboration with Spealman, he had a decade of invaluable experience to take on the understanding of the complex effects of this drug that had yielded equivocal effects in earlier studies (e.g., Griffiths et al. 1980; Henningfield and Goldberg 1983a, 1983b; Henningfield et al. 1981; Russell 1979).

Goldberg's approach flowed from his graduate program at the University of Michigan, Ann Arbor, where his graduate advisor was Charles Schuster, co-pioneer of primate IV drug SA with Travis Thompson (Schuster and Thompson 1962; Thompson and Schuster 1964, 1968). That program was a hotbed of established and emerging scientists including Maurice Seevers; Gerald Deneau; Tomoji Yanagita; Julian Villarreal; and fellow Schuster doctoral student, James Woods (Campbell 2007, 2009; May and Jacobson 1989; Schuster 1991). In this program, diverse substances were explored for potential reinforcing and dependence-producing effects (e.g., Deneau et al. 1969; Yanagita et al. 1963).

Goldberg's doctoral thesis addressed the importance of environmental stimuli in drug use, focusing on opioids (Goldberg 1970; Goldberg and Schuster 1970). He also studied the

effects of what seemed to be very small doses of opioids and the effects of experience on their subsequent behavioral effects (Goldberg et al. 1971). The importance of drug-associated stimuli (“conditioned stimuli”) in generating more persistent behavior than by the presentation of drug alone was an area of particular interest in his studies involving opioids and cocaine (Goldberg 1973). This had been a focus of research and clinical application by addiction pioneers such as the early ARC director Abraham Wikler (Campbell 2007; Goldberg 1976; Wikler 1965, 1973). By the 1970s, behavioral pharmacology studies of cigarette were also beginning to elucidate the importance of environmental stimuli on cigarette smoking (e.g., Gritz 1978). Goldberg thus came to understand that the strength and persistence of behavior leading to SA of a drug was due to factors far beyond the pharmacology of the drug. It included what he described as the functional behavioral effects of the drug that could be greatly increased by the conditions of drug availability (“schedule of reinforcement”), dosing conditions, and conditioned environmental stimuli (Goldberg 1976; Goldberg personal communication to JEH 1982–1983).

Goldberg subsequently extended his work examining interactions of drug dose and the conditions of drug availability (“schedule of reinforcement”) and conditioned stimuli with Hoffmeister and colleagues at Bayer’s Institute of Pharmacology in Germany (e.g., Goldberg et al. 1971). He continued this work in the Laboratory of Psychobiology, Harvard Medical School, in collaboration with Roger Kelleher, William Morse, and Roger Spealman (e.g., Goldberg and Kelleher 1976; Spealman and Goldberg 1978). Of particular relevance to cigarette smoking were his studies involving second-order schedules of reinforcement in which stimuli associated with drug administration came to serve as reinforcing stimuli, capable of sustaining complex and persistent chains of behavior in the absence of drug administration and with only intermittent drug administration that was paired with those stimuli. Goldberg and colleagues applied this approach to cocaine (Goldberg 1973; Goldberg and Kelleher 1976) and morphine (Goldberg et al. 1975, 1976, 1979; Goldberg and Tang 1977) before studying nicotine. He also learned to evaluate the conditions under which electric shock, cocaine, and opioids could serve to maintain the behavior that led to their administration (as positive reinforcers) or to the prevention of their administration (negative reinforcers) (Barrett and Stanley 1980; Goldberg 1980; Spealman 1979). By the time he took on the challenge of evaluating nicotine, he was well experienced in characterizing the positive and negative reinforcing drug effects. He had also refined procedures for evaluating the importance of conditioned environmental stimuli in extended chains of behavior for intermittent drug reinforcement by varying the parameters of the schedules or conditions of drug reinforcement following emerging principles of behavioral pharmacological assessment (e.g., Thompson and Schuster 1968) (see Table 3).

All of this perspective and experience came together in the design of the 1981 study published in science (Goldberg et al. 1981). In that study, squirrel monkeys could receive injections of very small doses of nicotine (30µg/kg) by pressing levers. Up to 12 injections could be obtained in the 90-min test sessions on a fixed interval (FI) schedule of either 1 or 2 min in which pressing the lever ten times (fixed ratio or FR 10) after the FI of a 1- or 2-min interval had elapsed. Injections were paired with the illumination of a green light that was also illuminated upon completion of every FR 10. Although the animals only had to press

the lever ten times at the end of the FI schedule to receive a nicotine injection, the animals would press the lever rapidly and complete many FR 10 schedules.

The main findings were summarized in the abstract of the paper as follows: “*Squirrel monkeys pressed a lever at high rates under a second-order schedule of reinforcement in which lever pressing produced a brief visual stimulus that was occasionally contiguous with an intravenous injection of nicotine. The rate of lever pressing could be markedly reduced either by substituting saline for nicotine injections or by blocking the effects of nicotine with mecamylamine. The rate of lever pressing could also be reduced by eliminating the brief visual stimulus. These results show that nicotine can function as an effective reinforcer under a second-order schedule of drug self-administration and that an environmental stimulus associated with nicotine intake can contribute to the maintenance of persistent drug-seeking behavior*” (Goldberg et al. 1981, p. 573).

Goldberg et al. thus elucidated an important key to nicotine’s potentially powerful reinforcing effects: a combination of small rapidly delivered doses, each under the control of the organism, in the context of discrete environmental stimuli, and under intermittent schedules of reinforcement (1981). In the opinion of these authors, this was the first published robust preclinical laboratory model for cigarette smoking. As discussed further on, studies that Goldberg would complete involving nicotine in animals and humans would apply many of these same techniques and thereby contribute to the understanding of nicotine as a behavior-controlling and addicting drug.

Review of other intravenous nicotine self-administration research

1960s–1980s: overview of intravenous nicotine self-administration research

There were few IV nicotine SA studies prior to the Goldberg et al. 1981 study, and they have been reviewed elsewhere (Corrigall 1999; Griffiths et al. 1980; Henningfield 1984; Henningfield and Goldberg 1983a, 1983b; U.S. DHHS 1988, 2010). In brief, they demonstrated that nicotine SA could occur under certain conditions but the emerging behavior was not strong enough to lead to the conclusion that nicotine could serve as a robust reinforcer similar to prototypic substances of abuse such as morphine, cocaine, or alcohol (cf. Griffiths et al. 1980; Henningfield et al. 1981; Russell 1979).

The first study in the 1960s that was widely acknowledged as important in IV nicotine SA research was actually a cigarette smoke SA study. Led by Schuster, the study involved the method of administering a drug to subjects who were free to self-administer the same drug by the same or a different route of administration (cf. Griffiths et al. 1980; Howell and Fantegrossi 2009; Meisch 1977, 2001; Meisch and Lemaire 1993; Poling and Byrne 2000). Specifically, Lucchesi et al. (1967) allowed cigarette smokers to smoke ad libitum in test chambers. The subjects had been catheterized to enable infusion of either saline or nicotine. Nicotine was slowly infused (each dose over 20 min once per hour) for a total of 6 mg per 6-h session in one group ($n = 4$) and 22 mg in the other group ($n = 5$). These doses “did not produce subjective effects” (Lucchesi et al. 1967, p.795); nonetheless, the higher dose significantly decreased cigarettes smoked and the amount of each cigarette that was smoked, leading to the conclusion “that nicotine plays a small but significant role in the smoking

habit and that part of the craving for a cigarette can be satisfied by the intravenous administration of the alkaloid” (p. 795).

About the same time as the Lucchesi et al. study and in the same laboratory where Goldberg was training, Deneau and Inoki (1967) conducted the first study demonstrating nicotine SA. Nicotine was available for IV SA by seven rhesus monkeys at several doses. While the description of the protocol was not detailed, it appears that a single lever press was programmed to produce an injection. There was no description of potentially associated stimuli. Protocols that allow for more conclusive determination of the drug’s reinforcing potential, such as comparison to saline or manipulation of the schedule of reinforcement, were not employed (cf. Ator and Griffiths 2003; Howell and Fantegrossi 2009; Meisch 1977, 2001; Pickens and Thompson 1968, 1970; Thompson and Schuster 1968). Nicotine SA rates were highly variable within and across monkeys, although in general, as the doses were increased, SA rates tended to decrease. The authors’ conclusions were appropriately cautious: “*It is clear that under certain circumstances, monkeys will self-administer nicotine intravenously... the fact that monkeys will self-administer nicotine at all suggests that this alkaloid may be one of the substances in tobacco smoke which is responsible for man’s use of tobacco... Other routes of self-administration by experimental animals should also be tested before any conclusions can be drawn concerning the relationship of self-administration of nicotine by animals and tobacco smoking in man*” (Deneau and Inoki 1967, p. 279).

Subsequently, Yanagita, who had trained with Deneau in the Michigan laboratory (e.g., Deneau et al. 1969), evaluated nicotine in a primate SA model in Japan under a broader range of conditions, confirming that nicotine SA could occur but with a reinforcing effectiveness that appeared substantially weaker than the comparator drug, cocaine (Yanagita et al. 1974; see also Manzardo et al. 2002). Griffiths et al. (1979) evaluated IV nicotine SA in baboons: it did not serve as a reinforcer. However, subsequent studies in the same laboratory (Ator and Griffiths 1980, 1983) demonstrated that nicotine could serve as a reinforcer, albeit an apparently weak one. Independently, a doctoral trainee of Thompson and Pickens, Dougherty and his colleagues (1981) used a second-order schedule technique resulting in nicotine reinforcement; however, the model required several months of training, and the SA behavior was not robust; the investigators did not continue the research.

A series of studies in the late 1970s and early 1980s on nicotine SA in hooded rats was conducted at the University of Melbourne and La Trobe University in Victoria, Australia (Lang et al. 1977; Latiff et al. 1980; Singer et al. 1978, 1982; Smith and Lang 1980). They demonstrated nicotine SA; however, the behavior was not robust and dose-response relationships were inconsistent. Somewhat similar results were obtained by Hanson et al. (1979) at the Merck Institute for Therapeutic Research in Pennsylvania. Hanson et al. also found that the centrally acting nicotinic antagonist mecamylamine, but not the peripherally acting antagonist pentolinium, altered nicotine SA, suggesting that central effects of nicotine were of functional importance in SA.

In the early 1980s, a promising IV nicotine SA model in rodents was developed by Philip Morris researchers DeNoble and Mele in its Richmond Virginia laboratory. DeNoble had

done a postdoctoral fellowship under Meisch and Thompson at the University of Minnesota and was well trained in behavioral pharmacology methods and drug SA. DeNoble and Mele established nicotine SA in rodents, employed placebo controls, manipulated the dose and reinforcement schedule, and evaluated the effects of various pretreatment drugs to explore the reinforcing effects of nicotine. Unfortunately, the DeNoble and Mele results were suppressed by Philip Morris and were virtually unknown outside of Philip Morris until they were disclosed in a congressional testimony in 1994 by Henningfield and Kessler (FDA 1995; Henningfield 1994a, 2004; Kessler 1994, 2001), in a subsequent congressional hearing by DeNoble and Mele (DeNoble 1994; Mele 1994), and in a special issue of Psychopharmacology in 2005 (Barry 2006; Henningfield et al. 2006a; DeNoble and Mele 2006) (see Tables 4 and 5).

Thus, the field had to wait for a viable rodent model of IV nicotine SA until the 1989 publication by Corrigall and Coen at the Addiction Research Foundation in Toronto, Canada. Independently of DeNoble and Mele, Corrigall and Coen developed a rodent model that was similar in many respect to that of DeNoble and Mele. They demonstrated robust nicotine SA and clear evidence of dose-related positive reinforcement by way of several control procedures (Corrigall and Coen 1989). They went on to use the model to more thoroughly understand the effects of nicotine as compared to those of cocaine and other drugs, as well as physiological mechanisms of action as discussed further in the next section of this article (Corrigall et al. 1992, 1994; Corrigall and Coen 1991a, 1991b). The Corrigall and Coen model opened the door to an era of rapid advance in the understanding of tobacco dependence and its neuropharmacology and molecular genetics and to the more rapid evaluation of potential treatment medications.

Other self-administration research by Goldberg and colleagues during the 1980s—Goldberg's nicotine SA work advanced rapidly after he joined the NIDA ARC in 1979. Modeling several aspects of Goldberg's model, Henningfield and Yanagita protégé, Miyasato, established IV nicotine SA in cigarette smokers (Henningfield et al. 1983). This led to collaborations between Henningfield and Goldberg that included their development of human studies specifically designed to closely parallel Goldberg's non-human primate studies in the nature of the schedules of reinforcement and various experimental manipulations and use of injection-associated visual stimuli as discussed earlier (e.g., Henningfield and Goldberg 1983a,b; Goldberg and Henningfield 1988).

Goldberg, in collaboration with Spealman at Harvard, and Risner and Henningfield, at NIDA, continued IV nicotine SA research. They demonstrated robust maintenance of animal and human SA behavior under second-order schedules of drug reinforcement, dose-related effects, and also demonstrated that nicotine, like cocaine, can serve as a negative reinforcer and sustain behavior that would prevent automatically programmed injections from being administered. Increasing the fixed ratio requirements led to increased rates of responding that were generally comparable in monkeys and humans (Goldberg and Henningfield 1988; Goldberg and Spealman 1982, 1983; Henningfield and Goldberg 1983a, 1983b; Risner and Goldberg 1983; Spealman and Goldberg 1982).

