

**B. NICOTINE IS ADDICTIVE****1. Major Public Health Groups and Leading Experts Concur**

Until the 1980's, nicotine was not widely appreciated to be an addictive drug. Within the past 15 years, however, broad international agreement has developed within the scientific community that nicotine in tobacco is a highly addictive or dependence-producing substance. The terms "addictive" and "dependence-producing" are generally used interchangeably; both terms refer to the persistent and repetitive intake of psychoactive substances despite evidence of harm and a desire to quit.<sup>31</sup> Some scientific organizations have replaced the term "addictive" with "dependence-producing" to shift the focus to dependent patterns of behavior and away from the moral and social issues associated with addiction.<sup>32</sup> Both terms are equally relevant for purposes of understanding the drug effects of nicotine, and in this section, the terms will be used interchangeably. The current broad recognition that nicotine is an addictive substance has been due to: 1) an evolution in the understanding of the science of addiction (e.g., the recognition that a substance does not have to be intoxicating when used at addictive levels);<sup>33</sup> 2) epidemiological evidence establishing the high percentage of tobacco

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<sup>31</sup> Surgeon General's Report. 1988. *Nicotine Addiction*. Page 7.

<sup>32</sup> *Id.* at p. 11.

<sup>33</sup> U.S. Public Health Service. *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control. PHS Publication No. 1103, 1964. (Hereafter cited as Surgeon General's Report. 1964. *Smoking and Health*.) The 1964 Surgeon General's Report considered nicotine to be "habituating" rather than addictive because it did not appear to produce intoxication or cause physical dependence, and its users did not tend to increase the dose. These were considered to be the features of addictive drugs.

At that time, cocaine and amphetamines were also regarded as not causing physical dependence. *See:*

Wesson DR, Smith DE. Cocaine: Its Use for Central Nervous System Stimulation Including Recreational

users who display the clinical symptoms of addiction; and 3) the accumulation of evidence in the last two decades demonstrating, in both laboratory animals and humans, that nicotine is a psychoactive drug that produces pharmacological effects similar to those seen with other addictive substances.

Scientists' understanding of addiction has evolved over the past 30 years. Earlier definitions of addiction suggested that addiction was predominately the result of weakness in the personality of the user rather than the result of the pharmacological effects of the addicting substance.<sup>34</sup> More recently, animal and human research has revealed the pharmacological basis of addiction.<sup>35</sup> It has been shown that addictive substances produce

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and Medical Uses. In: Cocaine: 1977. NIDA Research Monograph. DHEW Publication Number (ADM) 77-471. Department of Health, Education, and Welfare. Rockville, MD. 1977. Page 145.

Winkler A. The Etiology of Opioid Dependence. In: Opioid Dependence: Mechanisms and Treatment. Winkler A (ed). 1980. Plenum Press. New York, NY. Page 26.

Winkler A. The Problems of Drug Dependence. In: Opioid Dependence, *supra*, at p. 13.

<sup>34</sup> See:

The Committee on Nomenclature and Statistics of the American Psychiatric Association. 1952. *Diagnostic and Statistical Manual, Mental Disorders with Special Supplement on Plans for Revision*. American Psychiatric Association. Washington, DC. Page 39.

Surgeon General's Report. 1964. *Smoking and Health*. Page 351.

Surgeon General's Report. 1988. *Nicotine Addiction*. Page 248.

<sup>35</sup> See:

Hanson HM, Ivester CA, Morton BR. Nicotine self-administration in rats. In: *Cigarette Smoking as a Dependence Process, NIDA Research Monograph 23*. U.S. Department of Health, Education, and Welfare. 1979. Pages 70-90.

Goldberg SR, Spealman RD, Goldberg DM. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science*. 1981;214:573-575.

Griffiths RR, Henningfield JE, Bigelow GE. Human cigarette smoking: manipulation of number of puffs per bout, interbout interval and nicotine dose. *J Pharmacol Exp Ther*. 1981;220(2):256-265.

definable chemical effects in the brain that reinforce continued use of these substances and cause physiological and/or psychological dependence on these substances.<sup>36</sup> The contemporary understanding of addiction also places a major emphasis on the intrinsic pharmacological ability of a substance to cause compulsive, regular use and on the inability of users to stop using the substance, even when they are strongly motivated to do so.<sup>37</sup>

In 1986, the Office of the U.S. Surgeon General issued a report concluding that nicotine in smokeless tobacco is addictive.<sup>38</sup> In 1988, the Surgeon General issued an additional report concluding that nicotine in cigarettes and other forms of tobacco is addictive.<sup>39</sup>

The landmark 1988 report by the Surgeon General ("the 1988 report") noted that the

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Griffiths RR, Henningfield JE. Pharmacology of cigarette smoking behavior. *Trends Pharmacol Sci.* 1982;3:260-263.

Henningfield JE, Goldberg SR. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacol Biochem Behav.* 1983;19(6):989-992.

<sup>36</sup> Surgeon General's Report. 1988. *Nicotine Addiction*. Pages 170-279.

<sup>37</sup> See:

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. American Psychiatric Association. Washington, DC. Page 176. (Hereafter cited as American Psychiatric Association. 1994. *DSM IV*.)

World Health Organization. 1992. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization. Geneva, Switzerland. Page 76. (Hereafter cited as World Health Organization. 1992. *ICD-10*.)

Surgeon General's Report. 1988. *Nicotine Addiction*. Pages 248-250.

<sup>38</sup> U.S. Department of Health and Human Services. *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General, 1986*. U.S. Department of Health and Human Services, Public Health Service, Bethesda, MD. NIH Publication No. 86-2874, April 1986. Pages 144-145, 166. (Hereafter cited as Surgeon General's Report. 1986. *Smokeless Tobacco*.)

