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Review

Initial tobacco use episodes in children and adolescents: current knowledge, future directions

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Contents

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Abstract

Approximately three-quarters of adult tobacco users report that their first tobacco use occurred between ages 11 and 17, while many adults who do not regularly use tobacco report that they experimented with it as adolescents. Surprisingly little is known about the effects of these initial tobacco use episodes and their influence on adult tobacco use patterns. In particular, understanding the role that nicotine plays in these early tobacco use experiences may be important in understanding the development of regular tobacco use and concomitant nicotine dependence. One goal of this review is to summarize current knowledge regarding the effects of initial tobacco use episodes in adolescents and to discuss nicotine exposure in initial tobacco use episodes. Another goal is to outline a research agenda designed to learn more about initial tobacco use episodes and the effects of nicotine in children. An ethical rationale and some potential methods for this research agenda are presented.

Keywords: Adolescent smoking; Children; Tobacco; Cigarettes; Experimental tobacco use; Initial tobacco use; Review

1. Introduction

Approximately three-quarters of adult tobacco users (i.e. cigarette and cigar smokers and users of smokeless tobacco, or SLT) report that their first tobacco use occurred during childhood or adolescence (11–17 years; United States Department of Health and Human Services, 1994a,b; Riley et al., 1996). Similarly, many adults who do not regularly use tobacco report that they have experimented with it, usually as adolescents (McNeill, 1991). There are no definitive data on how important these initial use episodes are in determining who becomes a regular tobacco user and who does not, though one estimate suggests that 94% of individuals who smoke four or more cigarettes go on to use them regularly (Russell, 1990). Nonetheless, there are suggestions that the effects of the first tobacco use episode may play a role in initiating or preventing a regular pattern of tobacco use by producing positive effects in the eventual regular user, but producing aversive effects in the eventual non-regular user (Kozlowski and Harford, 1976; Silverstein et al., 1980, 1982; Pomerleau et al., 1993). Knowing the role that nicotine plays in the effects of these early tobacco use experiences may be important in understanding the development of nicotine dependence. For adult tobacco users, nicotine is delivered in pharmacologically active doses either through the lungs (cigarette smokers) or oral mucosa (cigar smokers; smokeless tobacco users, SLT). In adults, nicotine's direct pharmacologic activity, as well as the withdrawal produced by tobacco/nicotine abstinence are thought to play an important part in maintaining tobacco use behavior in adults. Whether an adolescent's initial tobacco use episode results in delivery of pharmacologically active doses of nicotine has not been addressed directly. However, this issue may be central to understanding the role that nicotine plays in continued tobacco use in the adolescent population.

Unfortunately, controlled examination of the effects of tobacco use in children or adolescents can be difficult for at least two reasons. First, experiments involving self-administration of an addictive drug in this vulnerable population present ethical and practical challenges, including maintaining confidentiality while obtaining parental consent, and potentially furthering the addictive process. Second, identifying adolescent tobacco users early in their history of use can be problematic because traditional methods of detection (e.g. salivary cotinine, carbon monoxide levels) may be unreliable when tobacco use is intermittent (McNeill et al., 1987a). Nonetheless, the fact that tobacco use is implicated in the premature deaths of over 400 000 Americans and costs over $50 billion in health care expenses annually drives the need to understand what causes some individuals who use tobacco to become nicotine-dependent while others do not. Additionally, reports indicating that experimental smoking during adolescence doubles the risk of adult smoking (Chassin et al., 1990) and that over 42% of high school students use tobacco (United States Department of Health and Human Services, 1998a), highlight the need to understand the effects of initial tobacco use episodes in young people.

The purpose of this review is to examine existing data on initial tobacco use episodes in adolescents, with particular attention to:

1. the effects adolescents experience after their initial tobacco use episode;
2. nicotine exposure during initial use episodes; and
3. how adolescents use tobacco (i.e. topography of use).