Unfortunately, their work also attracted attention of the tobacco industry and the eventual pressure by the White House director of the Office of National Drug Policy, Carlton Turner, in 1985, to suggest to ARC Director and Acting NIDA Director Jaffe that Henningfield and Goldberg should discontinue the nicotine human research (Kessler 2001). Henningfield and Goldberg were not pleased to discontinue their research; however, they believed that by that point, enough research had been published that there was little question on nicotine's function as a powerful positive reinforcer for humans, and they agreed to discontinue the human studies in 1985 (cf. Henningfield 2004; Kessler 2001; McGarity and Wagner 2008). Some of the work that had been in progress was eventually published as discussed in the next section (Harvey et al. 2004). The human IV drug SA model was applied to other drugs, and Henningfield and Goldberg, in collaboration with other NIDA colleagues, conducted parallel human and squirrel monkey studies on cocaine and morphine SA (Henningfield et al. 1987; Lamb et al. 1991; Panlilio and Goldberg 2007; Panlilio et al. 2005).

Conclusions from the intravenous self-administration research through the 1980s—The main outcome of IV nicotine SA research from the 1960s to the 1980s was the establishment of IV SA models in rodents, non-human primates, and humans. The findings of these studies were important in supporting the conclusion that nicotine is appropriately categorized as an addictive or dependence-producing drug. In a mini-review, Goldberg and Henningfield (1988, p. 233) summarized their findings as follows: “*The series of studies reviewed show that nicotine by itself can serve as an effective reinforcer for humans and experimental animals, but it does so under a more limited range of conditions than do other reinforcers such as IV cocaine injection or food presentation. It is plausible that tobacco vehicles for nicotine administration (e.g., cigarette, chewing tobacco) provide the analogous factors of paired stimuli (e.g., taste and smell of tobacco) and intermittent dosing (e.g., multiple cigarettes and multiple puffs within each cigarette) which appear to strengthen the control of the drug over behavior*”. By the 1990s, nicotine SA models were extended to address a far broader range of questions and applications.

1990s–2016: diverse applications serving medication development, regulation, and public health policy

With the reasonably well-established and validated SA models of the 1980s, the 1990s began a new era of nicotine SA research. It was an era of applying these models to new lines of research, discovery, treatment development, and support of regulation and policy. Goldberg and his colleagues continued to contribute. Below, we describe some of these methodological variations, including recent preclinical research that has contributed to expanding our understanding of nicotine reinforcement and dependence.

Variations in nicotine self-administration training and maintenance procedures—As established by Goldberg and colleagues decades earlier, the schedule of reinforcement used for nicotine SA has a large impact on the rate and pattern of SA. Contemporary researchers most often use an FR schedule in which a specific number of responses are required to receive a single IV infusion along with visual cues (Ator and Griffiths 2003; Corrigan 1992; Corrigan and Coen 1989; Donny et al. 1995; Howell and Fantegrossi 2009). Cue delivery appears to be a critical factor in obtaining high rates of

responding for nicotine (Caggiula et al. 2009). Other schedules of reinforcement test the robustness of nicotine as a primary reinforcer by asking whether responding for nicotine is maintained when the “cost” of nicotine (number of required responses) is progressively escalated (progressive ratio or PR schedules) (Diergaarde et al. 2012; Donny et al. 1999; Grebenstein et al. 2015; Roane 2008; Smith et al. 2015; Stafford et al. 1998). These schedules may be thought of as tests of the value of a reinforcer (Hursh and Roma 2013), and indeed, they demonstrate that, similarly to other drugs of abuse, subjects will continue to respond to nicotine in the face of escalating costs.

The increasing use of nicotine SA since the 1990s has resulted in considerable variation in the model across experiments and between laboratories. Some researchers increase the speed of acquisition of nicotine SA by training rats to respond to another reinforcer (e.g., sucrose) before switching the reinforcer to nicotine (Garcia et al. 2014). Studies also vary in the operandum they use for SA. Lever-pressing has historically been the operant used because it occurs at a low rate without any reinforcement. However, some researchers have recently started using nose-poking instead (Smith et al. 2013, 2014), which is a more naturalistic response for rats and may increase the proportion that acquire SA and the rate of acquisition for studies in which rats acquire SA spontaneously (Clemens et al. 2010). At least one paper has also argued that delivering nicotine more slowly with each infusion more closely models the delivery profile of nicotine seen in tobacco smokers (Sorge and Clarke 2009). However, recent work by colleagues of Goldberg suggested that slower infusion rates decreased acquisition of SA (Wing and Shoaib 2013). Recently, some of Goldberg’s colleagues have further modified the SA model by concurrently providing sucrose as a secondary reinforcer in order to better model competing reinforcers more likely to be present in a natural environment (Panlilio et al. 2015).

Further modifications to SA procedures in recent years include increasing the length of SA sessions from 1 to 2 h per day to 22–23 h per day. Extended access sessions produce similar nicotine SA dose-response curves (Matta et al. 2007), although the number of infusions and responses made each day tend to be greater in an extended-access session. Extended-access sessions may more closely model the patterns of exposure that results in dependence of smokers on nicotine, as rats have shown withdrawal signs after the termination of extended access sessions (O’Dell et al. 2007). However, some researchers have argued that extended access and limited-access sessions produce comparable levels of dependence if limited-access sessions are conducted 7 days per week (Paterson and Markou 2004). Recently, one group of researchers provided rats with intermittent extended access, where the rats experienced 24-h breaks from the extended SA sessions. In this case, rats self-administer nicotine at a higher rate and showed increased somatic signs of withdrawal (Cohen et al. 2012). It has been argued that this pattern of exposure and responding better models the development of nicotine dependence in smokers (Cohen et al. 2012).

Self-administration as tool for understanding the role of other stimuli in tobacco dependence—As discussed already, the second-order schedules used by Goldberg utilized the pairing of environmental stimuli with nicotine delivery, and his research was among the first to establish that the delivery of environmental stimuli that are occasionally paired with nicotine may be necessary for generating high rates of behavior in a

model for smoking behavior. The more contemporary nicotine SA work has continued to build upon that notion by dissecting the role of environmental stimuli in maintaining reinforcement by nicotine. First, the stimuli may elicit a conditioned response similar to that of a nicotine effect, even in the absence of future nicotine delivery (i.e., the stimuli may act as conditioned stimuli). Second, the stimuli can come to act as conditioned reinforcers through frequent pairing with nicotine, an unconditioned reinforcer. Researchers have shown that these stimuli can maintain responding for nicotine in the absence of nicotine delivery (Palmatier et al. 2007). Third, the stimuli can act as discriminative stimuli by signaling that an operant response will result in nicotine reinforcement.

The nicotine SA model has also helped reveal nicotine as a general reinforcement enhancer. Non-contingently-administered nicotine increases the value of other rewards in the environment (i.e., reinforcement enhancement) (Caggiula et al. 2009; Rupprecht et al. 2015). Researchers have shown that rats will respond more for nicotine when it is delivered with a moderately reinforcing visual stimulus than they will for nicotine alone, and this effect is synergistic in that responding for nicotine along with the visual stimulus is greater than the sum of responding for nicotine alone and the visual stimulus alone (Caggiula et al. 2009). This effect has since been generalized to reinforcers such as sucrose (Barrett and Bevins 2013), contexts that have been paired with sucrose and cocaine in a conditioned place preference paradigm (Buffalari et al. 2014), and music in human smokers (Perkins and Karelitz 2013a, 2013b). Nicotine can also enhance the value of conditioned stimuli that have become reinforcers through previous pairing with nicotine (Palmatier et al. 2007). Indeed, the high response rates for nicotine observed on second-order schedules of reinforcement by Goldberg may have been partially driven by nicotine enhancing the value of the environmental stimuli that were occasionally paired with nicotine. This effect is non-associative in that once the reinforcing value has been established, nicotine does not need to be paired with the stimulus in order for enhancement to occur (Donny et al. 2003). This may have implications for the etiology of nicotine dependence because people often use tobacco in the context of many other stimuli (friends, alcohol, taste or feel of a cigarette). If nicotine increases the value of these other rewards, the persistence of smoking may increase. Consistent with the interpretation that reinforcement enhancement is involved in maintaining smoking behavior, some smoking cessation medications (bupropion and varenicline) also enhance other reinforcers in animal models (Palmatier et al. 2009; Schassburger et al. 2015).

More recently, some researchers have used nicotine SA to understand the relationship between nicotine and other tobacco constituents. Such research has explored whether constituents support SA alone, in combination, or in a nicotine solution (Arnold et al. 2014; Bardo et al. 1999; Belluzzi et al. 2005; Brennan et al. 2013, 2015; Caine et al. 2014; Clemens et al. 2009; Smith et al. 2015). The state of this science is still in its infancy, but the SA model is being used as the gold standard for assessing whether these constituents alter the abuse liability of nicotine.

Self-administration as a tool for understanding risk factors for nicotine reinforcement and dependence—While many individuals experiment with smoking, only a subset of the population transitions to regular smoking, and there is a great deal of variation among regular smokers in terms of rate of smoking and successful quit attempts

(Agaku et al. 2014; Arrazola et al. 2015; Centers for Disease Control and Prevention 2011, 2012; Jamal et al. 2014). The source of this variability remains unclear, but animal models can be useful for isolating possible risk factors and better understand the relationship between each factor and nicotine reinforcement. Indeed, Goldberg and his colleagues studied variables that might contribute to the risk of acquiring nicotine SA. For example, they have shown that exposure to other drugs, like caffeine and THC, may promote the acquisition of nicotine SA (Panlilio et al. 2013; Shoaib et al. 1999). They have also shown that variability in the expression of $\alpha 4\beta 2^*$ receptors prior to any drug exposure is related to motivation to self-administer nicotine, as measured by a progressive-ratio schedule (Le Foll et al. 2009).

The impact of age, sex, and genetics on nicotine reinforcement has been evaluated in IV nicotine SA studies. Adolescents represent a particularly important subpopulation for SA research because of the ethical limitations associated with conducting human adolescent research. The majority of research in this area has demonstrated an enhanced vulnerability to the reinforcing effects of nicotine in adolescent rodents (Chen et al. 2007; Levin et al. 2003; Natividad et al. 2013), and some researchers suggest that adolescent females might be especially vulnerable (Li et al. 2014; Lynch 2009). However, two recent reports have shown that adolescent rodents may be less sensitive to low doses than adults, with no sex differences (Schassburger et al. 2016; Shram et al. 2008). Conflicting results from these studies could be due to a range of methodological factors including cue condition, training, feeding regimen, and the age of adolescents. In adults, Donny et al. (2000) showed that females acquire nicotine SA more quickly than male rats do at very low doses and respond more on a progressive-ratio schedule of reinforcement, suggesting increased motivation to obtain nicotine (Donny et al. 2000). Female rats may also respond more for higher doses of nicotine, with no difference at low to moderate doses (Chaudhri et al. 2005; Feltenstein et al. 2012; Grebenstein et al. 2013). Several studies have also shown that female rats respond at a higher rate on the inactive lever than male rats do and respond more during the time-out period than do male rats, suggesting an increased sensitivity to the cues that have previously been paired with nicotine (Chaudhri et al. 2005; Donny et al. 2000). Goldberg and his colleagues also found that there are differences between strains of rats in propensity to acquire nicotine SA (Shoaib et al. 1997).

Self-administration as a tool for understanding the neurobiology of reinforcement and dependence

—Self-administration provides a unique opportunity to investigate the brain mechanisms involved in tobacco use and nicotine dependence. Genetic and pharmacological manipulations allow for investigation of whether or not a given mechanism is sufficient and/or necessary for various nicotine SA outcomes. While most of the research in this area has focused on the cholinergic system and nicotinic receptors, Goldberg and his colleagues studied the relationship between the cholinergic and cannabinoid systems (Gamaledin et al. 2012; Scherma et al. 2008; Shoaib 2008; for a review see Scherma et al. 2016) contributing to the evaluation of potential tobacco dependence treatment medications that target the cannabinoid system (discussed below).

The work on nicotinic receptors has been useful for elucidating the role of specific subunits of the nAChR. It is now known that knockout mice missing the $\beta 2$ nAChR subunit will not

self-administer nicotine (Epping-Jordan et al. 1999; Picciotto et al. 1998; Pons et al. 2008), and this is strong evidence that $\beta 2$ subunits are necessary for nicotine reinforcement. Evidence regarding the $\alpha 4$ subunit is more mixed, with one study showing that knockout mice missing the $\alpha 4$ subunit will not self-administer nicotine into the tail vein (Pons et al. 2008) and another study showing they have similar rates of SA when a more traditional procedure is used (Cahir et al. 2011). Knock-in mice, which have $\alpha 4$ receptor subunits that are hypersensitive, show increased nicotine SA (30 $\mu\text{g/kg}$ / infusion) (Cahir et al. 2011). Rather than contributing to reinforcement, the $\alpha 5$ receptor subunit may be involved in regulating an upper limit on nicotine intake. Knockout mice lacking the $\alpha 5$ subunit self-administer nicotine at higher rates and at higher doses than do rats with the $\alpha 5$ subunit. Re-expressing the $\alpha 5$ subunit in the medial habenular removed this effect (Fowler et al. 2011).

Self-administration as a tool for medication development—Goldberg's work on the cannabinoid system led to an interest in whether drugs that target this system had potential as smoking cessation aids (Gamaledin et al. 2013; Le Foll and Goldberg, 2005; Schindler et al. 2016). However, his contributions extended to other neural targets including α -type peroxisome proliferator-activated receptors (PPAR α) (Justinova et al. 2015; Panlilio et al. 2012), group II metabotropic glutamate receptors (mGluR2 and mGluR3) (Justinova et al. 2015, 2016), dopamine receptors (Yan et al. 2012), and $\alpha 1$ -adrenoreceptors (Forget et al. 2010). Clearly, the SA model has emerged as the gold standard for medication development (Chang et al. 2015; Cippitelli et al. 2015; George et al. 2011; Lee et al. 2014; Le Foll et al. 2012; Levin et al. 2008, 2010, 2011 O'Connor et al. 2010; Rollema et al. 2007a, 2007b; Shoaib and Buhidma 2016).