<sup>39</sup> Surgeon General's Report. 1988. *Nicotine Addiction*. Page 9.

main features of the definitions of addiction used by groups throughout the world are highly consistent. The 1988 report adopted a set of criteria based on the common criteria of these definitions. The primary criteria for drug dependence relied on in the Surgeon General's Report were:

1. highly controlled or compulsive use (even despite a desire, or repeated attempts, to quit);
2. psychoactive ("mood altering") effects produced by the action of the drug substance on the brain; and
3. drug-motivated behavior caused by "reinforcing" effects of the psychoactive substance.<sup>40</sup>

The 1988 report identified the following additional criteria for identifying drug dependence:

- repetitive and stereotyped patterns of use;
- persistent use despite adverse physical, social or psychological effects;
- quitting episodes followed by relapse;
- recurrent cravings for the drug, especially during abstinence;
- development of tolerance (diminished responsiveness to the drug's effects, sometimes accompanied by increased intake);
- withdrawal symptoms that can motivate further use of the drug; and
- pleasant (euphoriant) effects produced by the drug.<sup>41</sup>

The 1988 report exhaustively reviewed the available data on the effects of nicotine on the body, the metabolism of nicotine within the body, the dependence-producing properties of

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<sup>40</sup> *Id.* at p. 7.

<sup>41</sup> *Id.* at pp. 7-8.

nicotine, tobacco use compared to other drug dependencies, the pharmacological effects of nicotine that promote tobacco use, and treatment of tobacco dependence. Applying the criteria for drug dependence listed above to these data, the 1988 Surgeon General's Report concluded that:

1. Cigarettes and other forms of tobacco are addicting;
2. Nicotine is the drug in tobacco that causes addiction; and
3. The pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.<sup>42</sup>

Major public health organizations and leading experts have concluded that nicotine is an addictive or dependence-producing substance.

- The World Health Organization, the American Medical Association, the American Psychiatric Association, the American Psychological Association, the Royal Society of Canada, and the Medical Research Council in the United Kingdom have all recognized that nicotine is an addictive or dependence-producing drug.<sup>43</sup>

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<sup>42</sup> *Id.* at pp. 6-9.

<sup>43</sup> *See:*

World Health Organization. 1974. *World Health Organization Technical Report Series No. 551. WHO Expert Committee on Drug Dependence, Twentieth Report.* World Health Organization. Geneva, Switzerland. Pages 15-16.

World Health Organization. 1992. *ICD-10.* Page 324.

American Medical Association. 1993 *AMA Policy Compendium. Ethyl alcohol and nicotine as addictive drugs.* American Medical Association. 1993.

American Psychiatric Association. 1980. *Quick Reference to the Diagnostic Criteria from DSM-III.* American Psychiatric Association. Washington, DC. Page 99.

American Psychological Association. Statement of the American Psychological Association before the U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment on the subject of The 1988 Surgeon General's Report, *The Health Consequences of*

- On August 2, 1994, FDA's Drug Abuse Advisory Committee, an independent group composed primarily of experts on addiction science, concluded that cigarettes and other forms of tobacco are addicting, and that nicotine is the drug in tobacco that causes addiction. The FDA advisory committee also concluded that all currently marketed cigarettes contained addicting levels of nicotine.
- In a 1991 survey, the vast majority of scientists funded by the tobacco industry stated that they believed that cigarette smoking is addictive.<sup>44</sup> According to this report, among the principal investigators of research projects funded by the tobacco industry in 1989, 83.3% strongly agreed and 15.3% agreed somewhat that cigarette smoking is addictive.<sup>45</sup>

Furthermore, the medical community has, since the early 1980's, come to recognize that nicotine addiction is a clinical disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, and the International Statistical Classification of Disease and Related Health Problems (ICD), published by the

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*Smoking: Nicotine Addiction*. July 29, 1988. Page 1.

Royal Society of Canada. *Tobacco, Nicotine, and Addiction: A Committee Report*. Prepared at the request of The Royal Society of Canada for The Health Protection Branch, Health and Welfare Canada. August 31, 1989. Pages 8-9.

Medical Research Council. *The Basis of Drug Dependence. MRC Field Review*. Medical Research Council. 1994. Page 11.

<sup>44</sup> Cummings KM, Sciandra R, Gingrass A, Davis R. What scientists funded by the tobacco industry believe about the hazards of cigarette smoking. *Am. J of Pub Health*. 1991;81(7)894.

<sup>45</sup> *Id.* at p. 895.

World Health Organization, use very similar criteria to identify dependence.<sup>46</sup> Like the criteria specified by the U.S. Surgeon General, these criteria emphasize the ability of a substance to produce compulsive use, withdrawal and/or tolerance, inability to control or terminate drug use despite efforts to quit or reduce use, and continued use despite harmful effects. (See Appendix 1 for a description and history of the criteria for identifying addiction.)

Nicotine has been recognized as dependence-producing under the DSM criteria since 1980. The most recent version of DSM (DSM-IV) recognizes two substance use disorders

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<sup>46</sup> The most recent version of DSM (DSM-IV) defines "substance dependence" as substance use that produces three or more of the following symptoms in users:

- marked tolerance;
- a withdrawal syndrome and/or the substance is taken to relieve or avoid withdrawal symptoms;
- the substance is often taken in larger amounts over a longer period of time than intended;
- persistent desire or unsuccessful efforts to cut down or control substance use;
- a great deal of time spent in activities necessary to obtain the substance, use the substance (e.g., chain smoking), or recover from its effects;
- important social, occupational, or recreational activities are given up or reduced because of substance use; and
- use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

DSM-IV explains how the following criteria are apparent in nicotine dependence: tolerance, withdrawal, desire to quit, great deal of time using, and continued use despite medical problems. American Psychiatric Association. 1994. *DSM IV*. Pages 181, 243.