Where possible, this review will focus on data collected from children or adolescents regarding their

initial tobacco use episodes. Where data from children or adolescents are not available, information gained from adult smokers will be used, with the understanding that information from adult smokers might be helpful in guiding future research into adolescent smoking. The review will conclude with a summary of what information would be most helpful in furthering the understanding of initial tobacco use episodes in adolescents and some methods that might be used to obtain that information.

2. The effects of initial tobacco use episodes in children and adolescents

A potential method of investigating initial tobacco use episodes might be to identify adolescents before their first tobacco use and then to observe them during their first use — perhaps by collecting subjective and physiological response data immediately before and after the first use episode. This idealized experiment presents several potential ethical concerns, however, as well as obvious difficulties in identifying subjects. Less ideally, but more practically, potentially valuable data can be obtained by asking adolescents who have used tobacco at least once to report the effects of that use retrospectively. Selective recall and other psychological factors may complicate the interpretation of these retrospective data and these complications may intensify as subjects age (Gorsuch and Butler, 1976). Because these complicating factors are likely more pronounced in adults, data from adult smokers asked to retrospectively report their initial tobacco use experience (Pomerleau et al., 1998) are not included in this review. Rather, the review focuses on studies where adolescent subjects have been asked to recall and report their initial tobacco use episode. Results from these studies are generally consistent and suggest that a low incidence and/or severity of aversive effects after initial tobacco use may be important in determining which adolescents become regular users of tobacco. Interestingly, many of the retrospectively reported effects of tobacco use are consistent with the delivery of pharmacologic doses of nicotine. These data are reviewed below.

2.1. Retrospective data from children and adolescents

In one of the first studies to examine retrospective reports of the effects of tobacco use in children (Bewley et al., 1974), an initial survey of 7115 English children aged 10–12 was used to identify heavy smokers (≥ 1 cigarette/day; cpd), light smokers (< 1 cpd), and experimental smokers (ever puffed or smoked a cigarette). Having identified members of each category, heavy smokers and light smokers were randomly sampled and matched for school class and age with experimental smokers. Due to a low proportion of girls in each group, only data from boys (29 heavy, 48 light, and 77 experimental smokers) were presented. These smokers responded to a self-administered questionnaire designed, in part, to elicit reports about the feeling produced by each smoker's first cigarette. The data suggest that fewer heavy smokers were made sick by their first cigarette: 20.7% of heavy, 39.6% of light, and 35.5% of experimental smokers reported they felt sick after their first cigarette. More regular smokers (heavy and light) reported positive effects and that they enjoyed their first cigarette (27.6% of heavy, 22.9% of light) as compared to experimental smokers (13.2%). In each group $\sim 31\%$ reported that they felt nothing from their first cigarette. In another survey study of 1431 US high school students, similar results were observed. Persistent experimentation with tobacco products (i.e. greater than ten uses; 37% of the sample) was associated with more reports of 'feeling high' and fewer reports of 'feeling sick' after the cigarette, relative to minimal experimentation, especially amongst girls (Curry et al., 1989). Even amongst the persistent users, however, only 40% of the boys and 41% of the girls reported 'feeling high' (Curry et al., 1989). These retrospective data are consistent with the idea that the effects produced during a first tobacco use episode may help to predict later regular use of tobacco. Importantly, data from these studies suggest that pleasurable effects of smoking are, at best, of moderate importance in maintaining smoking behavior; for example, only 28.7% of subjects in one study indicated that they thought smoking was enjoyable (Bewley et al., 1974).

Data indicating that the first smoking experience is often reported as aversive (Bewley et al., 1974) are consistent with data collected from American college undergraduates (Kozlowski, 1975; unpublished data, as cited in Kozlowski and Harford, 1976). Kozlowski (1975) identified non-smoking subjects who had smoked at least one cigarette and compared them to current smokers by asking them to recollect any physical discomfort after smoking their first cigarette. Of those who could recall any reaction, 80% of the non-smokers and 10% of the smokers reported moderate or extreme physical discomfort ($P < 0.01$; Kozlowski and Harford, 1976). Thus, physical sensitivity to tobacco's effects, particularly aversive effects, may predict future tobacco use.