Self-administration studies have been useful in understanding the mechanism by which smoking cessation medications impact smoking. Some medications decrease the impact of nicotine withdrawal, but they may also decrease acute reinforcement from smoking or enhance the value of other reinforcers. As first established in 1967 by Lucchesi and colleagues (discussed earlier), delivering continuous infusions of nicotine (a model of nicotine replacement therapy) can decrease nicotine SA (LeSage et al. 2002, 2003; Lucchesi et al. 1967). Likewise, pretreatment with varenicline decreases nicotine SA (George et al. 2011; Le Foll et al. 2012; O'Connor et al. 2010; Rollema et al. 2007b). Interestingly, although varenicline itself is not self-administered, it increases responding for a modestly reinforcing stimulus (Schassburger et al. 2015), suggesting that it may facilitate smoking cessation because it substitutes for nicotine's reinforcement enhancing effect. Data on bupropion are less clear. In some cases, bupropion has been shown to decrease nicotine SA (Rauhut et al. 2003, 2005), but in others, it increases nicotine SA or shows no change (Rauhut et al. 2003; Shoaib et al. 2003), and researchers have suggested that this depends on the dose of bupropion as well as the rate of responding for nicotine. Like varenicline, bupropion can increase responding for a moderately reinforcing visual stimulus, so it may also function to facilitate smoking cessation by acting as a reinforcement enhancer (Palmatier et al. 2009).

Self-administration as a tool to guide potential tobacco regulation—One of the more novel ways in which nicotine SA is being utilized is as a tool for the ongoing science

of tobacco regulation (Donny et al. 2012). The 2009 Act granting FDA authority to regulate tobacco emphasized the importance of the science base for regulation (US Congress 2009). One area of regulatory science addresses the concept of FDA setting a limit (“performance standard”) on the nicotine in cigarettes to reduce their risk of producing dependence (Benowitz and Henningfield 1994, 2013; Benowitz et al. 2016; Donny et al. 2014; Henningfield et al. 1998; World Health Organization 2015). FDA- and NIH-supported clinical trials have begun to evaluate this concept in human volunteers (Benowitz et al. 2012; Donny et al. 2015; Hatsukami et al. 2010, 2013). Preclinical IV SA research that has evaluated the threshold nicotine dose for maintaining behavior suggests that threshold likely lies between 3.75 and 7.5 µg/kg/infusion delivered over approximately 1 s (Grebstein et al. 2013, 2015; Smith et al. 2013). The threshold nicotine dose for maintaining behavior appears the same regardless of whether nicotine is reduced gradually across sessions or immediately from one session to the next (Smith et al. 2013). Furthermore, this threshold appears to be similar for acquisition of SA in rats that do not have a history with higher doses of nicotine (Smith et al. 2014). The threshold is similar in males and females, but females have higher levels of baseline intake and lower levels of compensation (Grebstein et al. 2013). Nicotine metabolism rate may also predict the threshold nicotine dose for maintaining behavior, with faster metabolizers having lower thresholds (Grebstein et al. 2015). Although in early stages, IV SA models appear promising in informing FDA evaluation of this regulatory approach.

Discussion

The consequences of the IV nicotine SA studies by Goldberg and others helped to fundamentally change the conception of cigarette smoking from “habituation” or “habit” to that of a true drug addiction or dependence disorder as concluded in the 1988 Surgeon General’s report (US DHHS 1988), the FDA (1995, 1996), and the World Health Organization (2007, 2012, 2016a) (see Table 4). This had far-reaching implications for tobacco control efforts aimed at preventing the development of tobacco dependence and promoting and aiding cessation efforts (US DHHS 2014; WHO 2016a). The understanding of nicotine as an addictive drug and smoking as a dependence disorder incentivized pharmaceutical companies to develop medications. It was also critical in FDA’s determination that it had the authority to regulate cigarettes as drugs on the premise that people used them for their dependence producing and other effects (Ballin 1991; FDA 1995, 1996; Kessler 2001; Schultz 1997; US Congress 2009). Today, ongoing IV nicotine SA research is funded by the FDA and NIH to continue to advance the science base for tobacco control efforts including tobacco product regulation with much of this research supported by user fees collected from the tobacco industry (FDA 2016a).

There were also far-reaching consequences for litigation efforts against the tobacco industry. Put simply, as concluded in a Tobacco Institute document, “... the entire matter of addiction is the most potent weapon a prosecuting attorney can have in a lung cancer/cigarette case. We can’t defend continued smoking as ‘free choice’ if the person was ‘addicted’ (Knopick 1980; Henningfield et al. 2006b).” Furthermore, these findings were important in litigation that was settled with or won against major US tobacco companies in Mississippi in 1997, in Florida in 1997, in Texas in 1998, and in Minnesota in 1998, by 46 US State Attorney

Generals in 1998 and by the US Department of Justice in 2006 (Henningfield et al. 2006b; Hurt et al. 2009, US District Court 2006). This litigation included the core premise that tobacco products are appropriately categorized as producing dependence.

Of particular relevance to tobacco product regulation is the understanding that the reinforcing effectiveness and hence addictiveness of tobacco products is not simply a function of nicotine but that the associated sensory stimuli are also important. Part of the key to the addictiveness of nicotine in tobacco products is likely the sensory factors modeled by Goldberg and colleagues as described in their 1981 publication: *“If nicotine smoking, it is likely that its reinforcing effects are magnified by interactions with interceptive [e.g., CNS drug effects] and exteroceptive [e.g., environmental and sensory] stimuli associated with smoking such as taste, tactile sensation, and social setting. The temporal contiguity of these stimuli with the reinforcing effects of nicotine may result in the stimuli’s acquiring conditioned reinforcing properties which further strengthen behavior. Consequently, nicotine might function more effectively to maintain self-administration behavior by laboratory animals if it were studied under conditions in which responding resulted not only in nicotine injections but also in presentations of environmental stimuli associated with injections”* (p. 573).

Further, *“There has been a continuing need for a sensitive laboratory method for evaluating the reinforcing effects of nicotine”* (p. 575).

Goldberg’s model and findings from that model (as reflected in the above quote) capture the reality that there is low addiction risk for some forms of nicotine (e.g., nicotine gum) and very high in others forms (e.g., tobacco cigarette). As much as we have learned about the determinants of nicotine’s effects, there is still need for research to examine the diverse sensory effects related to stimuli provided by tobacco products (e.g., organoleptic stimuli including tactile, visual, olfactory, and flavor sensations) and their packaging and marketing, as discussed elsewhere (Henningfield et al. 2011; National Cancer Institute 2008; Scientific Committee on Emerging and Newly Identified Health Risks 2010; U.S. DHHS 2010; WHO 2007, 2012). An application of this knowledge is the refinement of existing medicines and or development of new products (e.g., modified risk tobacco products, electronic nicotine delivery systems) that have the potential to be substitutes for smoking without the same degree of abuse potential.¹ Current NRT products, despite their limitations in attractiveness and abuse liability, were steps in that direction and demonstrated the concept.

Going forward in public health efforts to control tobacco use and disease, IV nicotine SA studies may be of increasing importance as implied in the 2014 Surgeon General’s report which discussed the potential importance of novel alternative nicotine delivery systems for mass migration away from combusted tobacco products for those who are unable or unwilling to completely give up some form of tobacco and nicotine (US DHHS 2014). For example, finding the right balance of attractiveness and abuse liability, while minimizing

¹The FDA guidance document addressing modified risk tobacco products does not advocate for zero or minimal abuse potential of a modified risk tobacco product (MRTP) but requires evidence relevant to its pharmacological abuse liability and attractiveness in behavioral studies of youth, former smokers, and vulnerable populations (FDA 2012). The level of abuse liability that is “too much” for a MRTP is not defined but will be evaluated by FDA and experts in the MRTP application review process.

hazard potential, is a major challenge for the development and regulation of electronic nicotine delivery systems (Abrams 2014, 2015; Abrams and Niaura 2015; Brandon et al. 2015; Cobb et al. 2015; Evans and Hoffman 2014; Henningfield 2014, 2015; Shihadeh and Eissenberg 2015; Truth Initiative 2015; Vansickel et al. 2012). Further understanding of sensory, environmental, and behavioral economic factors, as have already been explored in SA studies, seems essential for fully understanding these novel nicotine products.

While we have come far from the 1960 conceptualization of cigarette smoking as a voluntary habit, there is much to be done to turn the tide of one of the most devastating epidemics in history (Koop 2003, 2010; US DHHS 2014; WHO 2016a). Challenges include the following:

- Increased development and application of oral and inhalation SA models
- Increased attention to the importance of sensory factors such as menthol in the risk of developing dependence and difficulty in quitting smoking
- Increased approaches to reducing the abuse liability of combusted tobacco
- Increased attention to factors specific to alternative nicotine delivery systems, including electronic nicotine delivery systems.

Finally, while the focus of this article has been on the approach and contributions of Steven Goldberg, it is also homage to the environment and community of researchers in which he developed and worked. The field of behavioral pharmacology that provided his scientific foundation must be highlighted given that Goldberg was nurtured by behavioral pharmacology pioneers such as Kelleher, Morse, and Schuster and worked in the outstanding laboratories of the University of Michigan, Harvard, and NIDA. Given his many collaborations and lifetime of accomplishments, it is likely that his work and thinking will be contributing for generations of scientists yet to come.

Acknowledgments

The time and effort of Fant, Henningfield, and Kleykamp were supported by PinneyAssociates without input from any such commercial interests. The effort of Donny was supported by the National Institute on Drug Abuse and FDA Center for Tobacco Products (CTP) (U54 DA031659). The effort of Smith was supported by the National Cancer Institute (T32 CA186783). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration. The authors are grateful for the care and efforts of Evan Schnoll and Jonathan Gougelet with editing and referencing.

References

- Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA. 2014; 311(2):135–136. [PubMed: 24399548]
- Abrams, DB. What science says: operationalizing methods to estimate net public health impact. Data trumps dogma; Presented at the E-Cigarette Summit, Royal Society; London. November 12, 2015; 2015.
- Abrams DB, Niaura R. The importance of science-informed policy and what the data really tell us about e-cigarettes. Isr J Health Policy Res. 2015; 4(22)
- Agaku IT, King BA, Dube SRC. Centers for Disease and Prevention. Current cigarette smoking among adults—United States, 2005–2012. MMWR Morb Mortal Wkly Rep. 2014; 63(2):29–34. [PubMed: 24430098]

- American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 3. American Psychiatric Publishing; Arlington, VA: 1980. (DSM-III)
- American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 4. American Psychiatric Publishing; Arlington, VA: 1994. (DSM-IV)
- American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 5. American Psychiatric Publishing; Arlington, VA: 2013. (DSM-V)
- Arnold MM, Loughlin SE, Belluzzi JD, Leslie FM. Reinforcing and neural activating effects of norharmaline, a non-nicotine tobacco constituent, alone and in combination with nicotine. *Neuropharmacology*. 2014; 85:293–304. [PubMed: 24907588]
- Arrazola RA, Singh T, Corey CG, Husten CG, Neff LJ, Apelberg BJ, Bunnell RE, Choiniere CJ, King BA, Cox S, McAfee T, Caraballo RSC. Centers for Disease and Prevention. Tobacco use among middle and high school students—United States, 2011–2014. *MMWR Morb Mortal Wkly Rep*. 2015; 64(14):381–385. [PubMed: 25879896]
- Ator NA, Griffiths RR. Intravenous self-administration of nicotine in the baboon. *Fed Proc*. 1980; 40:298.
- Ator NA, Griffiths RR. Nicotine self-administration in baboons. *Pharmacol Biochem Behav*. 1983; 19:993–1003. [PubMed: 6657733]
- Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. *Drug Alcohol Depend*. 2003; 70:S55–S72. [PubMed: 12759197]
- Ballin, S. [Accessed 13 Sept 2016] Chairman of the Coalition on Smoking and Health, letter to the Food and Drug Administration recommending that insofar as tobacco use was sustained by the addictive drug effects of nicotine, the FDA should regulate tobacco products as drugs. 1991. <https://goo.gl/photos/zB2ri72GZiZGVdug7>
- Bardo MT, Green TA, Crooks PA, Dwoskin LP. Nicotine is self-administered intravenously by rats. *Psychopharmacology*. 1999; 146(3):290–296. [PubMed: 10541729]
- Barrett JE, Stanley JA. Maintenance of responding by squirrel monkeys under a concurrent shock-postponement, fixed-interval shock-presentation schedule. *J Exp Anal Behav*. 1980; 34(1):117–129. [PubMed: 7420009]
- Barrett ST, Bevins RA. Nicotine enhances operant responding for qualitatively distinct reinforcers under maintenance and extinction conditions. *Pharmacol Biochem Behav*. 2013; doi: 10.1016/j.pbb.2013.10.012
- Barry H. Censorship by a tobacco company. *Psychopharmacology*. 2006; 184(3):273–273. [PubMed: 16001120]
- Belluzzi JD, Wang R, Leslie FM. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. *Neuropsychopharmacology*. 2005; 30(4):705–712. [PubMed: 15496937]
- Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: The implications for tobacco regulation. *N Engl J Med*. 1994; 331(2):123–125. [PubMed: 7818638]
- Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tob Control*. 2013; 22(1):2012–050860.
- Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomark Prev*. 2012; 21(5):761–769.
- Benowitz NL, Donny EC, et al. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. *Addiction*. 2016; doi: 10.1111/add.13534
- Brady, JV., Lukas, SE. Testing drugs for physical dependence potential and abuse liability. NIDA research Monograph 52. U.S. Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse. U.S. Government Printing Office; Washington, D. C.: 1984.
- Branch MN. How research in behavioral pharmacology informs behavioral science. *J Exp Anal Behav*. 2006; 85(3):407–423. [PubMed: 16776059]
- Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Hobin JA, Ostroff JS, Shields PG, Toll BA, Tyne CA, Viswanath K, Warren GW. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. *J Clin Oncol*. 2015; 33(8):952–963. [PubMed: 25572671]