"Dependence syndrome" is characterized under the ICD-10 as a cluster of effects after repeated use of a substance resulting in three or more of the following symptoms:

- a strong desire or sense of compulsion to take the substance;
- an impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use;
- substance use with the intention of relieving withdrawal symptoms and with awareness that this strategy is effective;
- a physiological withdrawal state;
- evidence of tolerance such that the increased doses of the substance are required in order to achieve effects originally produced by lower doses;
- progressive neglect of alternative pleasures or interests in favor of the substance; and
- persisting with substance use despite clear evidence of overtly harmful consequences.

World Health Organization. 1992. *ICD-10*. Pages 75-76, 321.

associated with nicotine: nicotine dependence and nicotine withdrawal.<sup>47</sup>

The ICD has included tobacco as a dependence-producing substance since 1992. Previously, the ICD recognized the existence of tobacco dependence, but tobacco was treated separately from other addictive drugs because tobacco differed in its psychotoxic effects<sup>48</sup> when used at usual doses. With the publication of ICD-10 in 1992, however, tobacco was included with the other addictive drugs.<sup>49</sup>

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<sup>47</sup> See American Psychiatric Association. 1994. *DSM IV*, note 37, *supra*, at p. 99. An individual is classified as having **physiologic** (in addition to psychological) dependence on a substance under DSM-IV if there is evidence of tolerance to or withdrawal from the substance. *Id.*

<sup>48</sup> World Health Organization. 1978. *Mental Disorders: Glossary and Guide to Their Classification in Accordance with the Ninth Revision of the International Classification of Diseases*. World Health Organization. Geneva, Switzerland. Page 43.

<sup>49</sup> World Health Organization. 1992. *ICD-10*. Page 75.



## **2. Epidemiological Data Establishes That Tobacco Users Display the Clinical Symptoms of Addiction**

### **a. Studies Documenting Symptoms of Addiction in Smokers**

Population studies of smokers conducted in recent years clearly demonstrate that nicotine produces regular, compulsive use, that such use is persistent despite both attempts to quit and an appreciation of cigarette's harmful effects, and that abstinence from nicotine produces withdrawal symptoms:

#### Regular, compulsive use:

- 87% of people who smoke cigarettes smoke every day;<sup>50</sup> and
- Nearly two-thirds of smokers have their first cigarette within the first half-hour after they wake up.<sup>51</sup>

#### Use persists despite attempts to quit or reduce use:

- In one study, 84.3% of those who smoked a pack or more per day had unsuccessfully tried to reduce the number of cigarettes smoked.<sup>52</sup>
- A smoker who makes a serious attempt to stop smoking has a less than 5% chance of being off cigarettes a year later;<sup>53</sup>
- Each year in the United States, 15 million people try to quit smoking, but less than 3%

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<sup>50</sup> Centers for Disease Control. *1991 National Health Interview Survey*. Atlanta, GA. U.S. Department of Health and Human Services, 1991.

<sup>51</sup> Centers for Disease Control. *1987 National Health Interview Survey*. Atlanta, GA. U.S. Department of Health and Human Services, 1987.

<sup>52</sup> Henningfield JE, Clayton R, Pollin W. Involvement of tobacco in alcoholism and illicit drug use. *British Journal of Addiction*. 1990;85:280.

<sup>53</sup> Sachs DPL, Leischow SJ. Pharmacologic Approaches to Smoking Cessation. *Clinics in Chest Medicine*. 1991;12(4):788.

have long-term success;<sup>54</sup>

- In one study, 70% of current smokers reported they would "like to completely stop smoking",<sup>55</sup> and
- 83% to 87% of cigarette smokers who smoke more than 26 cigarettes a day believe they are addicted.<sup>56</sup>

Use persists despite harmful consequences:

- In one survey, 90% of smokers agreed with the general proposition that smoking is harmful to health, 65% believed that smoking had already affected their health, and 77% believed that they could avoid or decrease serious health problems by quitting smoking;<sup>57</sup>
- Almost half of the smokers who undergo surgery for lung cancer resume smoking;<sup>58</sup> and
- Even after smokers have had their larynxes removed, 40% try smoking again.<sup>59</sup>

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<sup>54</sup> Centers for Disease Control. *Morbidity and Mortality Weekly Report*. "Cigarette Smoking Among Adults-United States, 1993." December 23, 1994. Page 927.

<sup>55</sup> *Id.*

<sup>56</sup> Substance Abuse and Mental Health Services Administration. *1991/1992 National Household Survey on Drug Abuse*. U.S. Department of Health and Human Services.

<sup>57</sup> Thomas RM, Larsen MD. *Smoking prevalence, beliefs, and activities by gender and other demographic indicators*. Princeton, NJ. The Gallup Organization, Inc. 1993.

<sup>58</sup> Davison G, Duffy M. Smoking habits of long term survivors of surgery for lung cancer. *Thorax*. 1982;37:331-333.

<sup>59</sup> West R, Himbury S. Smoking habits after laryngectomy. *Br Med J*. 1985;291:514-515.

**Abstinence produces withdrawal symptoms:**

- Abstinence from smoking is often accompanied by powerful cravings for a cigarette;<sup>60</sup>
- Smokers in a position to compare the effects of nicotine with the effects of other addictive drugs say they are comparable;<sup>61</sup> and
- Nicotine replacement therapy significantly reduces withdrawal symptoms in smokers who are attempting to quit.<sup>62</sup>

Data from clinical research evaluating nicotine replacement therapy (nicotine gum and patches) as aids in smoking cessation support the conclusion that a high proportion of smokers are addicted. The studies, submitted to the FDA as part of new drug applications for nicotine replacement products, were conducted in male and female smokers who smoked about a pack to a pack and a half of cigarettes (about 20 to 30 cigarettes) per day. The subjects were recruited from the general population by advertisement, from primary health care settings, and from medically based smoking cessation programs.<sup>63</sup>

Participants in these studies clearly demonstrated addiction to nicotine delivered from cigarettes. All reported symptoms of nicotine addiction at trial entry, and all suffered withdrawal symptoms after smoking cessation. These withdrawal symptoms were relieved

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<sup>60</sup> See:

Benowitz NL. Cigarette smoking and nicotine addiction. *Medical Clinics of North America*. 1992;76(2):423.