Two relatively recent studies (Friedman et al., 1985; Hahn et al., 1990) using structured interview techniques in adolescents, support the conclusion that aversive nicotine-like effects are experienced by some first-time tobacco users, but that these effects may become less intense with repeated tobacco exposure. For example, 157 persistent and minimal 7–12th grade smokers were interviewed regarding their first three smoking

episodes (Friedman et al., 1985). As a whole, few subjects who had tried at least three cigarettes reported pleasant effects (e.g. high, relaxed), but reports of unpleasant effects (dizziness, sickness) were more frequent. These unpleasant effects decreased in frequency across the first three smoking episodes, suggesting some form of tolerance. Similarly, 320 7–10th graders were interviewed regarding their first and most recent tobacco use episodes; SLT users ($n = 62$) were also included in this sample (Hahn et al., 1990). Overall, 50% of the subjects interviewed reported negative effects of first tobacco use (e.g. headache or sickness), 40% reported no effects, and 10% reported feeling 'buzzed'. Reports of negative effects decreased from first to most recent use, but positive effects did not increase. In both studies, reports of pleasant effects of smoking were more likely in persistent users relative to minimal users (Friedman et al., 1985; Hahn et al., 1990). Thus, the results of these two studies indicate that tobacco produces both aversive and positive effects in initial users, and that both of these effects may be important in determining the likelihood of continued use.

In an effort to understand the factors that influence progression from a first cigarette to regular smoking, Hirschman et al. (1984) conducted a 30–40-min, tape-recorded, structured interview with 386 urban public school children in grades 2–10. Items in the interview included the effects of the first three smoking episodes, as well as the latency to the second cigarette. Of those interviewed, 183 (47.4%) students reported having tried a first and 59 (32.2%) a second cigarette. For the first cigarette, 87.9% of the subjects interviewed reported at least one of the following effects: coughing, dizziness, sickness, burning throat, headache, or nausea. Of these effects, dizziness was reported by 44.0%, sickness by 37.6%, headache by 33.3%, and nausea by 23.1% of respondents. Interestingly, reports of dizziness (and not coughing) after the first cigarette were associated in a stepwise regression with a quick progression to a second cigarette (i.e. second cigarette within a week, $n = 23$). Thus, this subjective effect may seem aversive by its description, but may function as a reinforcer of smoking behavior. In contrast to other reports (Bewley et al., 1974; Kozlowski and Harford, 1976), aversive effects such as burning throat, headache, sickness, or nausea did not influence subsequent use in the Hirschman et al. (1984) sample.

One factor that may influence how the effects of tobacco are perceived among first-time users is the presence or absence of more experienced users during the first use episode. Experienced users may minimize the importance of negative effects, such as nausea while identifying other effects, such as dizziness, with positive descriptors, such as 'rush' or 'buzz'. In one study, $\sim 89\%$ of smokers were accompanied by others during their first three smoking episodes, and continued smoking was associated with an increased number of people present during these initial episodes (Friedman et al., 1985). These results are consistent with a more recent report indicating that tobacco experimentation most often occurs in small, same-sex, peer and sibling groups (Hahn et al., 1990) but are not consistent with another report suggesting that the presence of other smokers during an initial smoking episode was not associated with persistent experimentation (Curry et al., 1989). Identifying the exact role that these groups play in the initial tobacco use episode will be an important part of understanding the transition from initial to continued tobacco use.