- Brandt, EN, Jr. Comprehensive Smoking Prevention Education Act, Hearing before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, Ninety-Seventh Congress, second session on H. R. 5653 and H. R 4957. March 5, 11, and 12, 1982. Serial no. 97–106. U. S. Government Printing Office; Washington: 1982. Statements of Edward N. Brandt, Jr., M. D., Assistant Secretary of Health, and Dr. C. Everett Coop, Surgeon General, Public Health Service Department of Health and Human Services, accompanied by Dr. Vincent T. DeVita, Director, National Cancer Institute, and Dr. William Pollin, Director, National Institute on Drug Abuse; p. 278-350.
- Brandt, AM. The cigarette century: the rise, fall, and deadly persistence of the product that defined America. Basic Books; New York: 2007.
- Brennan KA, Putt F, Truman P. Nicotine-, tobacco particulate matter- and methamphetamine-produced locomotor sensitisation in rats. *Psychopharmacology*. 2013; 228(4):659–672. [PubMed: 23519574]
- Brennan KA, Crowther A, Putt F, Roper V, Waterhouse U, Truman P. Tobacco particulate matter self-administration in rats: differential effects of tobacco type. *Addict Biol*. 2015; 20(2):227–235. [PubMed: 24750334]
- Buffalari DM, Marfo NY, Smith TT, Levin ME, Weaver MT, Thiels E, Sved AF, Donny EC. Nicotine enhances the expression of a sucrose or cocaine conditioned place preference in adult male rats. *Pharmacol Biochem Behav*. 2014; 124:320–325. [PubMed: 24967870]
- Caggiula AR, Donny EC, Palmatier MI, Liu X, Chaudhri N, Sved AF. The role of nicotine in smoking: a dual-reinforcement model. *Neb Symp Motiv*. 2009; 55:91–109.
- Cahir E, Pillidge K, Drago J, Lawrence AJ. The necessity of $\alpha 4\beta 2$ nicotinic receptors in nicotine-driven behaviors: dissociation between reinforcing and motor effects of nicotine. *Neuropsychopharmacology*. 2011; 36(7):1505–1517. [PubMed: 21430644]
- Caine SB, Collins GT, Thomsen M, Wright C, Lanier RK, Mello NK. Nicotine-like behavioral effects of the minor tobacco alkaloids nornicotine, anabasine, and anatabine in male rodents. *Exp Clin Psychopharmacol*. 2014; 22(1):9–22. [PubMed: 24490708]
- Calderon SN, Klein M. A regulatory perspective on the abuse potential evaluation of novel stimulant drugs in the United States. *Neuropharmacology*. 2014; 87:97–103. [PubMed: 24727212]
- Campbell, WI. Testimony of William I. Campbell, President, Philip Morris U. S. A., accompanied by Kathy Ellis, Director of Research; James W. Johnston, Chairman, RJ Reynolds Tobacco Co., accompanied by Andy Schindler, Head of Manufacturing, and Richard Cooper, counsel; Thomas E. Sandefur, Jr., Chairman, Brown & Williamson Tobacco Corp., accompanied by Tilford F. Riehl, Vice President; Andrew H. Tisch, Chairman, Lorillard Tobacco Co., accompanied by Alexander Spears III, Vice Chairman; Donald S. Johnston, President, American Tobacco Co.; Edward A. Horrigan, Jr., Chairman, Liggett Group, Inc.; and Joseph Taddeo, President, U.S. Tobacco Co. Regulation of Tobacco Products (part 1) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session. March 25 and April 14, 1994. Serial no. 103–149. U. S. Government Printing Office; Washington, D. C: 1994. p. 542-546.
- Campbell, ND. Discovering addiction. The University of Michigan Press; Ann Arbor: 2007.
- Campbell ND. The history of a public science: how the addiction research center became the NIDA intramural research program. 2009; 107(1):108–112.
- Carter LP, Griffiths RR. Principles of laboratory assessment of drug abuse liability and implications for clinical development. *Drug Alcohol Depend*. 2009; 105(suppl 1):S15–S25.
- Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. *Cancer Epidemiol Biomark Prev*. 2009; 18:3241–3262.
- Centers for Disease and C. and Prevention. Quitting smoking among adults—United States, 2001–2010. *MMWR Morb Mortal Wkly Rep*. 2011; 60(44):1513–1519. [PubMed: 22071589]
- Centers for Disease and C. and Prevention. Current tobacco use among middle and high school students—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012; 61(31):581–585. [PubMed: 22874835]
- Chang Q, Hanania T, Mash DC, Maillet EL. Noribogaine reduces nicotine self-administration in rats. *J Psychopharmacol*. 2015; 29(6):704–711. [PubMed: 25995321]

- Chaudhri N, Caggiula AR, Donny EC, Booth S, Gharib MA, Craven LA, Allen SS, Sved AF, Perkins KA. Sex differences in the contribution of nicotine and nonpharmacological stimuli to nicotine self-administration in rats. *Psychopharmacology*. 2005; 180(2):258–266. [PubMed: 15682294]
- Chen H, Matta SG, Sharp BM. Acquisition of nicotine self-administration in adolescent rats given prolonged access to the drug. *Neuropsychopharmacology*. 2007; 32(3):700–709. [PubMed: 16794562]
- Cippitelli A, Wu J, et al. AT-1001: a high-affinity alpha3beta4 nAChR ligand with novel nicotine-suppressive pharmacology. *Br J Pharmacol*. 2015; 172(7):1834–1845. [PubMed: 25440006]
- Clemens KJ, Caille S, Stinus L, Cador M. The addition of five minor tobacco alkaloids increases nicotine-induced hyperactivity, sensitization and intravenous self-administration in rats. *Int J Neuropsychopharmacol*. 2009; 12(10):1355–1366. [PubMed: 19366487]
- Clemens KJ, Caille S, Cador M. The effects of response operandum and prior food training on intravenous nicotine self-administration in rats. *Psychopharmacology*. 2010; 211(1):43–54. [PubMed: 20437028]
- Cobb CO, Hendricks PS, Eissenberg T. Electronic cigarettes and nicotine dependence: evolving products, evolving problems. *BMC Medicine*. 2015; 13(1):1–4. [PubMed: 25563062]
- Cohen A, Koob GF, George O. Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. *Neuropsychopharmacology*. 2012; 37(9):2153–2160. [PubMed: 22549121]
- Committee on Problems of Drug Dependence. Testing for dependence liabilities in animals and man (revised 1972). *Bull Narc*. 1973; 25:25–39.
- Corrigall, WA. A rodent model for nicotine self-administration. In: Boulton, A. Baker, G., Wu, P., editors. *Neuromethods*. Humana Press, Clifton; New Jersey: 1992. p. 315–344.
- Corrigall WA. Nicotine self-administration in animals as a dependence model. *Nicotine Tob Res*. 1999; 1:11–20. [PubMed: 11072385]
- Corrigall WA, Coen KM. Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology*. 1989; 99(4):473–478. [PubMed: 2594913]
- Corrigall WA, Coen KM. Opiate antagonists reduce cocaine but not nicotine self-administration. *Psychopharmacology*. 1991a; 104:167–170. [PubMed: 1876660]
- Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology*. 1991b; 104:171–176. [PubMed: 1876661]
- Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS. The mesolimbic dopamine system is implicated in the reinforcing effects of nicotine. *Psychopharmacology*. 1992; 107:285–289. [PubMed: 1615127]
- Corrigall WA, Coen KM, Adamson KL. Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. *Brain Res*. 1994; 653:278–284. [PubMed: 7982062]
- Deneau GA, Inoki R. Nicotine self-administration in monkeys. *Ann N Y Acad Sci*. 1967; 142:227–279.
- Deneau GA, Yanagita T, Seevers MH. Self-administration of psycho-active substances by the monkey. *Psychopharmacologia (Berl)*. 1969; 16:30–48.
- DeNoble, VJ. Regulation of Tobacco Products (Part 2) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session (Serial No. 103–153). U. S. Government Printing Office; Washington, D. C.: 1994. Testimony of Victor John DeNoble, senior behavior analyst, Delaware Community Mental Retardation Program, accompanied by Paul C. Mele, Armed Forces Radiobiology Research Institute; p. 4–156.
- DeNoble VJ, Mele PC. Intravenous nicotine self-administration in rats: effects of mecamylamine, hexamethonium and naloxone. *Psychopharmacology*. 2006; 184:266–272. [PubMed: 16088413]
- Diergaarde L, van Mourik Y, Pattij T, Schoffelemeier AN, De Vries TJ. Poor impulse control predicts inelastic demand for nicotine but not alcohol in rats. *Addict Biol*. 2012; 17(3):576–587. [PubMed: 21966927]
- Donny EC, Caggiula AR, Knopf S, Brown C. Nicotine self-administration in rats. *Psychopharmacology*. 1995; 122(4):390–394. [PubMed: 8657839]

- Donny EC, Caggiula AR, Mielke MM, Booth S, Gharib MA, Hoffman A, Maldovan V, Shupenko C, McCallum SE. Nicotine self-administration in rats on a progressive ratio schedule of reinforcement. *Psychopharmacology*. 1999; 147(2):135–142. [PubMed: 10591880]
- Donny EC, Caggiula AR, Rowell PP, Gharib MA, Maldovan V, Booth S, Mielke MM, Hoffman A, McCallum S. Nicotine self-administration in rats: estrous cycle effects, sex differences and nicotinic receptor binding. *Psychopharmacology*. 2000; 151(4):392–405. [PubMed: 11026746]
- Donny EC, Chaudhri N, Caggiula AR, Evans-Martin FF, Booth S, Gharib MA, Clements LA, Sved AF. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology*. 2003; 169(1):68–76. [PubMed: 12774186]
- Donny EC, Taylor TG, LeSage MG, Levin M, Buffalari DM, Joel D, Sved AF. Impact of tobacco regulation on animal research: new perspectives and opportunities. *Nicotine Tob Res*. 2012; 14(11):1319–1338. [PubMed: 22949581]
- Donny EC, Hatsukami DK, et al. Reduced nicotine product standards for combustible tobacco: Building an empirical basis for effective regulation. *Prev Med*. 2014:17–22.
- Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al' Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med*. 2015; 373(14):1340–1349. [PubMed: 26422724]
- Dougherty J, Miller D, Togg G, Kostenbauder HB. Reinforcing and other behavioral effects of nicotine. *Neurosci Biobehav*. 1981; 5:487–495.
- Drug Enforcement Administration (DEA). Title 21 United States Code (USC) Controlled Substances Act. Department of Justice, Drug Enforcement Administration; Springfield, VA: 2016.
- Epping-Jordan MP, Picciotto MR, Changeux JP, Pich EM. Assessment of nicotinic acetylcholine receptor subunit contributions to nicotine self-administration in mutant mice. *Psychopharmacology*. 1999; 147(1):25–26. [PubMed: 10591862]
- Evans SE, Hoffman AC. Electronic cigarettes: abuse liability, topography and subjective effects. *Tob Control*. 2014; 23(suppl 2):i23–ii29. [PubMed: 23792324]
- Expert Panel, The. Abuse liability assessment of CNS drugs: conclusions, recommendations, and research priorities. *Drug Alcohol Depend*. 2003; 70(3 suppl):S107–S114. [PubMed: 12759201]
- Feltenstein MW, Ghee SM, See RE. Nicotine self-administration and reinstatement of nicotine-seeking in male and female rats. *Drug Alcohol Depend*. 2012; 121(3):240–246. [PubMed: 21945235]
- Food and Drug Administration (FDA). Regulations restricting the sale and distribution of cigarettes and smokeless tobacco products to protect children and adolescents; proposed rule analysis regarding FDA's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products; notice. Department of Health and Human Services, Food and Drug Administration. Federal Register. Vol. 60. Silver Spring, MD; 1995. p. 41314–41792.
- Food and Drug Administration (FDA). Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents; final rule. Department of Health and Human Services, Food and Drug Administration. Federal Register. Vol. 61. Silver Spring, MD; 1996. p. 44396–45318.
- Food and Drug Administration (FDA). Guidance for industry: assessment of abuse potential of drugs, draft guidance. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Silver Spring, MD: 2010a.
- Food and Drug Administration (FDA). Report to Congress: progress and effectiveness of the implementation of the Family Smoking Prevention and Tobacco Control Act. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Silver Spring, MD: 2010b.
- Food and Drug Administration (FDA). Guidance for industry: modified risk tobacco product applications, draft guidance. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products. Silver Spring, MD: 2012.