West R, Schneider N. Craving for Cigarettes. *British Journal of Addiction*. 1987;82:407.

<sup>61</sup> Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *J Pharmacol Exp Ther*. 1985;234(1):4-5.

<sup>62</sup> NDA 20-076 Habitrol (Ciba), NDA 20-150 Nicotrol (Kabi), NDA 19-983 ProStep (Elan), NDA 20-165 Nicoderm (Alza), NDA 20-066 Nicorette (Merrell Dow).

<sup>63</sup> *Id.*, NDA's for Habitrol (Ciba), ProStep (Elan), and Nicoderm (Alza).

entirely or partly by medical administration of nicotine.

Smokers using the above nicotine replacement products (in the dosage range of 14 to 24 mg/nicotine per day) had an initial quit rate of about 50%, twice that of smokers receiving placebo. This two-fold difference was maintained throughout a full year of follow-up, and was associated with reductions in craving, withdrawal symptoms, and the desire to smoke.<sup>64</sup> In studies in which nicotine replacement therapy was provided for a year or more, relapse rates were nearly half those of studies in which nicotine replacement was halted after a fixed interval (usually about 6 to 12 weeks).<sup>65</sup>

Data from these studies demonstrate how tenacious nicotine addiction is, even for adults who express a strong desire to quit smoking and who receive optimal medical care. Only half of the patients studied were able to stop smoking for as long as 1 week, and the long-term failure rate was more than 80% after patients were withdrawn from nicotine replacement. The fact that nicotine replacement therapy in smokers reduces relapse rates provides strong evidence that it is the nicotine in tobacco products that creates and sustains addiction to cigarettes.

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<sup>64</sup> See:

Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. *JAMA*. 1994;271(24):1940-47.

NDA 20-076 Habitrol (Ciba), NDA 20-150 Nicotrol (Kabi), NDA 19-983 ProStep (Elan), NDA 20-165 Nicoderm (Alza), NDA 20-066 Nicorette (Merrell Dow).

<sup>65</sup> *Id.*

**b. Studies Documenting Symptoms of Addiction in Smokeless Tobacco Users**

Smokeless tobacco users can also develop a dependence on nicotine similar to that experienced by cigarette smokers.<sup>66</sup> The Surgeon General's 1986 report concluded that smokeless tobacco is addictive.<sup>67</sup> This is not surprising, since smokeless tobacco users can absorb at least as much nicotine as smokers.<sup>68</sup> The 1986 report states that:

*... given the nicotine content of smokeless tobacco, its ability to produce high and sustained blood levels of nicotine, and the well-established data implicating nicotine as an addictive substance, one may deduce that smokeless tobacco is capable of producing addiction in users.*<sup>69</sup>

Studies have shown that smokeless tobacco is associated with compulsive use,<sup>70</sup> persistent use despite efforts to quit,<sup>71</sup> persistent use despite harmful consequences,<sup>72</sup> and

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<sup>66</sup> Benowitz NL. Pharmacology of smokeless tobacco use: nicotine addiction and nicotine-related health consequences. In: *Smokeless Tobacco or Health, An International Perspective*. Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Page 227.

<sup>67</sup> Surgeon General's Report. 1986. *Smokeless Tobacco*. Pages 182-183.

<sup>68</sup> Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Page 40.

<sup>69</sup> *Id.* at p. 141.

<sup>70</sup> See Benowitz, note 66, *supra*, at p. 223.

<sup>71</sup> See:

Ary DV, Lichtenstein E, Severson HH, Weissman W, Seeley JR. An in-depth analysis of male adolescent smokeless tobacco users: interview with users and their fathers. *J. Behavioral Medicine*. 1989;12:449-467.

Severson HH. Enough snuff: ST cessation from the behavioral, clinical, and public health perspectives. In: *Smokeless Tobacco or Health, An International Perspective*. Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Pages 281-282.

<sup>72</sup> Connolly GN, Winn DM, Hecht SS, Henningfield JE, Hoffman D, Walker B. The re-emergence of smokeless tobacco. *N. Engl J. Med.* 1986;314(16):1020-1026.

withdrawal symptoms when use is discontinued.<sup>73,74</sup>

Fewer clinical and epidemiological data are available on the prevalence of addiction among smokeless tobacco users than among smokers. However, some users of smokeless tobacco products do meet addiction criteria.<sup>75</sup> A 1986 report of the Office of the Inspector General of the Department of Health and Human Services found that 37% of young users of smokeless tobacco (also called "spit" tobacco) continue use because they are addicted.<sup>76</sup> In a study involving 675 men enrolled in a cessation program, 68% reported an average of four unsuccessful attempts to quit.<sup>77</sup> Other studies of smokeless tobacco cessation programs reveal that many users continue consuming the product despite their desire to quit.<sup>78</sup> Glover reported a 2.3% quit rate at 6 months and concluded that smokeless tobacco may be more addicting than cigarette smoking.<sup>79</sup> Other researchers have found that over one-third of the current

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<sup>73</sup> Hatsukami D, Gust W, Keenan R. Physiologic and subjective changes from smokeless tobacco withdrawal. *Clin Pharmacol Ther.* 1987;41(1):103-107.

<sup>74</sup> *Id.*

See also Severson, note 71, *supra*, at p. 282.