2.2. Summary

Data from these studies, in which adolescent subjects were asked to recall their initial experience with tobacco, provide some support for the notion that adolescent smokers who eventually become regular tobacco users report fewer dysphoric effects from their initial use episode than adolescents who do not become regular users. However, in some studies, eventual regular users reported that they felt more positive effects (Friedman et al., 1985; Hahn et al., 1990), as has been reported for adult smokers (Pomerleau et al., 1998). More experienced peers may influence how first-time users perceive some tobacco effects. The methodology of all of these studies involved retrospective questionnaire data, which may be biased by poor and/or selective recall. Also, none of the studies included biochemical validation of smoking status, thus accurate categorization of subjects into groups defined by tobacco use frequency may have been limited. Nonetheless, these studies have the virtue of including adolescent subjects whose early use episodes were likely recent, relative to the time of data collection. Adult tobacco users, whose early use episodes would likely be less recent, may bias recollection of the effects of those episodes in order to be consonant with their current use status. Clearly, prospective studies that avoid issues of biased recall will be most informative.

Several of the effects of tobacco reported by adolescent users suggest that their tobacco use may include self-administration of a pharmacologically active compound. There are over 4000 potentially biologically active constituents of tobacco smoke. Precisely identifying which constituent produces which reported effect may be challenging. For example, the action of two tobacco smoke constituents, nicotine and carbon

monoxide (CO), may explain reported effects of dizziness. Some of the negative effects of tobacco use, especially in adolescents who do not use tobacco regularly, are similar to the effects reported by non-smoking adults presented with either i.v., s.c., or intranasal nicotine (Perkins et al., 1994; Soria et al., 1996; Foulds et al., 1997). For example, Foulds et al. (1997) administered two injections of 0.6 mg nicotine s.c. (spaced 40 min apart) to adult never-smokers and 24-h abstinent smokers. Both groups reported increased dysphoric symptoms (e.g. sweating, nausea, dizziness, etc.), but the never-smokers' symptom ratings were significantly greater than the smokers' (Fig. 1). This difference between never-smokers and smokers may have been due to tolerance in the smokers to nicotine's subjective effects. However, smokers were not tolerant to nicotine's effects on heart rate: both smokers' and non-smokers' heart rate increased comparably following nicotine administration (Foulds et al., 1997). A similar difference, greater dysphoria and less euphoria in adults who were non-smokers as compared to smokers, was reported after i.v. nicotine administration (Soria et al., 1996) and after intranasal nicotine administration (Perkins et al., 1994). These results from adults, along with some of the retrospective data from adolescents reviewed above, are consistent with the idea that people who become regular tobacco users may be less sensitive to nicotine's dysphoric effects than those who remain non-users. This decreased sensitivity to nicotine-induced dysphoria may reflect an underlying physiological difference in response to nicotine and/or a more rapid acquisition of acute and/or chronic tolerance to these dysphoric effects (Perkins et al., 1994); other mechanisms, such as sensitization to the rewarding effects of tobacco constituents, may also contribute to the likelihood that an individual who tries tobacco will become a tobacco user.

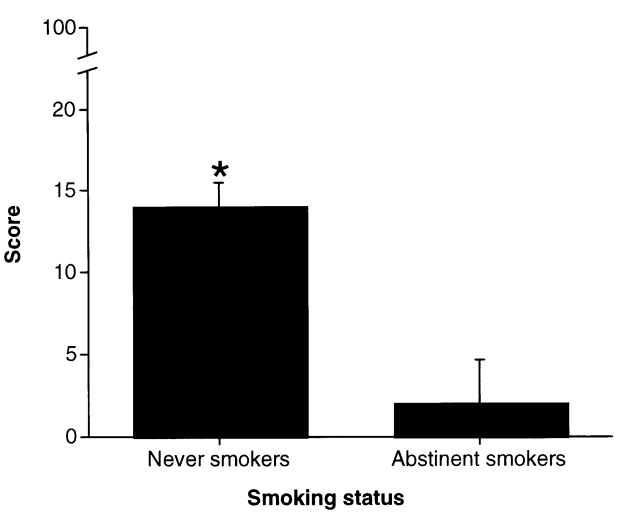

Fig. 1. Adult never smokers' ($n = 18$) and abstinent smokers' ($n = 18$) average response on an adverse nicotine symptoms checklist after receiving 0.6 mg nicotine s.c. Data are taken from Foulds et al. (1997) (pp. 109, 113). Bars are ± 1 S.E.M. * Indicates a significant between-group difference ($P < 0.001$) by Student's t-test.