- Food and Drug Administration (FDA). Abuse-deterrent opioids— evaluation and labeling. guidance for industry. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Silver Spring; MD: 2015.
- Food and Drug Administration (FDA). [Accessed 31 Aug 2016] User fees. FDA. 2016a. <http://www.fda.gov/TobaccoProducts/Guidance/ComplianceRegulatoryInformation/Manufacturing/ucm417012.htm>
- Food and Drug Administration (FDA). [Accessed 12 Sept 2016] Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. (Docket No. FDA-2014-N-0189). Federal Register. 2016b. <https://www.federalregister.gov/articles/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the>
- Forget B, Wertheim C, et al. Noradrenergic [alpha]1 receptors as a novel target for the treatment of nicotine addiction. *Neuropsychopharmacology*. 2010; 35(8):1751–1760. [PubMed: 20357760]
- Fowler CD, Lu Q, Johnson PM, Marks MJ, Kenny PJ. Habenular alpha5 nicotinic receptor subunit signalling controls nicotine intake. *Nature*. 2011; 471(7340):597–601. [PubMed: 21278726]
- Gamaledin I, Wertheim C, et al. Cannabinoid receptor stimulation increases motivation for nicotine and nicotine seeking. *Addict Biol*. 2012; 17(1):47–61. [PubMed: 21521420]
- Gamaledin I, Guranda M, et al. AM404 attenuates reinstatement of nicotine seeking induced by nicotine-associated cues and nicotine priming but does not affect nicotine- and food-taking. *J Psychopharmacol*. 2013; 27(6):564–571. [PubMed: 23427192]
- Garcia KL, Le AD, Tyndale RF. Effect of food training and training dose on nicotine self-administration in rats. *Behav Brain Res*. 2014; 274:10–18. [PubMed: 25101539]
- George O, Lloyd A, et al. Varenicline blocks nicotine intake in rats with extended access to nicotine self-administration. *Psychopharmacology*. 2011; 213(4):715–722. [PubMed: 20924754]
- Goldberg, SR. Relapse to opioid dependence: the role of conditioning. In: Harris, RT, McIsaac, WM., Schuster, CR., Jr, editors. *Drug dependence*. University of Austin Texas Press; Austin and London: 1970. p. 170-197.
- Goldberg, SR. Control of behavior by stimuli associated with drug injections. In: Goldberg, L., Hoffmeister, F., editors. *Psychic dependence*. Springer-Uerlag; Berlin: 1973. p. 1-7.
- Goldberg, SR. The behavioral analysis of drug addiction. In: Glick, SD., Goldfarb, J., editors. *Behavioral pharmacology*. C. V. Mosby Company; Saint Louis: 1976. p. 283-316.
- Goldberg SR. Histamine as a punisher in squirrel monkeys: effects of pentobarbital, chlordiazepoxide and H1- and H2-receptor antagonists on behavior and cardiovascular responses. *J Pharmacol Exp Ther*. 1980; 214(3):726–736. [PubMed: 6105208]
- Goldberg SR, Henningfield JE. Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. *Pharmacol Biochem Behav*. 1988; 30(1):227–234. [PubMed: 3051048]
- Goldberg SR, Kelleher RT. Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. *J Exp Anal Behav*. 1976; 25:93–104. [PubMed: 814192]
- Goldberg SR, Schuster CR. Conditioned nalorphine-induced abstinence changes: persistence in post morphine-dependent monkeys. *J Exp Anal Behav*. 1970; 14(1):33–46. [PubMed: 4988589]
- Goldberg SR, Spealman RD. Maintenance and suppression of responding by intravenous nicotine injections in squirrel monkeys. *Fed Proc*. 1982; 41:216–220. [PubMed: 7060749]
- Goldberg SR, Spealman RD. Suppression of behavior by intravenous injections of nicotine or by electric shocks in squirrel monkeys: effects of chlordiazepoxide and mecamylamine. *J Pharmacol Exp Ther*. 1983; 224(2):334–339. [PubMed: 6822959]
- Goldberg SR, Tang AH. Behavior maintained under second-order schedules of intravenous morphine injection in squirrel and rhesus monkeys. *Psychopharmacology*. 1977; 51(3):235–242. [PubMed: 403538]
- Goldberg SR, Hoffmeister F, Schlichting UU, Wuttke W. A comparison of pentobarbital and cocaine self-administration in rhesus monkeys: effects of dose and fixed-ratio parameter. *J Pharmacol Exp Ther*. 1971; 179(2):277–283. [PubMed: 5002482]

- Goldberg SR, Kelleher RT, Morse WH. Second-order schedules of drug injection. *Fed Proc.* 1975; 34(9):1771–1776. [PubMed: 1149889]
- Goldberg SR, Morse WH, Goldberg DM. Behavior maintained under a second-order schedule by intramuscular injection of morphine or cocaine in rhesus monkeys. *J Pharm Exp Ther.* 1976; 199:278–286.
- Goldberg SR, Spealman RD, Kelleher RT. Enhancement of drug-seeking behavior by environmental stimuli associated with cocaine or morphine injections. *Neuropharmacology.* 1979; 18:1015–1017. [PubMed: 119167]
- Goldberg SR, Spealman RD, Goldberg DM. Persistent high-rate behavior maintained by intravenous self-administration of nicotine. *Science.* 1981; 214:573–575. [PubMed: 7291998]
- Grebenstein PE, Burroughs D, et al. Sex differences in nicotine self-administration in rats during progressive unit dose reduction: implications for nicotine regulation policy. *Pharmacol Biochem Behav.* 2013; 114–115:70–81.
- Grebenstein PE, Burroughs D, Roiko SA, Pentel PR, LeSage MG. Predictors of the nicotine reinforcement threshold, compensation, and elasticity of demand in a rodent model of nicotine reduction policy. *Drug Alcohol Depend.* 2015; 151:181–193. [PubMed: 25891231]
- Griffiths, RR., Brady, JV., Bradford, LD. Predicting the abuse liability of drugs with animal drug self-administration procedures: psychomotor stimulants and hallucinogens. In: Thompson, T., Dews, PB., editors. *Advances in behavioral pharmacology.* Vol. 2. Academic Press; New York: 1979. p. 163-208.
- Griffiths, RR., Bigelow, GE., Henningfield, JE. Similarities in animal and human drug taking behavior. In: Mello, NK., editor. *Advances in substance abuse.* JAI Press; Greenwich, CT: 1980. p. 1-90.
- Gritz, ER. Patterns of puffing in cigarette smokers. In: Krasnegor, NA., editor. *Self-administration of abused substances: methods for study.* U.S. Government Printing Office; Washington, D. C: 1978. p. 221-235.
- Hanson, HM., Ivester, CA., Morton, BR. Nicotine self-administration in rats. In: Krasnegor, NA., editor. *Cigarette smoking as a dependence process.* U.S. Government Printing Office; Washington, D. C: 1979. p. 70-90.
- Harvey DM, Yasar S, Heishman SJ, Panlilio LV, Henningfield JE, Goldberg SR. Nicotine serves as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. *Psychopharmacology.* 2004; 175:134–142. [PubMed: 14997277]
- Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, Hecht SS. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction.* 2010; 105(2):343–355. [PubMed: 20078491]
- Hatsukami DK, Hertsgaard LA, Vogel RI, Jensen JA, Murphy SE, Hecht SS, Carmella SG, al' Absi M, Joseph AM, Allen SS. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiol Biomark Prev.* 2013; 22(6):1015–1024.
- Henningfield, JE. Behavioral pharmacology of cigarette smoking. In: Thompson, T., Dews, PB., Barrett, JE., editors. *Advances in behavioral pharmacology.* Vol. 4. Academic Press, Inc; New York: 1984. p. 132-198.
- Henningfield, JE. Statement of David A. Kessler, Commissioner of Food and Drugs, Food and Drug Administration, accompanied by Jack E. Henningfield, chief, clinical pharmacology branch, National Institute on Drug Abuse. In: *Regulation of Tobacco Products (part 1) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session. March 25 and April 14, 1994. Serial no. 103–149.* U. S. Government Printing Office; Washington, D. C: 1994a. p. 28-71.
- Henningfield, JE. Regulation of Tobacco Products (part 1) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session. March 25 and April 14, 1994. Serial no. 103–149. U. S. Government Printing Office; Washington, D. C: 1994b. Letter to Henry Waxman, May 3, 1994; p. 37
- Henningfield, JE. [Accessed 31 Aug 2016] Testimony in United States of America v. Philip Morris USA, Inc. Litigation Against Tobacco Companies Home. U. S. Department of Justice. 2004.

https://www.justice.gov/sites/default/files/civil/legacy/2014/09/11/Henningfield%20Written%20Direct_0.pdf

- Henningfield JE. Tobacco psychopharmacology and public health policy: it takes a community. *Exp Clin Psychopharmacol*. 2011; 19(4):249–262. [PubMed: 21728446]
- Henningfield JE. The tobacco endgame: It's all about behavior. *Prev Med*. 2014; 68:11–16. [PubMed: 25236479]
- Henningfield, JE. Pharmacokinetic and dynamic factors in abuse potential: Historical perspectives from research on opioids, stimulants and nicotine; Symposium X: The interplay of pharmacokinetics and pharmacodynamics in abuse potential: Modeling madness? College on Problems of Drug Dependence annual meeting; Arizona Biltmore, Phoenix. June 13–18, 2015; 2015.
- Henningfield JE, Goldberg SR. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacol Biochem Behav*. 1983a; 19(6):989–992. [PubMed: 6657732]
- Henningfield JE, Goldberg SR. Control of behavior by intravenous nicotine injections in human subjects. *Pharmacol Biochem Behav*. 1983b; 19:1021–1026. [PubMed: 6657720]
- Henningfield JE, Zeller M. Nicotine psychopharmacology research contributions to United States and global tobacco regulation: a look back and a look forward. *Psychopharmacology*. 2006; 184:286–291. [PubMed: 16463054]
- Henningfield, JE., Griffiths, RR., Jasinski, DR. Human dependence on tobacco and opioids: common factors. In: Thompson, T., Johanson, CE., editors. *Behavioral pharmacology of human drug dependence*. U. S. Government Printing Office; Washington, D.C: 1981. p. 210-234.
- Henningfield JE, Miyasato K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav*. 1983; 19:887–890. [PubMed: 6647522]
- Henningfield, JE., Nemeth-Coslett, R., Katz, JL., Goldberg, SR. Intravenous cocaine self-administration by human volunteers: second-order schedules of reinforcement. In: Harris, LS., editor. *Problems of drug dependence, 1986. NIDA research monograph 76*, Department of Health and Human Services. U. S. Government Printing Office; Washington, D. C: 1987. p. 266-273.
- Henningfield JE, Benowitz NL, et al. Reducing the addictiveness of cigarettes. Council on scientific affairs, American Medical Association. *Tob Control*. 1998; 7(3):281–293. [PubMed: 9825424]
- Henningfield JE, Stolerman IP, Miczek KA. Nicotine psychopharmacology research: advancing science, public health, and global policy. *Psychopharmacology*. 2006a; 184:263–265. [PubMed: 16463193]
- Henningfield JE, Rose CA, Zeller M. Tobacco industry litigation position on addiction: continued dependence on past views. *Tob Control*. 2006b; 15(Suppl 4):v27–iv36.
- Henningfield JE, Shiffman S, et al. Tobacco dependence and withdrawal: science base, challenges and opportunities for pharmacotherapy. *Pharmacol Ther*. 2009; 123(1):1–16. [PubMed: 19362108]
- Henningfield JE, Hatsukami DK, Zeller M, Peters E. Conference on abuse liability and appeal of tobacco products: conclusions and recommendations. *Drug Alcohol Depend*. 2011; 116(1–3):1–7. [PubMed: 21376479]
- Howell, LL., Fantegrossi, WE. Intravenous drug self-administration in nonhuman primates. In: Buccafusco, JJ., editor. *Methods of behavior analysis in neuroscience*. 2. CRC Press/Taylor & Francis; Boca Raton: 2009. Chapter 9
- Hursh SR, Roma PG. Behavioral economics and empirical public policy. *J Exp Anal Behav*. 2013; 99(1):98–124. [PubMed: 23344991]
- Hurt RD, Ebbert JO, Muggli ME, Lockhart NJ, Robertson CR. Open doorway to the truth: legacy of the Minnesota tobacco trial. *Mayo Clin Proc*. 2009; 84(5):446–456. [PubMed: 19411441]
- Jamal A, Agaku IT, O'Connor E, King BA, Kenemer JB, Neff L. Current cigarette smoking among adults—United States, 2005–2013. *MMWR Morb Mortal Wkly Rep*. 2014; 63(47):1108–1112. [PubMed: 25426653]
- Jarvik, ME., Cullen, JW., Gritz, ER., Vogt, TM., West, LJ. Research on smoking behavior. NIDA research monograph 17. Department of Health, Education and Welfare; Washington, D.C: 1979.
- Justinova Z, Panlilio LV, et al. Effects of fatty acid amide hydrolase (FAAH) inhibitors in non-human primate models of nicotine reward and relapse. *Neuropsychopharmacology*. 2015; 40(9):2185–2197. [PubMed: 25754762]