<sup>75</sup> Benowitz NL. Pharmacology of Smokeless Tobacco Use: Nicotine Addiction and Nicotine-Related Health Consequences. In: *Smokeless Tobacco or Health, Smoking and Tobacco Control Monograph 2*. U.S. Department of Health and Human Services. 1993. Page 224.

<sup>76</sup> U.S. Department of Health and Human Services. *Spit Tobacco and Youth*. Washington DC. U.S. Department of Health and Human Services, Office of the Inspector General. 1992. Page 7.

<sup>77</sup> See Severson, note 71, *supra*, at pp. 281-282.

<sup>78</sup> See:

Glover ED. Conducting smokeless tobacco cessation clinics. *Am. J. Pub. Health.* 1986;76(2):207.

Hatsukami D, Nelson R, Jensen J. Smokeless tobacco: Current status and future directions. *Brit. J. of Addiction.* 1991;86:559-563.

<sup>79</sup> See:

Glover ED, Glover PN. Smokeless tobacco cessation and nicotine reduction therapy. In: *Smokeless*

smokeless tobacco users report an unsuccessful attempt to quit, despite the fact that 92% of those surveyed believed that there are health risks associated with smokeless tobacco use.<sup>80</sup>

Studies suggest that tolerance to nicotine develops with prolonged smokeless tobacco use. One study noted that a higher percentage of older users of smokeless tobacco used brands with a higher nicotine content compared with younger users.<sup>81</sup> A World Health Organization study group reported on another study that showed a positive relationship between the number of years of smokeless tobacco use, the number of minutes per day of reported use, and urinary nicotine and cotinine<sup>82</sup> levels. These relationships are consistent with the development of tolerance and physical dependence.<sup>83</sup>

Biglan and coworkers demonstrated that nicotine reinforces smokeless tobacco use. In one study that describes the drug-reinforcing behavior of the product, smokeless tobacco users were found to titrate the level of nicotine in their bodies by adjusting use to maintain a specified level of nicotine. In another study in which men used both snuff and cigarettes, the subjects smoked more cigarettes when smokeless tobacco use was restricted, and consumed

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*Tobacco or Health, An International Perspective*. Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Pages 291-295.

Glover, note 78, *supra*, at p. 207.

<sup>80</sup> See Ary, note 71, *supra*.

<sup>81</sup> Browson RC, DiLorenzo TM, Van Tuinen M, Finger WW. Patterns of cigarette and smokeless tobacco use among children and adolescents. *Preventive Medicine*. 1990;19:170-180.

<sup>82</sup> Cotinine is a major metabolite of nicotine and an indicator of nicotine absorption.

<sup>83</sup> World Health Organization. 1988. *WHO Technical Report Series No 773. Smokeless Tobacco Control: Report of a WHO Study Group*. World Health Organization. Geneva, Switzerland. Page 36.

more smokeless tobacco when cigarette use was restricted.<sup>84</sup>

Smokeless tobacco users who are addicted experience withdrawal symptoms similar to those reported by smokers.<sup>85</sup> One study found that among daily smokeless tobacco users ages 10 to 22 who had previously tried to quit, 93.3% experienced at least one symptom of nicotine withdrawal.<sup>86</sup> It has been concluded that "dependence on smokeless tobacco may be no less tenacious than dependence on cigarettes."<sup>87</sup> (See Appendix 1 for a more complete discussion of the definition of addiction and rates of dependence.)

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<sup>84</sup> See Benowitz, note 66, *supra*, at pp. 223-224.

<sup>85</sup> See:  
Hatsukami, note 73, *supra*, at pp.103-107.

Severson, note 71, *supra*, at p. 282.

<sup>86</sup> U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. *Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993*. *MMWR*. 1994;43(41):745-750.

<sup>87</sup> Jarvis MJ. Dependence on smokeless tobacco. In: *Smokeless Tobacco or Health, An International Perspective*. Smoking and Tobacco Control, Monograph 2. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NIH Publication No. 93-3461. 1993. Page 243.



### **3. Laboratory Studies Establish That Nicotine Produces Pharmacological Effects Similar to Those of Other Addictive Substances**

Evidence gathered in the last two decades demonstrates, in both laboratory animals and humans, that nicotine is a psychoactive drug that produces pharmacological effects similar to those of other addictive substances. Many of the advances in the understanding of the psychopharmacological and addictive aspects of nicotine have come from recent laboratory studies using both animals and human volunteers.

Animal studies have the advantage of being able to assess the pharmacological actions of a potentially addictive substance, independent of such factors as the taste of the substance, the personality of the user, or social factors such as peer pressure. Studies using human volunteers have the advantage of allowing the subject to directly inform the researcher of the subjective effects of the drug being studied.

Two kinds of studies are used to determine whether a substance may be an addictive drug: "drug discrimination" studies and "self-administration" studies. There is a strong correlation between the results of these studies in animals and humans. Substances that animals identify as similar to known psychoactive drugs in drug discrimination studies and substances that animals self-administer in self-administration studies are highly likely to be addictive in humans. With very few exceptions, substances that are addictive in humans are self-administered by animals.<sup>88</sup>

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<sup>88</sup> Gardner EL. Brain Reward Mechanism. In: *Substance Abuse, A Comprehensive Textbook*. 2nd ed. Baltimore, MD: Williams and Wilkins; 1992:70.

**a. Animal studies**

An impressive number of animal studies have demonstrated that nicotine has pharmacological properties common to many other addictive drugs. These studies establish that nicotine, like other addictive drugs, has psychoactive properties that exert control over behavior.

**(i) Drug Discrimination Studies**

Drug discrimination studies are used to evaluate the subjective effects (discriminative stimulus properties) of a drug and to make direct comparisons of these effects to known dependence-producing drugs.<sup>89</sup> The ability of a substance to produce discriminative stimulus effects is one characteristic of an addictive substance. In drug discrimination studies, animals identify nicotine as having a highly specific discriminative stimulus profile and some similarity with the discriminative stimulus effects of cocaine and amphetamine.<sup>90</sup> (See

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<sup>89</sup> Balster RL. Drug abuse potential evaluation in animals. *Br J Addiction*. 1991; 86:1549-1588.