The idea that tobacco-delivered nicotine can produce dysphoric effects in the initial user, and that an initial dysphoric response decreases the probability of a user progressing to regular use is apparently known in the tobacco industry, where marketing strategies reduce the likelihood of a dysphoric response in beginning users (most likely, adolescents). For example, so-called 'starter products' for SLT users provide a measured tobacco 'dose' with less nicotine than normal SLT products (Henningfield and Nemeth-Coslett, 1988; Kessler et al., 1997). Similarly, the introduction of 'low nicotine' cigarettes may have contributed to the increase in adolescent smoking by decreasing the likelihood of nicotine intoxication in novice smokers (Silverstein et al., 1980). Clearly, more data regarding the interaction of initial use behavior with nicotine dose and the effects of nicotine dose on future smoking habits are necessary.

3. Tobacco smoke and nicotine exposure during initial use episodes

Many of the effects of initial tobacco use episodes that have been reported by adolescents are consistent with the effects of nicotine, CO, and/or other constituents of tobacco smoke. However, the actual dose of these constituents delivered during an initial use episode are unknown. For nicotine, dose is directly related to tobacco nicotine content and other tobacco-specific factors (Henningfield and Nemeth-Coslett, 1988). Also, for smokers, the dose of virtually any smoke constituent is probably influenced by puff topography (i.e. puff number, volume, duration, and/or intensity) and smoke pH. For SLT users nicotine dose is probably related to amount of tobacco, volume and pH of saliva, and location of SLT in the mouth (Henningfield and Nemeth-Coslett, 1988). This section presents evidence suggesting that adolescent tobacco users are exposed to nicotine during their first few tobacco uses, and then briefly examines the relationship between smoking topography and blood nicotine levels in adult tobacco users with the goal of determining which topography measures are most predictive of nicotine dose.

3.1. Adolescent tobacco users may be exposed to nicotine

Initial tobacco use episodes need not necessarily result in nicotine administration, especially if smoke is not inhaled or SLT does not remain in the mouth. However, biochemical markers of nicotine intake, such as salivary levels of the nicotine metabolite cotinine, suggest that