- Justinova Z, Le Foll B, et al. Differential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on nicotine versus cocaine self-administration and relapse in squirrel monkeys. *Psychopharmacology*. 2016; 233(10):1791–1800. [PubMed: 26149611]
- Kessler, D. Regulation of Tobacco Products (part 1) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session. March 25 and April 14, 1994. Serial no. 103–149. U. S. Government Printing Office; Washington, D. C: 1994. Statement of David A. Kessler, Commissioner of Food and Drugs, Food and Drug Administration, accompanied by Jack E. Henningfield, chief, clinical pharmacology branch, National Institute on Drug Abuse; p. 28–71.
- Kessler D. Where there's smoke. Talk November. 1999; 1999:183–192. 229.
- Kessler, D. A question of intent: a great American battle with a deadly industry. Public Affairs; New York: 2001.
- Kluger, R. Ashes to ashes: America's hundred-year cigarette war, the public health, and the unabashed triumph of Philip Morris. Alfred A. Knopf; New York: 1996.
- Knopick, P. [Accessed 12 Sept 2016] Memo Re: National Institute of Drug Abuse desire to have 'addictive' added to cigarette warnings. 1980. <http://www.tobaccofreedom.org/issues/documents/landman/addictive/>
- Koop CE. Tobacco addiction: accomplishments and challenges in science, health, and policy. *Nicotine Tob Res*. 2003; 5:613–619. [PubMed: 14577977]
- Koop, CE. Tobacco: the public health disaster of the twentieth century. In: Boyle, P.Gray, N.Henningfield, JE.Seffrin, J., Zatoński, W., editors. Tobacco an public health: science and policy. 2. Oxford University Press; Oxford: 2010. v-xvii
- Krasnegor, NA., editor. Self-administration of abused substances: methods for study. NIDA research monograph 20. National Institute on Drug Abuse; Rockville, MD: 1978.
- Krasnegor, NA. Cigarette smoking as a dependence process. NIDA research monograph 23. U. S. Department of Health, Education, and Welfare, Public Health Service; Washington, D. C: 1979a.
- Krasnegor, NA. The behavioral aspects of smoking. NIDA research monograph 26. U. S. Department of Health, Education, and Welfare, Public Health Service; Washington, D. C: 1979b.
- Lamb RJ, Preston KL, Schindler CW, Meisch RA, Davis F, Katz JL, Henningfield JE, Goldberg SR. The reinforcing and subjective effects of morphine in post-addicts: a dose-response study. *J Pharmacol Exp Ther*. 1991; 259(3):1165–1173. [PubMed: 1762068]
- Lang WJ, Latiff AA, McQueen A, Singer G. Self-administration of nicotine with and without a food delivery schedule. *Pharmacol Biochem Behav*. 1977; 7:65–70. [PubMed: 905328]
- Latties VG. Behavior analysis and the growth of behavioral pharmacology. *Behav Anal*. 2003; 26(2): 235–252. [PubMed: 22478405]
- Latiff AA, Smith LA, Lang WJ. Effects of changing dosage and urinary pH in rats self-administering nicotine on a food delivery schedule. *Pharmacol Biochem Behav*. 1980; 13:209–213. [PubMed: 7413693]
- Le Foll B, Goldberg SR. Cannabinoid CB1 receptor antagonists as promising new medications for drug dependence. *J Pharmacol Exp Ther*. 2005; 312(3):875–883. [PubMed: 15525797]
- Le Foll B, Chefer SI, et al. Baseline expression of $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors predicts motivation to self-administer nicotine. *Biol Psychiatry*. 2009; 65(8):714–716. [PubMed: 19095220]
- Le Foll B, Chakraborty-Chatterjee M, et al. Varenicline decreases nicotine self-administration and nicotine- and cue-induced reinstatement of nicotine-seeking behavior in rats when a long pretreatment time is used. *Int J Neuropsychopharmacol*. 2012; 15(9):1265–1274. [PubMed: 21939589]
- Lee AM, Arreola AC, et al. Administration of the nicotinic acetylcholine receptor agonists ABT-089 and ABT-107 attenuates the reinstatement of nicotine-seeking behavior in rats. *Behav Brain Res*. 2014; 274:168–175. [PubMed: 25128791]
- LeSage MG, Keyler DE, et al. Continuous nicotine infusion reduces nicotine self-administration in rats with 23-h/day access to nicotine. *Pharmacol Biochem Behav*. 2002; 72(1–2):279–289. [PubMed: 11900798]

- LeSage MG, Keyler DE, et al. Effects of continuous nicotine infusion on nicotine self-administration in rats: relationship between continuously infused and self-administered nicotine doses and serum concentrations. *Psychopharmacology*. 2003; 170(3):278–228. [PubMed: 12898121]
- Levin ED, Rezvani AH, Montoya D, Rose JE, Swartzwelder HS. Adolescent-onset nicotine self-administration modeled in female rats. *Psychopharmacology*. 2003; 169(2):141–149. [PubMed: 12764575]
- Levin ED, Slade S, Johnson M, Petro A, Horton K, Williams P, Rezvani AH, Rose JE. Ketanserin, a 5-HT₂ receptor antagonist, decreases nicotine self-administration in rats. *Eur J Pharmacol*. 2008; 600(1–3):93–97. [PubMed: 18950618]
- Levin ED, Rezvani AH, Xiao Y, Slade S, Cauley M, Wells C, Hampton D, Petro A, Rose JE, Brown ML, Paige MA, McDowell BE, Kellar KJ. Sazetidine—a, a selective $\alpha 4\beta 2$ nicotinic receptor desensitizing agent and partial agonist, reduces nicotine self-administration in rats. *J Pharmacol Exp Ther*. 2010; 332(3):933–939. [PubMed: 20007754]
- Levin ED, Johnson JE, Slade S, Wells C, Cauley M, Petro A, Rose JE. Lorcaserin, a 5-HT_{2C} agonist, decreases nicotine self-administration in female rats. *J Pharmacol Exp Ther*. 2011; 338(3):890–896. [PubMed: 21636655]
- Li S, Zou S, Coen K, Funk D, Shram MJ, Le AD. Sex differences in yohimbine-induced increases in the reinforcing efficacy of nicotine in adolescent rats. *Addict Biol*. 2014; 19(2):156–164. [PubMed: 22784103]
- Lucchesi BR, Schuster CR, Emley GS. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. *Clin Pharmacol Ther*. 1967; 8(6):789–796. [PubMed: 6059284]
- Lynch WJ. Sex and ovarian hormones influence vulnerability and motivation for nicotine during adolescence in rats. *Pharmacol Biochem Behav*. 2009; 94(1):43–50. [PubMed: 19619575]
- Manzardo AM, Stein L, Belluzzi JD. Rats prefer cocaine over nicotine in a two-lever self-administration choice test. *Brain Res*. 2002; 924(1):10–19. [PubMed: 11743990]
- Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiula AR, Craig CR, Collins AC, Damaj MI, Donny EC, Gardiner PS, Grady SR, Heberlein U, Leonard SS, Levin ED, Lukas RJ, Markou A, Marks MJ, McCallum SE, Parameswaran N, Perkins KA, Picciotto MR, Quik M, Rose JE, Rothenfluh A, Schafer WR, Stolerman IP, Tyndale RF, Wehner JM, Zirger JM. Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology*. 2007; 190(3):269–319. [PubMed: 16896961]
- May EL, Jacobson AE. The committee on problems of drug dependence: a legacy of the National Academy of Sciences. A historical account. *Drug Alcohol Depend*. 1989; 23(3):183–218. [PubMed: 2666074]
- McGarity, TD., Wagner, WE. *Bending science: how special interests corrupt public health research*. Harvard University Press; Cambridge and London: 2008.
- Meisch, RA. Ethanol self-administration: infrahuman studies. In: Thompson, T., Dews, PB., editors. *Advances in behavioral pharmacology*. Vol. 1. Academic Press; New York: 1977.
- Meisch RA. Oral drug self-administration: an overview of laboratory animal studies. *Alcohol*. 2001; 24(2):117–128. [PubMed: 11522433]
- Meisch, RA., Lemaire, GA. Drug self-administration. In: van Haaren, F., editor. *Methods in behavioral pharmacology*. Elsevier Science Publishers B.V.; Amsterdam: 1993. p. 257-300.
- Meisch, RA., Thompson, T. Ethanol as a reinforcer: an operant analysis of ethanol dependence. In: Singh, JM., Lal, H., editors. *Drug addiction, vol 3: neurobiology and influences on behavior*. Symposia Specialists; Miami: 1974. p. 117-133.
- Mele, PC. Regulation of Tobacco Products (Part 2) Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, One Hundred Third Congress, Second Session (Serial No. 103–153). U. S. Government Printing Office; Washington, D. C: 1994. Testimony of Victor John DeNoble, senior behavior analyst, Delaware Community Mental Retardation Program, accompanied by Paul C. Mele, Armed Forces Radiobiology Research Institute; p. 4-156.

- National Cancer Institute. The role of the media in promoting and reducing tobacco use. Tobacco control monograph no. 19. U. S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. NIH pub. no. 07-6242. Bethesda, MD: 2008.
- National Institute on Drug Abuse (NIDA). [Accessed 30 Aug 2016] The science of drug abuse and addiction: the basics. 2014. <https://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics>
- Natividad LA, Torres OV, Friedman TC, O'Dell LE. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behav Brain Res.* 2013; 257:275–285. [PubMed: 24120402]
- O'Connor EC, Parker D, et al. The alpha4beta2 nicotinic acetylcholine-receptor partial agonist varenicline inhibits both nicotine self-administration following repeated dosing and reinstatement of nicotine seeking in rats. *Psychopharmacology.* 2010; 208(3):365–376. [PubMed: 19967529]
- O'Dell LE, Chen SA, Smith RT, Specio SE, Balster RL, Paterson NE, Markou A, Zorrilla EP, Koob GF. Extended access to nicotine self-administration leads to dependence: circadian measures, withdrawal measures, and extinction behavior in rats. *J Pharmacol Exp Ther.* 2007; 320(1):180–193. [PubMed: 17050784]
- Palmatier MI, Liu X, Matteson GL, Donny EC, Caggiula AR, Sved AF. Conditioned reinforcement in rats established with self-administered nicotine and enhanced by noncontingent nicotine. *Psychopharmacology.* 2007; 195(2):235–243. [PubMed: 17676401]
- Palmatier MI, Levin ME, Mays KL, Donny EC, Caggiula AR, Sved AF. Bupropion and nicotine enhance responding for nondrug reinforcers via dissociable pharmacological mechanisms in rats. *Psychopharmacology.* 2009; 207(3):381–390. [PubMed: 19760281]
- Panlilio LV, Goldberg SR. Self-administration of drugs in animals and humans as a model and an investigative tool. *Addiction.* 2007; 102(12):1863–1870. [PubMed: 18031422]
- Panlilio LV, Yasar S, et al. Human cocaine-seeking behavior and its control by drug-associated stimuli in the laboratory. *Neuropsychopharmacology.* 2005; 30(2):433–443. [PubMed: 15536497]
- Panlilio LV, Justinova Z, et al. Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: preclinical findings. *Neuropsychopharmacology.* 2012; 37(8):1838–1847. [PubMed: 22453137]
- Panlilio LV, Zanettini C, Barnes C, Solinas M, Goldberg SR. Prior exposure to THC increases the addictive effects of nicotine in rats. *Neuropsychopharmacology.* 2013; 38(7):1198–1208. [PubMed: 23314220]
- Panlilio LV, Hogarth L, et al. Concurrent access to nicotine and sucrose in rats. *Psychopharmacology.* 2015; 232(8):1451–1460. [PubMed: 25366874]
- Paterson NE, Markou A. Prolonged nicotine dependence associated with extended access to nicotine self-administration in rats. *Psychopharmacology.* 2004; 173(1–2):64–72. [PubMed: 14712336]
- Perkins KA, Karelitz JL. Influence of reinforcer magnitude and nicotine amount on smoking's acute reinforcement enhancing effects. *Drug Alcohol Depend.* 2013a; 133(1):167–171. [PubMed: 23768842]
- Perkins KA, Karelitz JL. Reinforcement enhancing effects of nicotine via smoking. *Psychopharmacology.* 2013b; 228(3):479–486. [PubMed: 23494236]
- Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, Fuxe K, Changeux JP. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature.* 1998; 391(6663):173–177. [PubMed: 9428762]
- Pickens R, Thompson T. Cocaine-reinforced behavior in rats: effects of reinforcement magnitude and fixed-ratio size. *J Pharmacol Exp Ther.* 1968; 161(1):122–129. [PubMed: 5648489]
- Pickens, R., Thompson, T. Cocaine-reinforced behavior in rats: effects of reinforcement magnitude and fixed-ratio size. In: Thompson, T., Pickens, R., Meisch, R.A., editors. *Readings in behavioral pharmacology.* Meredith Corporation; New York: 1970. p. 298–309.
- Pinney, JM. Preface. In: Krasnegor, NA., editor. *Cigarette smoking as a dependence process*, NIDA research monograph 23. U. S. Department of Health, Education, and Welfare; Washington, D. C: 1979.
- Poling, A., Byrne, T. *Introduction to behavioral pharmacology.* Context Press; Reno: 2000.

- Pollin, W. Comprehensive Smoking Prevention Education Act of 1981, Hearing before the Committee on Labor and Human Resources, United States Senate, Ninety-Seventh Congress, Second Session on S. 1929, To amend the Public Health Service Act and the Federal Cigarette Labeling and Advertising Act to increase the availability to the American public of information on the health consequences of smoking and thereby improve informed choice, and for other purposes, March 16, 1982. U. S. Government Office; Washington, D. C: 1982. Statement of William Pollin, M. D., Director, National Institute on Drug Abuse.
- Pons S, Fattore L, Cossu G, Tolu S, Porcu E, McIntosh JM, Changeux JP, Maskos U, Fratta W. Crucial role of alpha4 and alpha6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. *J Neurosci*. 2008; 28(47):12318–12327. [PubMed: 19020025]
- Proctor, RN. Golden holocaust: origins of the cigarette catastrophe and the case for abolition. University of California Pres; Berkeley, CA: 2012.
- Rauhut AS, Neugebauer N, Dwoskin LP, Bardo MT. Effect of bupropion on nicotine self-administration in rats. *Psychopharmacology*. 2003; 169(1):1–9. [PubMed: 12811464]
- Rauhut AS, Dwoskin LP, Bardo MT. Tolerance does not develop to the decrease in nicotine self-administration produced by repeated bupropion administration. *Nicotine Tob Res*. 2005; 7(6): 901–907. [PubMed: 16298725]
- Risner ME, Goldberg SR. A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion. *J Pharmacol Exp Ther*. 1983; 224:319–326. [PubMed: 6822957]
- Roane HS. On the applied use of progressive-ratio schedules of reinforcement. *J Appl Behav Anal*. 2008; 41(2):155–161. [PubMed: 18595280]
- Rollema H, Coe JW, et al. Rationale, pharmacology and clinical efficacy of partial agonists of alpha4beta2 nACh receptors for smoking cessation. *Trends Pharmacol Sci*. 2007a; 28(7):316–325. [PubMed: 17573127]
- Rollema H, Chambers LK, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology*. 2007b; 52(3):985–994. [PubMed: 17157884]
- Rupprecht LE, Smith TT, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Behavioral mechanisms underlying nicotine reinforcement. *Curr Top Behav Neurosci*. 2015; 24:19–53. [PubMed: 25638333]
- Russell, MAH. Tobacco dependence: is nicotine rewarding or aversive?. In: Karsnegor, NA., editor. Cigarette smoking as a dependence process, NIDA research monograph 23, Department of Health, Education, and Welfare. U. S. Government Printing Office; Washington, D. C: 1979.
- Schassburger RL, Levin ME, Weaver MT, Palmatier MI, Caggiula AR, Donny EC, Sved AF. Differentiating the primary reinforcing and reinforcement-enhancing effects of varenicline. *Psychopharmacology*. 2015; 232(5):975–983. [PubMed: 25209677]
- Schassburger RL, Pitzer EM, Smith TT, Rupprecht LE, Thiels E, Donny EC, Sved AF. Adolescent rats self-administer less nicotine than adults at low doses. *Nicotine Tob Res*. 2016
- Scherma M, Panlilio LV, et al. Inhibition of anandamide hydrolysis by URB597 reverses abuse-related behavioral and neurochemical effects of nicotine in rats. *J Pharmacol Exp Ther*. 2008; 327(2): 482–490. [PubMed: 18725543]
- Scherma M, Muntoni AL, et al. Interactions between the endocannabinoid and nicotinic cholinergic systems: preclinical evidence and therapeutic perspectives. *Psychopharmacology*. 2016; 233(10): 1765–1177. [PubMed: 26728894]
- Schindler CW, Redhi GH, et al. Blockade of nicotine and cannabinoid reinforcement and relapse by a cannabinoid CB1-receptor neutral antagonist AM4113 and inverse agonist rimonabant in squirrel monkeys. *Neuropsychopharmacology*. 2016; 41(9):2283–2293. [PubMed: 26888056]
- Schultz WB. The FDA's decision to regulate tobacco products. *Pace L Rev*. 1997; 18(1):27–39.
- Schuster, CR. [Accessed 31 Aug 2016] Interview with Dr. Charles R. Schuster, interviewed by Dr. Robert Balster. The Centennial Project. American Psychological Association, Division of Psychopharmacology and Drug Abuse. 1991. <http://apadivisions.org/division-28/about/history/centennial/schuster.pdf>