<sup>90</sup> See:

Takada K, Swedberg MDG, Goldberg SR, Katz JL. Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys. *Psychopharmacology*. 1989;99:208-212.

Pratt JA, Stolerman IP, Garcha HS, Giardini V, Feyerabend C. Discriminative stimulus properties of nicotine: Further evidence for mediation at a cholinergic receptor. *Psychopharmacology*. 1983;81:54-60.

Goldberg SR, Risner ME, Stolerman IP, Reavill C, Garcha HS. Nicotine and some related compounds: effects on schedule-controlled behaviour and discriminative properties in rats. *Psychopharmacology*. 1989;97:295-302.

Chance WT, Murfin D, Krynock GM, Rosecrans JA. A description of nicotine stimulus and tests of its generalization to amphetamine. *Psychopharmacology*. 1977;55:19-26.

Stolerman IP, Garcha HS, Pratt JA, Kumar R. Role of training dose in discrimination of nicotine and related compounds by rats. *Psychopharmacology*. 1984;84:413-419.

Appendix 1 for a summary of the studies documenting nicotine's discriminative stimulus effects and the site of these actions.)

(ii) Self-Administration

The self-administration model is widely used to assess a drug's ability to induce and maintain drug-seeking behavior in animals.<sup>91</sup> Self-administration studies determine whether animals will press a lever to give themselves repeated doses of the test substance. The ability of a substance to cause self-administration in animals demonstrates that the substance is a positive reinforcer, *i.e.*, that it induces continued, compulsive use.<sup>92</sup> As noted above, having a positive reinforcing effect in animals is one of the key pieces of predictive evidence that a substance will produce addiction in humans.

Like many addictive drugs, such as cocaine, opiates, and hypnotics, nicotine has now been demonstrated through self-administration studies to be an effective positive reinforcer in animals.<sup>93</sup> This property of nicotine was not consistently demonstrated until the 1980s, when

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Stolerman IP. Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement. *Psychopharmacology*. 1989;97:131-138.

<sup>91</sup> See:

Schuster CR, Thompson T. Self-administration of behavioral dependence on drugs. *Annual Rev of Pharm*. 1969;9:483-502.

Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animal and human drug-taking behavior. *Advances in Substance Abuse*. 1980;1:1-90.

<sup>92</sup> See:

Schuster, note 91, *supra*, at pp. 483-502.

Griffiths, note 91, *supra*, at pp. 1-90.

<sup>93</sup> See:

Cox BM, Goldstein A, Nelson WT. Nicotine self-administration in rats. *British Journal of*

it was discovered that the reinforcing efficacy of nicotine is highly dependent on the schedule by which the drug is made available to the animals and the specific amount administered.<sup>94</sup> Intermittent availability of nicotine, which parallels the pattern of cigarette smoking, will induce self-administration in animals, while continuous administration (which was used in the earlier studies) is far less likely to do so. (See Appendix 1 for a summary of the studies establishing that nicotine is a positive reinforcer in animal self-administration studies.)

**b. Studies in Human Volunteers**

In addition to the extensive population-based epidemiological studies described above, a growing body of evidence gathered from laboratory and clinical settings using human volunteers, is providing further evidence of the addictive effects of nicotine.

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*Pharmacology*. 1984;83:49-55.

Goldberg, note 35, *supra*, at pp. 573-575.

Slifer BL, Balster RL. Intravenous self-administration of nicotine: with and without schedule-induction. *Pharmacol. Biochem. Behav.* 1985;22:61-69.

Corrigall WA, Franklin KBJ, Coen KM, Clarke PBS. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology*. 1992;107:285-289.

<sup>94</sup> See:

Goldberg, note 35, *supra*, at pp. 573-575.

Henningfield, note 35, *supra*, at pp. 989-992.

(i) Evaluation of Subjective Effects

In one study, smokers with histories of abuse of other drugs identified intravenous or inhaled nicotine as being a euphoriant similar to cocaine or amphetamine.<sup>95</sup> Using a common measure of the subjective effects of addictive drugs (the Addiction Research Center Inventory), nicotine produced a dose-related increase in the "euphoria" scale (also known as the morphine-benzedrine group scale).<sup>96</sup> This study shows that nicotine produces subjective effects that are similar to those of other addictive drugs. (See Appendix 1 for a summary of the studies on the subjective effects of nicotine.)

(ii) Self-Administration Studies

Human self-administration of nicotine has been demonstrated under controlled laboratory conditions. Smokers were provided the opportunity to give themselves injections of nicotine in test sessions where they were not allowed to smoke.<sup>97</sup> The subjects self-administered nicotine in a regular, orderly pattern, giving themselves roughly the same amount of nicotine as they were accustomed to getting from their cigarette smoking.<sup>98</sup> (See Appendix 1 for a summary of the studies establishing that nicotine is a positive reinforcer in

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<sup>95</sup> See:

Surgeon General's Report. 1988. *Nicotine Addiction*. Pages 177-178.

Henningfield et al, note 21, *supra*.

<sup>96</sup> *Id.*

<sup>97</sup> Henningfield JE, Miyasato K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharm Biochem Behav.* 1983;19:887-890.

<sup>98</sup> *Id.*

human self-administration studies.)