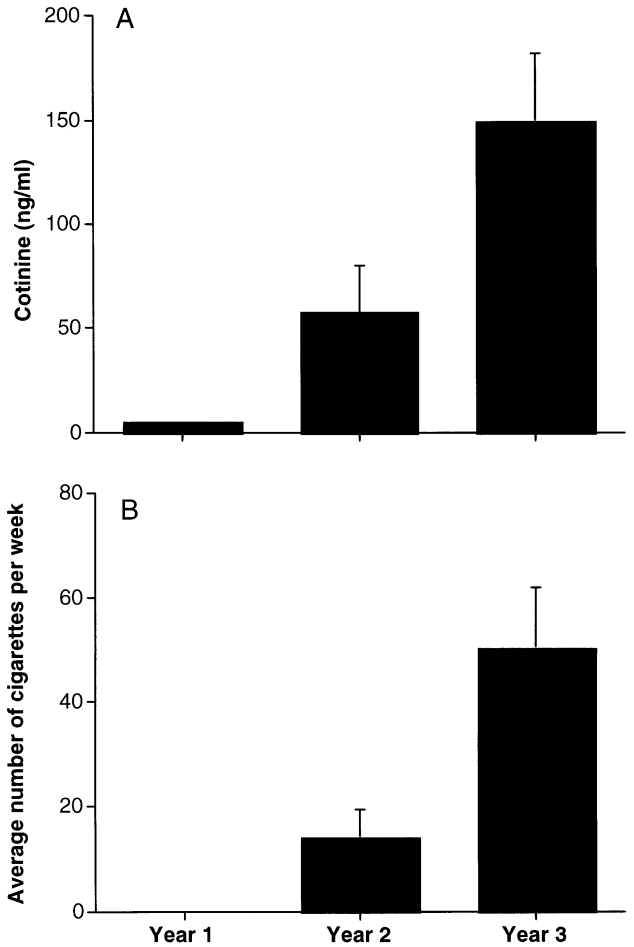

Fig. 2. Average cotinine levels (panel A) and number of cigarettes smoked (panel B) for 12 girls (age 11–15) who were non-smokers in year 1 but became smokers between years 1 and 2. Data from McNeill et al. (1989) (p. 174). Bars are ±1 S.E.M.

adolescent smokers self-administer nicotine early in their tobacco use history. For example, 173 11–16-year-old girls were surveyed with regard to their current smoking status and saliva samples were also collected for later analysis (McNeill et al., 1987b). Mean salivary cotinine level was directly related to self-reported number of cigarettes smoked each week: subjects who reported smoking less than one cigarette/week had the lowest level of salivary cotinine (mean = 13.1 ng/ml), those who smoked one to six cigarettes/week had a higher cotinine level (mean = 26.1 ng/ml) while those who smoked more than six cigarettes/week had the highest levels (mean = 200.8 ng/ml). By comparison, adult smokers sampled from the same country (England) 3 years earlier who smoked an average of 92 cigarettes/week had a mean saliva cotinine level of 309.9 ng/ml (Jarvis et al., 1984). These data show that adolescent smokers extract nicotine from cigarettes and that their salivary cotinine levels are similar to those that might be expected of adult smokers using comparable numbers of cigarettes.

3.1.1. Direct effects of tobacco use are consistent with nicotine exposure

A longitudinal study of 197 11–14-year-old girls also showed a direct positive relationship between cigarette intake and salivary cotinine (McNeill et al., 1989): for daily and occasional smokers, both weekly cigarette consumption and salivary cotinine increased over the 3-year study. This study is particularly noteworthy, as its longitudinal design allowed data collection from non-smokers in year 1 who became smokers in year 2 (average 14.3 cigarettes/week). For these 12 subjects, salivary cotinine concentrations increased from 5.3 (year 1) to 57.9 ng/ml (year 2), and then to 149.4 ng/ml (year 3) (Fig. 2). These data are important, as they demonstrate that adolescent smokers clearly receive nicotine from cigarettes early in their smoking careers and that their nicotine self-administration behavior increases with increased cigarette intake. Such longitudinal studies, perhaps with shorter intervals between measurements, may reveal more information about the nicotine exposure of initial tobacco use episodes in both smokers and SLT users.

There are few data characterizing the nicotine exposure of adolescent SLT users. Those data that exist make clear that these users are exposed to nicotine (Cohen et al., 1988; Noland et al., 1988; Bauman et al., 1989). However, measuring nicotine exposure from SLT in adolescent users can be challenging, as many adolescents who use SLT also smoke cigarettes (Noland et al., 1988). Both products can contribute to salivary and plasma levels of nicotine and/or cotinine. Nonetheless, careful measurement of several variables can aid in the detection of SLT use. For example, Bauman et al. (1989) sampled saliva from 1854 12–14 year olds and, using results from analyses for cotinine, thiocyanate, and alveolar carbon monoxide, determined that there were 76 SLT-only users in this group. These adolescent SLT-only users had a median salivary cotinine level of 46.8 ng/ml (range = 10.0–2908.8 ng/ml), indicating that even young SLT users self-administer measurable nicotine doses.