- Schuster CR, Henningfield JE. Conference on abuse liability assessment of CNS drugs. *Drug Alcohol Depend.* 2003; 70(3 Suppl):S1–S4.
- Schuster, CR., Thompson, T. Self-administration of morphine in physically dependent monkeys. University of Maryland, Laboratory of Psychopharmacology Technical Report no. 62–29; 1962.
- Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Addictiveness and attractiveness of tobacco additives. European Commission, Directorate-General for Health and Consumers, Scientific Committee on Emerging and Newly Identified Health Risks, European Union. 2010.
- Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. *Nicotine Tob Res.* 2015; 17(2):158–162. [PubMed: 25180079]
- Shoaib M. The cannabinoid antagonist AM251 attenuates nicotine self-administration and nicotine-seeking behaviour in rats. *Neuropharmacology.* 2008; 54(2):438–444. [PubMed: 18054052]
- Shoaib M, Buhidma Y. How can we improve on modeling nicotine addiction to develop better smoking cessation treatments? *Int Rev Neurobiol.* 2016; 126:121–156. [PubMed: 27055613]
- Shoaib M, Schindler WC, et al. Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. *Psychopharmacology.* 1997; 129(1):35–43. [PubMed: 9122361]
- Shoaib M, Swanner LS, Yasar S, Goldberg SR. Chronic caffeine exposure potentiates nicotine self-administration in rats. *Psychopharmacology.* 1999; 142(4):327–333. [PubMed: 10229056]
- Shoaib M, Sidhpura N, et al. Investigating the actions of bupropion on dependence-related effects of nicotine in rats. *Psychopharmacology.* 2003; 165(4):405–412. [PubMed: 12451438]
- Shram MJ, Funk D, et al. Nicotine self-administration, extinction responding and reinstatement in adolescent and adult male rats: evidence against a biological vulnerability to nicotine addiction during adolescence. *Neuropsychopharmacology.* 2008; 33(4):739–748. [PubMed: 17507913]
- Singer G, Simpson F, Lang WJ. Schedule-induced self injections of nicotine with recovered body weight. *Pharmacol Biochem Behav.* 1978; 9:387–389. [PubMed: 714988]
- Singer G, Wallace M, Hall R. Effects of dopaminergic nucleus accumbens lesions on the acquisition of schedule induced self injections of nicotine in the rat. *Pharmacol Biochem Behav.* 1982; 17:579–581. [PubMed: 7146054]
- Smith LA, Lang WJ. Changes occurring in self administration of nicotine by rats over a 28-day period. *Pharmacol Biochem Behav.* 1980; 13:215–220. [PubMed: 7413694]
- Smith TT, Levin ME, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Gradual and immediate nicotine reduction result in similar low-dose nicotine self-administration. *Nicotine Tob Res.* 2013; 15(11):1918–1925. [PubMed: 23817582]
- Smith TT, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Low-dose nicotine self-administration is reduced in adult male rats naive to high doses of nicotine: implications for nicotine product standards. *Exp Clin Psychopharmacol.* 2014; 22(5):453–459. [PubMed: 24999867]
- Smith TT, Schaff MB, Rupprecht LE, Schassburger RL, Buffalari DM, Murphy SE, Sved AF, Donny EC. Effects of MAO inhibition and a combination of minor alkaloids, beta-carbolines, and acetaldehyde on nicotine self-administration in adult male rats. *Drug Alcohol Depend.* 2015; 155:243–252. [PubMed: 26257022]
- Sorge RE, Clarke PBS. Rats self-administer intravenous nicotine delivered in a novel smoking-relevant procedure: effects of dopamine antagonists. *J Pharmacol Exp Ther.* 2009; 330(2):633–640. [PubMed: 19448141]
- Spealman RD. Behavior maintained by termination of a schedule of self-administered cocaine. *Science.* 1979; 204:1231–1233. [PubMed: 109920]
- Spealman RD, Goldberg SR. Drug self-administration by laboratory animals: control by schedules of reinforcement. *Annu Rev Pharmacol Toxicol.* 1978; 18:313–339. [PubMed: 348062]
- Spealman RD, Goldberg SR. Maintenance of schedule-controlled behavior by intravenous injections of nicotine in squirrel monkeys. *J Pharmacol Exp Ther.* 1982; 223:402–408. [PubMed: 7131295]
- Spillane J, McAllister WB. Keeping the lid on: a century of drug regulation and control. *Drug Alcohol Depend.* 2003; 70:S5–S12. [PubMed: 12759194]
- Stafford D, LeSage MG, Glowa JR. Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: a review. *Psychopharmacology.* 1998; 139:169–184. [PubMed: 9784071]

- Thompson T, Schuster CR. Morphine self-administration, food-reinforced and avoidance behaviors in rhesus monkeys. *Psychopharmacologia*. 1964; 5:87–94. [PubMed: 14137126]
- Thompson, T., Schuster, CR. Behavioral pharmacology. Prentice-Hall, Inc; Englewood Cliffs, NJ: 1968.
- Truth Initiative. [Accessed 20 Apr 2016] The truth about: electronic nicotine delivery systems. 2015. http://truthinitiative.org/sites/default/files/The_Truth_About_Electronic_Nicotine_Delivery_Systems.pdf
- U. S. Congress. H.R. 1256: Family Smoking Prevention and Tobacco Control Act. 111. 2009. First Session
- U. S. Department of Health and Human Services. Why people smoke cigarettes. Department of Health and Human Services, Public Health Service. U. S. Government Printing Office; Washington, D.C: 1984a.
- U. S. Department of Health and Human Services. Drug abuse and drug abuse research: the first in a series of triennial reports to Congress from the secretary, Department of Health and Human Services. Department of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse. U. S. Government Printing Office; Washington, D. C: 1984b.
- U. S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction: a report of the Surgeon General. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health. U. S. Government Printing Office; Washington, D. C: 1988.
- U. S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. U. S. Government Printing Office; Washington, D. C: 2010.
- U. S. Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Department of Health and Human Services, Public Health Service, Office of the Surgeon General. U. S. Government Printing Office; Washington, D. C: 2014.
- U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. Atlanta, GA: 2014.
- U. S. Department of Health, Education, and Welfare. Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service. Department of Health, Education, and Welfare, Public Health Service. U. S. Government Printing Office; Washington, D. C: 1964.
- U. S. Department of Health, Education, and Welfare. Smoking and health: a report of the Surgeon General. Department of Health, Education, and Welfare, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health. U. S. Government Printing Office; Washington, D. C: 1979.
- U. S. House of Representatives. Comprehensive Smoking Prevention Education Act: hearings before the Subcommittee on Health and Environment of the Committee on Energy and Commerce, House of Representatives, ninety-seventh Congress, second session on H. R. 5653 and H. R. 4957. March 5, 11, and 12, 1982. U. S. Government Printing Office; Washington, D. C: 1982.
- U.S. District Court. [Accessed 28 Apr 2016] Amended Final Opinion. 2006. <http://publichealthlawcenter.org/sites/default/files/resources/doj-final-opinion.pdf>
- Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction*. 2012; 107(8):1493–1500. [PubMed: 22229871]
- Wikler, A. Conditioning factors in opiate addiction and relapse. In: Wilner, DI., Kassenbaum, GG., editors. *Narcotics*. McGraw-Hill; New York: 1965.
- Wikler A. Dynamics of drug dependence: implications of a conditioning theory for research and treatment. *Arch Gen Psychiatry*. 1973; 28:611–616. [PubMed: 4700675]

- Wing VC, Shoaib M. Effect of infusion rate on intravenous nicotine self-administration in rats. *Behav Pharmacol.* 2013; 24(5 and 6):517–522. [PubMed: 23907378]
- World Health Organization (WHO). *International classification of diseases*. Vol. 10. Geneva, Switzerland: 1994.
- World Health Organization (WHO). *Monograph: advancing knowledge on regulating tobacco products*. Geneva, Switzerland: 2001.
- World Health Organization (WHO). *The scientific basis of tobacco product regulation*. WHO technical report series 945; Geneva, Switzerland: 2007.
- World Health Organization (WHO). *WHO study group on tobacco product regulation: Report on the scientific basis of tobacco product regulation: Fourth report of a WHO study group*. WHO technical report series 967; Geneva, Switzerland: 2012.
- World Health Organization (WHO). [Accessed 6 Sept 2016] *Global Nicotine Reduction Strategy: WHO study group on tobacco regulation*. 2015. http://www.who.int/tobacco/publications/prod_regulation/nicotine-reduction/en/
- World Health Organization (WHO). [Accessed 21 Apr 2016] *WHO Framework Convention on Tobacco Control*. 2016a. <http://apps.who.int/iris/bitstream/10665/42811/1/9241591013.pdf>
- World Health Organization (WHO). [Accessed 12 Sept 2016] *WHO Expert Committee on Drug Dependence*. 2016b. <http://www.who.int/medicines/access/controlled-substances/ecdd/en/>
- Yan Y, Pushparaj A, et al. Blockade of dopamine D4 receptors attenuates reinstatement of extinguished nicotine-seeking behavior in rats. *Neuropsychopharmacology*. 2012; 37(3):685–696. [PubMed: 22030716]
- Yanagita T, Deneau MH, Seevers MH. Methods for studying psychogenic dependence to opiates in the monkey. *Bulletin, Drug Addiction and Narcotics*, Appendix. 1963; 16:3379–3385.
- Yanagita, T., Ando, K., Oinuma, N., Ishida, K. Intravenous self-administration of nicotine and an attempt to produce smoking behavior in monkeys; *Proceedings of the 36th Annual Scientific Meeting, Committee on Problems of Drug Dependence, National Academy of Sciences*; 1974.
- Zilio D. Who, what, and when: Skinner's critiques of neuroscience and his main targets. *The Behavior Analyst*. 2016:1–22. [PubMed: 27606186]

Table 1

Timeline of events pertaining to tobacco and nicotine behavioral pharmacology science, regulation and the contributions of Steven Goldberg

Year	Event
1964	Surgeon General's report on Smoking and Health: Cigarette smoking was concluded to meet criteria for a "habituation" but not for an "addiction" (US HEW 1964)
1977	National Institute on Drug Abuse (NIDA) convenes expert meetings that included both addressing the potential characterization of nicotine and tobacco as dependence-producing substances and identifying gaps in scientific knowledge and research (Jarvik et al. 1979; Krasnegor 1978, 1979a, 1979b; Pinney 1979)
1979	Secretary of Health Education and Welfare, Joseph Califano, sends the Director of the Office on Smoking and Health, John Pinney, to meet with NIDA director William Pollin to request that NIDA conduct the necessary research to definitively determine whether or not nicotine met criteria as an addictive drug and cigarette smoking a form of drug addiction (John Pinney, personal communication to JEH 1979).
1979–81	Steven R. Goldberg recruited to the NIDA Intramural Research Program (Addiction Research Center) in 1979; primate nicotine self-administration paper published in Science, (Goldberg et al. 1981)
1980	American Psychiatric Association Diagnostic and Statistical Manual, Third Revision (APA DSM III, 1980), lists tobacco dependence as a substance use disorder, and tobacco withdrawal as an organic brain syndrome
1982	E. N. Brandt, Secretary, DHHS; C.E. Koop, Surgeon General; and W. Pollin, NIDA Director, testify that nicotine meets criteria as an addictive drug and cigarette smoking as a form of drug addiction or dependence (US House of Representatives 1982)
1985	Human nicotine self-administration program discontinued (cf. Henningfield 2004; Kessler 2001, p. 61; McGarity and Wagner 2008, pp. 177–178)
1994–1996	FDA Commissioner David Kessler announces launch of FDA investigation into whether or not cigarette and smokeless tobacco meet FDA criteria for regulation as drugs, leading to the Proposed Rule (1995) and Final Rule (1996).
2001	The FDA tobacco rule is overturned by the Supreme Court with Justices agreeing that tobacco warrants potential regulation but that this must emerge as an act of Congress (Brandt 2007).
2004–5	The World Health Organization Framework Convention on Tobacco Control (WHO FCTC) is ratified (2004), coming into force in 2005 with remarkably rapid ratification by more than 40 parties (WHO 2016a).
2009	President Obama signs into law the Family Smoking Prevention and Tobacco Control Act which gives FDA regulatory authority over cigarettes and smokeless tobacco and the mechanisms to potentially assert authority over other tobacco products. These mechanisms include funding (partly from tobacco industry fees) research in collaboration with the NIH to support tobacco product regulation and training experts in tobacco product regulation (FDA 2016a; US Congress 2009).
2016	FDA finalizes its rule to regulate all other tobacco products including electronic nicotine delivery systems (ENDS), cigars, and water pipes (hookahs) (FDA 2016b).