**c. Studies on Tolerance and Withdrawal**

"Tolerance" is produced by a substance when the effects of the substance, at a given dose, become less intense over time, or when an increasing dose over time is necessary to cause an effect or response of a specified intensity. It is well documented that nicotine produces tolerance in users. For example, novice smokers usually experience nicotine-related effects such as dizziness, nausea, vomiting, and headaches.<sup>99</sup> These effects are not produced in experienced smokers because they rapidly develop a tolerance to nicotine. Eventually, smokers increase the amount that they will smoke, always ensuring that the level of nicotine intake will fall below the level at which they would suffer undesirable physical effects and above the level at which they would begin to experience withdrawal symptoms.<sup>100</sup> Tolerance to nicotine is not complete, because even the heaviest smokers can experience symptoms, such as nausea and vomiting, when they suddenly increase their smoking rates.<sup>101</sup> Additionally, the amount of nicotine needed to maintain an addiction may plateau. (See Appendix 1 for a summary of studies demonstrating tolerance to nicotine.)

Clinical studies on nicotine withdrawal have demonstrated that physiological effects

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<sup>99</sup> Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Page 138.

<sup>100</sup> Rose JE, Behm FM, Levin ED. The role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharm Biochem and Behav*. 1993;44:891-900.

<sup>101</sup> See:  
Danaher BG. Research on rapid smoking: Interim summary and recommendations. *Addictive Behaviors*. 1977;2:151-166.

Surgeon General's Report. 1988. *Nicotine Addiction*. Page 50.

occur as a result of tobacco deprivation. These effects include decreased heart rate, decreased arousal evidenced by diminished alertness, central nervous system changes, decreases in blood pressure, and disruptions in sleep patterns.<sup>102</sup> Studies have also demonstrated that tobacco withdrawal can cause an increase in weight. This weight increase may be attributed to increased caloric intake, decreased metabolism, and decreased energy expenditure following nicotine withdrawal.<sup>103</sup>

After several weeks of nicotine exposure, users who are deprived of nicotine for more than a few hours develop withdrawal symptoms. The most common self-reported withdrawal symptoms in nicotine-deprived smokers and smokeless tobacco users are increased irritability, anxiety, difficulty concentrating, restlessness, impatience, and insomnia.<sup>104</sup> Withdrawal symptoms after quitting tobacco use can persist for months.<sup>105</sup> Although nicotine withdrawal is not as severe as withdrawal from heroin or alcohol, it is comparable to withdrawal from other stimulants such as cocaine, and can be highly disruptive to personal

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<sup>102</sup> See:

West RJ, Jarvis MJ, Russell MAH, Caruthers ME, Feyerabend C. Effect of nicotine replacement on the cigarette withdrawal syndrome. *British Journal of Addiction*. 1984;79(2):215-219.

Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*. 1986;43:289-294.

<sup>103</sup> See:

Wack JT, Rodin J. Smoking and its effect on body weight and the systems of caloric regulation. *The American Journal of Clinical Nutrition*. 1982;35(2):366-380.

Glauser SC, Glauser EM, Reidenberg MM, Reisy BF, Tallarida RJ. Metabolic changes associated with the cessation of cigarette smoking. *Archives of Environmental Health*. 1970;20:377-381.

<sup>104</sup> See Hughes, note 102, *supra*, at pp. 289-294.

<sup>105</sup> Ryan FJ. Cold Turkey in Greenfield, Iowa: A Follow-up Study. In: Dunn WL, ed. *Smoking Behavior: Motives and Incentives*. Washington, DC: VH Winston & Sons; 1973:231-234.

life.<sup>106</sup>

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<sup>106</sup> Benowitz NL. Cigarette smoking and nicotine addiction. *Medical Clinics of N. America*. 1992;76(2):415-437.



#### 4. Nicotine's Sensory Effects Are Secondary to its Psychoactive Effects

Nicotine is an irritant to the throat and upper respiratory system.<sup>107</sup> Its effects in the throat contribute to the harshness of tobacco smoke reported by smokers.<sup>108</sup> Many beginning smokers report that the taste of cigarettes is unpleasant.<sup>109</sup> Despite these facts, those who continue to smoke report that they enjoy the taste of commercial tobacco products.<sup>110</sup> In some studies, low-nicotine or nicotine-free products that replicate the taste, flavor, or throat and chest sensations of cigarette smoking can, in the very short term, reduce certain nicotine withdrawal symptoms, including craving for cigarettes.<sup>111</sup> Significantly, however, many of the positively perceived aspects of the harsh taste and flavor of commercial tobacco products are due to "secondary reinforcement." This is a phenomenon by which smokers associate the irritant effects of nicotine in the mouth and throat with desired psychoactive effects that occur immediately thereafter.<sup>112</sup> These irritant effects are then judged favorably, because they are

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<sup>107</sup> See Rose, note 100, *supra*.

<sup>108</sup> Rose JE, Sampson A, Levin ED, Henningfield JE. Mecamylamine Increases Nicotine Preference and Attenuates Nicotine Discrimination. *Pharm Biochem and Behav.* 1989;32:933-938.

<sup>109</sup> Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People.* Page 138.

<sup>110</sup> *Id.*

<sup>111</sup> See:

Rose JE, Behm F. Refined cigarette smoke as a method for reducing nicotine intake. *Pharmacology Biochemistry and Behavior.* 1987;28:305-310.

Levin ED, Rose JE, Behm F. Development of a citric acid aerosol as a smoking cessation aid. *Drug and Alcohol Dependence.* 1990;25:273-279.

Rose JE, Behm FM. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug and Alcohol Dependence.* 1994;34:225-229.

<sup>112</sup> See:  
Rose, note 100, *supra*.

associated with the delivery of the psychoactive properties of nicotine. The conditioning process is similar to that which occurs for other dependence-producing drugs in which effects that are disliked upon initial exposure come to be associated with desired psychoactive effects.<sup>113</sup> Experienced smokers can use the irritant effects of nicotine to assess how much nicotine they are delivering to themselves while they are smoking.<sup>114</sup>

Data indicate that long-term smoking is continued not because of the taste characteristics of tobacco but because of other factors, specifically the pharmacological effects of nicotine.<sup>115</sup> Evidence gathered from nicotine replacement products supports this position. As noted, two nicotine dosage forms are on the market for treatment of nicotine withdrawal as an aid to smoking cessation (nicotine polacrilex gum and nicotine transdermal patches). FDA is reviewing a New Drug Application (NDA) for a third dosage form, an aqueous nicotine nasal spray. The nicotine nasal spray was the subject of an August 1994 FDA Drug Abuse Advisory Committee meeting because of its possible addiction liability. Among subjects who used the spray for a year during one of the trials, several reported that they felt dependent on the spray, displayed withdrawal symptoms upon stopping the spray,

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Levin ED, Behm F, Rose JE. The use of flavor in cigarette substitutes. *Drug and Alcohol Dependence*. 1990;26:115-160.

Rose JE, Tashkin DP, Ertle A, Zinser MC, Lafer R. Sensory blockade of smoking satisfaction. *Pharmacology Biochemistry and Behavior*. 1985;23:289-293.

<sup>113</sup> Surgeon General's Report. 1988. Nicotine Addiction. Pages 264-265, 309.

<sup>114</sup> See Rose, note 100, *supra*.

<sup>115</sup> See:  
Rose, Tashkin, et al, note 112, *supra*.

Rose, note 100, *supra*.

and sometimes used the spray in larger quantities and more frequently than was required by the study protocol -- all despite the fact that use of the spray was unpleasant and caused nasal ulcers and other medical problems for some participants.<sup>116</sup>

The ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users seek nicotine primarily for its systemic pharmacological effects, and not for its acute sensory effects. The spray vehicle and dispensing system of the nicotine nasal spray are rudimentary; it is merely nicotine in water forced through an aspirator to make a nasal mist. In contrast to cigarette smoke, aqueous nicotine spray does not provide the user any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, can impart a very unpleasant taste if it runs down the nose and into the throat, and excessive use can cause ulcerations of the nasal mucosa. Notwithstanding the unpleasantness of the nicotine delivery mechanism, and the presence of painful ulcerations that were further aggravated by continued use of the spray, the spray was used to maintain nicotine dependence for many of the participants in its clinical trials.<sup>117</sup>

The dependence upon nicotine nasal spray illustrates a physical need for nicotine's pharmacological effects, not merely in the absence of any pleasurable sensory effects that may be associated with nicotine in cigarette smoke, but even in the face of rather unpleasant

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<sup>116</sup> E. Douglas Kramer, M.D. Testimony before the Drug Abuse Advisory Committee. August 1, 1994. Drug Abuse Advisory Committee Meeting Transcript. Pages 58-63. Nicotine nasal spray is unique among nicotine replacement therapies in that it produces peak blood levels of nicotine almost as quickly as inhalation of cigarette smoke.

<sup>117</sup> FDA Drug Abuse Advisory Committee Background Information. August 1, 1994. Joint Abuse Liability Review of Nicotine Nasal Spray.

and even painful sensations. This provides strong evidence that nicotine is sought by tobacco users who are dependent upon it for reasons other than its pleasurable, acute sensory effects in the mouth, nose, and throat.

## 5. Other Factors Associated with Tobacco Use Are Secondary

There are other factors that play a role in the decisions to begin and continue the use of tobacco.<sup>118</sup> For example, social and psychological factors play a role in the initiation of smoking and, to a lesser extent, the maintenance of tobacco use.<sup>119</sup> In particular, parents, peers, and older siblings greatly influence the likelihood that a young person will smoke cigarettes.<sup>120</sup> There is also evidence that adolescents begin to smoke because it promotes sociability, plays a part in establishing friendships, and because it makes them feel mature.<sup>121</sup> Tobacco advertising also plays a role in the decision to start using tobacco.<sup>122</sup> It is recognized

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<sup>118</sup> Tate JC, Pomerleau CS, Pomerleau OF. Pharmacological and non-pharmacological smoking motives: a replication and extension. *Addiction*. 1994;89:322.

<sup>119</sup> See:  
Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Pages 124-140.

Stepney R. Smoking behaviour: A psychology of the cigarette habit. *Br J Dis Chest*. 1980;74:325-344.

<sup>120</sup> See:  
Bewley BR, Bland JM, Harris R. Factors associated with the starting of cigarette smoking by primary school children. *Brit J Prev Soc Med*. 1974;28:37-44.

Murray M, Cracknell A. Adolescents' views on smoking. *J Psychosom Res*. 1980;24:248-249.

Banks MH, Bewley BR, Bland JM, Dean JR, Pollard V. Long-term study of smoking by secondary schoolchildren. *Arch Disease in Childhood*. 1978;53:14-16.

<sup>121</sup> See:  
Bewley, note 120, *supra*.

Bewley BR, Bland JM. Academic performance and social factors related to cigarette smoking by schoolchildren. *Brit J Prev Soc Med*. 1977;31:18-24.

Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Page 124.

<sup>122</sup> See:  
Surgeon General's Report. 1994. *Preventing Tobacco Use Among Young People*. Pages 191-192.

Cocores JA. Smokeless Tobacco. In: Cocores JA, ed. *The Clinical Management of Nicotine Dependence*. New York, NY: Springer-Verlag; 1991:49.

that many of the mannerisms and processes associated with smoking may, in the perception of the smoker, become pleasurable linked with tobacco use. These mannerisms or processes may deliver some element of pleasure to the smoker, independent of the inhalation of tobacco smoke.<sup>123</sup>

It is widely accepted, however, by medical and public health groups that the maintenance of tobacco use is due primarily to the addictive properties of nicotine and not solely to these social and psychological factors.

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<sup>123</sup> Christen AG, Glover ED. Psychological satisfactions derived from smoking cigarettes in fifty-seven dental patients. *J Drug Educ.* 1983;13(1):95-102.