Table 2

The role and approach of the US National Institute on Drug Abuse in assessing the abuse potential (liability) of substances

The 1970 Controlled Substances Act requires that drugs and substances meeting certain criteria be considered for scheduling as controlled substances appropriate to their potential to cause abuse, dependence, and harm. While the final scheduling determination is made by the Department of Justice's Drug Enforcement Administration (DEA), the Department of Health and Human Services provides the scientific and medical foundation for the scheduling recommendation, relying upon input from NIDA and the FDA. In the case of new medicines, the FDA, in consultation with NIDA, would determine if a new drug approved for therapeutic use should be controlled and scheduled (Calderon and Klein 2014; DEA 2016; FDA 2010a; Spillane and McAllister 2003).

There is no single test for determining if a substance should be regulated as a controlled substance; such determinations are based on multiple tests and lines of evidence (Calderon and Klein 2014; FDA 2010a). The pioneering work of what is now called NIDA's Intramural Research Program (established as the US Public Health Service's Addiction Research Center in 1935) characterized the fundamental properties of substances with the potential to cause abuse and dependence, including alcohol, marijuana, hallucinogens, opioids, sedatives, and stimulants (Campbell 2007). This work contributed to the development of the variety of tests that could be used to determine if a substance met criteria for a substance of abuse and dependence and if so, the qualitative nature (e.g., stimulant versus sedative opioid like) and the level of severity (e.g., cocaine vs weak stimulants, morphine vs tramadol, pentobarbital vs diazepam). These tests remain the cornerstone of abuse potential assessment today and are included in guidance documents by the Food and Drug Administration for assessing drugs and substances in general (FDA 2010a, 2015), and tobacco products in particular (FDA 2012), as well as by the World Health Organization's Expert Committee on Drug Dependence (WHO 2016b).

Findings from these tests contribute to the Controlled Substances Act's 8-factor assessment, which includes pharmacology, clinical effects, public health effects, clinical data, and epidemiological data (DEA 2016; FDA 2010a). By the 1970s, animal drug self-administration testing was increasingly recognized as a key preclinical method for abuse potential assessment (Brady and Lukas 1984; Committee on Problems of Drug Dependence 1973; Griffiths et al. 1980; Thompson and Schuster 1968) and remains an important methodology relied upon by NIDA, FDA, and DEA, as well as WHO (The Expert Panel 2003; FDA 2010a, 2015; Schuster and Henningfield 2003). The most important human counterpart in abuse/dependence potential assessment is self-report studies ("liking studies") of a drug's effects. Applying the 8-factor assessment, FDA determined that nicotine met criteria for potential control by placement in Schedule III of the Controlled Substances Act (FDA, 1995, 1996).

These methods of assessment were increasingly utilized to evaluate tobacco and nicotine in the 1970s (Carter and Griffiths 2009; Carter et al. 2009; US DHHS 1988). The cigarette provides an extraordinarily efficient and effective form of nicotine delivery that has been designed over decades based on research and market experience to optimize its reinforcing and addictive potential (FDA 1995, 1996; Kessler 2001; US DHHS 2010, 2014; WHO 2001). Both the US Controlled Substances Act and the international drug control treaties (Spillane and McAllister 2003) exempt tobacco and tobacco products along with alcohol and alcoholic beverages from international control and scheduling based on social and political factors rather than scientific evaluation. Nonetheless, the methods described above are among those recommended by FDA in its guidance documents pertaining to abuse liability assessment of tobacco products (FDA 2012). Nicotine in products regulated as medicines is not exempt from CSA scheduling, and medicines that rival cigarettes in abuse potential could be regulated as controlled substances (FDA 1995; Henningfield et al. 2009).

Table 3**Key definitions and concepts**

Term	Definition/concept
Abuse potential	A term used to describe the risk that a substance carries for sustaining self-administration due to central nervous system effects that are typically reinforcing and often pleasant yet associated with harm. Abuse potential is often used synonymously with abuse liability by FDA; however, abuse potential is most commonly used in FDA Guidance documents from the Center for Drug Evaluation and Research (e.g., FDA 2010a, 2015), whereas FDA's Center for Tobacco Products seems to prefer the term abuse liability (FDA 2010b, 2012).
Addiction	The more commonly used term for dependence (APA DSM-III and IV and WHO ICD-10) or substance use disorder (APA 1980, 1994, 2013; WHO 1994). Addiction has not been used in diagnostic nomenclature by APA since DSM-III or by WHO in its ICD 9 or ICD 10; however, APA, WHO, NIDA, and many other organizations used the term addiction in broader communications (Henningfield 2004; US DHHS 1988, and WHO 1994, 2016a). NIDA also provides a definition for addiction that can also be useful to explain its hallmarks at a general level: "addiction is a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use despite harmful consequences. It is considered a brain disease because drugs considered addictive produce measurable changes in brain structure and function presumed to be associated reinforcement, tolerance, physical dependence, and other effects. These brain changes can be long lasting and can lead to many harmful, often self-destructive, behaviors" (NIDA 2014).
Behavioral pharmacology	Behavioral pharmacology may be considered an outgrowth of B.F. Skinner's radical behaviorism catalyzed by his own early applications of behavior analysis to the characterization and understanding of the behavioral effects of drugs (Laties 2003). Even though other disciplines such as neuroscience increasingly employ behavioral pharmacology models, they remain independent disciplines. As Skinner put it, their "subject matters are distinct," with the former focused on characterizing and understanding observable behavior and its determinants, focusing on operant behavior (see below and discussion including various comments by Skinner brought together by Zilio 2016). Although a distinct discipline, behavioral pharmacology contributes to the broader field of the experimental analysis of behavior in general, as well as to neuroscience, drug and tobacco regulation, and other disciplines and applications (Branch 2006; Poling and Byrne 2000 Thompson and Schuster 1968; Zilio 2016).
Classical or Pavlovian conditioning	This process involves automatic, (i.e., naturally occurring reflexive responses) called unconditioned responses (UR) or unconditioned stimuli (US), (e.g., food; sex; water; cocaine; or aversive stimuli such as electric shock, physical assault, or sickness-inducing substances) in which the association of a previously neutral stimulus (e.g., auditory, visual, taste, or olfactory stimulus) comes to elicit the same physiological and emotional responses (e.g., salivation, increased heart rate blood pressure, nausea, eye blink, "pleasure," or "fear") as the US. When the neutral stimulus elicits similar responses to the US, it is then termed a conditioned/conditional stimulus (CS) and the response that occurs following the presentation of the CS then termed a conditioned/ conditional response (CR).
Operant or instrumental conditioning	<p>Pioneered by B.F. Skinner, this process is a "voluntary" behavior that is maintained by its consequences, e.g., by the response-producing presentation of primary ("intrinsically") positively reinforcing stimuli such as food, sweet flavor, or cocaine or by response producing removal or avoidance of primary negatively reinforcing stimuli such as electric shock, temperature extremes, or drug withdrawal. Thus, if presentation of the stimulus increases the frequency of the behavior (e.g., drug self-administration), then the reinforcer is technically functioning as a positive reinforcer (generally referred to as a reinforcer or even more colloquially as a reward). A negative reinforcer has the same effect on behavior but is demonstrated when removal of a stimulus leads to increasing the frequency of the preceding behavior. Conversely its presentation following the emission of a behavior can suppress that behavior (operationally referred to as a punisher or punishment). Stimuli that come to serve as reinforcers (positive or negative) following association with primary reinforcers are termed conditioned reinforcers. Stimuli that set the occasion for behaviors that will lead to the presentation of positive reinforcers or avoidance of negative reinforcers (whether primary or conditioned) are termed discriminative stimuli.</p> <p>Outside of the laboratory, the interrelationships between stimuli and behavior become extended and complex with initially neutral stimuli acquiring multiple functions. For a heroin user or cigarette smoker, word talk of heroin or cigarettes or the sights or smells associated with the substances may elicit feelings associated with substance administration and/or withdrawal including craving, and occasionally behaviors leading to the self-administration of the substance. Several hours of deprivation of either substance may be associated with internal (interoceptive) feelings associated with the onset of withdrawal, which may occasionally cause substance seeking. This process is powerfully maintained both by both avoiding the adverse impending effects of withdrawal and by the positively reinforcing effects of substance administration. Most of the behavior of people is in fact occasioned by discriminative stimuli and reinforced or suppressed by conditioned stimuli and not the physiologically needed or biologically reinforcing or punishing stimuli that may have been important in endowing once neutral stimuli with such powerful behavior modifying effects.</p>
Physical (or "physiological") dependence and withdrawal	Physical or physiological dependence refers to the state of the organism after repeated ("chronic") administration of a drug such that tolerance (diminished responsiveness to the drug) is present and a state of neuroadaptation is presumed to have occurred. When this has occurred, abrupt abstinence of the drug (or administration of an antagonist drug) will lead to the emergence of the clinical syndrome or disorder that is termed withdrawal.

Table 4

Main conclusions of the 1988 Report of the Surgeon General on the Health Consequences of Cigarette Smoking: Nicotine Addiction (US DHHS, 1988)

I.	Cigarettes and other forms of tobacco are addicting
II.	Nicotine is the drug in tobacco that causes addiction
III.	The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine (US DHHS, 1988)

Table 5

Suppression of DeNoble and Mele's nicotine self-administration research was brought to the attention of the US Congress

In 1983, Henningfield was charged with developing a report on the state of tobacco and nicotine research to be provided as part of NIDA's first Triennial Report to Congress "Drug Abuse and Drug Abuse Research" by the Secretary of the Department of Health and Human Services (US DHHS 1984b). He was assisted by a colleague at The Johns Hopkins University School of Medicine, Thomas Burling, in writing this report. Henningfield mailed letters of request to tobacco and nicotine researchers, including DeNoble. In response, DeNoble provided manuscript drafts of papers that were described as "in press." Some months later, Philip Morris ordered DeNoble and Mele to withdraw the papers submitted for publication and request that potential citations of the unpublished work be rescinded. DeNoble and Mele were required to turn all materials related to the studies in their possession to Philip Morris and to close the laboratory (Barry 2006; FDA 1995, 1996; Henningfield et al. 2006a; Kessler 2001). DeNoble telephoned Henningfield and, without discussing the foregoing detail, asked Henningfield not to cite the DeNoble work mentioning only that his approval to publish it had been rescinded by his employer. Henningfield deleted mention of DeNoble and Mele's work from the NIDA report to congress and other papers he was working on; however, inadvertently, he failed to retract a one-sentence mention in a subsequently published article (Henningfield 1984, 1994b).

Apparently, unbeknownst to DeNoble and Mele, Henningfield's copies of the draft paper (and another) were retained in his NIDA files, dormant until the 1994 FDA investigation of tobacco products that led to his providing copies to FDA Commissioner Kessler in March 1994 and their subsequent disclosure before the US Congress; Kessler had clearly come to appreciate the scientific and regulatory importance of such self-administration work that was done by a company whose public position had been to deny that nicotine met criteria as an addictive drug. Kessler described the paper as "a bombshell" (Kessler 1999, 2001). As described in the text of this review, Kessler and Henningfield disclosed the existence of the paper and the main findings in the March 25, 1994 congressional hearing. Subsequently in the April 14, 1994 congressional testimony, Philip Morris's President William Campbell (1994) pointed out that Henningfield had made mention of DeNoble's work in a 1984 review article (Henningfield, 1984). This precipitated a letter of explanation by Henningfield to Congressman Waxman to apologize for his inadvertent and forgotten inclusion of a sentence in the review article that did mention DeNoble and Mele's research and for not disclosing this in his March 25 congressional testimony (Henningfield 1994b).

From scientific, public health, and policy perspectives, censorship of DeNoble and Mele's studies was most unfortunate, as the model they had developed, along with important initial findings, would likely have served the field well as was evidenced by Corrigan and Coen publishing their similar and independently developed rodent nicotine self-administration model in 1989. DeNoble and Mele, had, in fact, conducted a series of studies that evaluated nicotine under a broad range of conditions, including the various parametric manipulations such as dose and work effort ("response cost" according the reinforcement schedule). Additionally, they included appropriate control procedures such a saline substitution for drug, making drug available again, and the various types of antagonists to evaluate the selectivity of nicotine's behavioral actions. In other words, they employed state-of-the-art behavioral pharmacology strategies helpful in characterizing the reinforcing effects and abuse liability of substances as described by others contemporarily and more recently (e.g., Ator and Griffiths 2003; Carter and Griffiths 2009; FDA 2010a; Griffiths et al. 1980; Howell and Fantegrossi 2009; Meisch and Thompson 1974; Meisch 1977, 2001).

Additionally, DeNoble and Mele found that other chemicals found in cigarette smoke could contribute to the reinforcing effects of nicotine. In particular, it was found that the common tobacco smoke constituent acetaldehyde can serve as a reinforcer in its own right and is a contributor to the dependence-producing effects of alcohol (DeNoble 1994; Henningfield and Zeller 2006; Mele 1994). This work was important in helping to understand why pure nicotine, e.g., as administered in NRT products, does not and cannot mimic or fully replace the effects of smoke-delivered nicotine. Of course, many other factors contribute as well, including the rapid spiking arterial boli produced by inhalation of nicotine smoke but not by nicotine replacement medications. Taken together, the results suggested that DeNoble and Mele had established a model that would be useful in further elucidation of the abuse liability of nicotine, its mechanisms of action, as well as in the evaluation of potential therapeutic medications in a rodent model.