In adult habitual SLT users, plasma nicotine levels are equal to or greater than levels achieved by smokers (Gritz et al., 1981; Russell et al., 1981; Pershagen, 1996; Benowitz, 1997; Fant et al., 1998). For example, a recent study with adult subjects using a variety of SLT products demonstrates that SLT users can attain fairly high levels of plasma nicotine (Fant et al., 1998). Adult SLT users used 2 gm SLT (Skoal Bandits®, Skoal Wintergreen®, Skoal Copenhagen®) for 30 min. After 30-min use, plasma nicotine increased in these subjects by ~5–20 ng/ml, depending on the SLT product. Skoal Bandits® produced the smallest increases; Copenhagen® produced the largest increases in blood nicotine levels (i.e. 20 ng/ml). While blood nicotine levels in adult SLT users may be equal to or sometimes greater than those found in adult smokers, these levels can be

maintained in SLT users for a much longer time than in the smoker (Benowitz et al., 1988). If experienced, habitual adolescent SLT users are like adult SLT users, they are likely to receive prolonged high levels of nicotine once they progress from starter products such as Skoal Bandits®. Unfortunately, relatively little is known about adolescent SLT users despite the fact that an estimated 824 000 adolescents each year experiment with SLT (Tomar and Giovino, 1998), that SLT use is increasing in young people (Henningfield et al., 1997), and that SLT use may serve as a 'gateway' to cigarette use in young people (Pershagen, 1996).

3.1.2. Tobacco abstinence effects are consistent with nicotine exposure

When abstaining from tobacco, adolescent smokers report withdrawal symptomatology similar to that of abstaining adult smokers (McNeill, 1986; McNeill, 1991; Ershler et al., 1989; United States Department of Health and Human Services, 1994a; Stanton, 1995; Prokhorov et al., 1996; Rojas et al., 1998). For example, 249 10th grade smokers who had tried to quit smoking in the past reported that they experienced withdrawal symptoms such as: needing to smoke, nervousness, restlessness, irritability, hunger, and difficulty concentrating (McNeill et al., 1986; Rojas et al., 1998). Abstaining adult SLT users also experience similar tobacco withdrawal symptoms (Hatsukami et al., 1992; Boyle et al., 1995), as do abstaining adolescents (United States Department of Health and Human Services, 1994a). These results indicate that like adults, adolescents become tobacco-dependent; this dependence is likely due in part to nicotine self-administration.

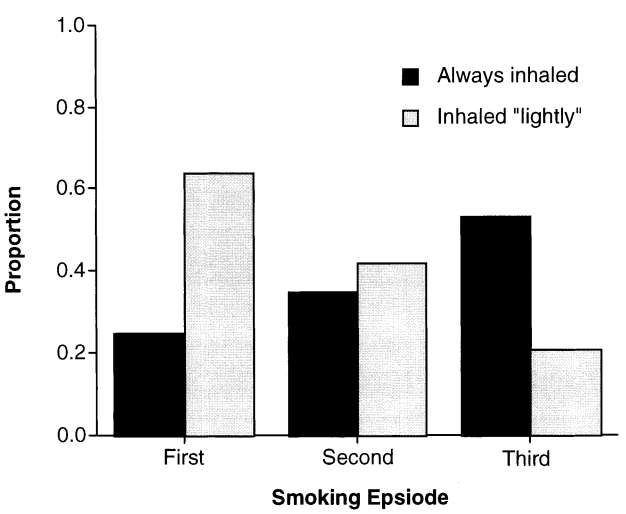

Fig. 3. Proportion of teenagers who indicated that they always inhaled (stippled bars) and inhaled lightly (filled bars) during their 1st, 2nd, and 3rd smoking episode. Data are taken from Friedman et al. (1985) (p. 6). The number of subjects varies across smoking episode, but is always >27.

3.2. Tobacco use factors that influence nicotine exposure

Nicotine exposure is related to the pattern of tobacco use as well as tobacco-specific factors such as nicotine level, additives, etc. One type of analysis of tobacco use involves measuring the amount of tobacco used each day (e.g. cigarettes/day; 'dips'/day), and amount used is directly related to cotinine levels in adolescents (McNeill et al., 1989) and adults (Benowitz, et al., 1983). A finer analysis of tobacco use involves the nicotine delivery of each use episode. For smoked tobacco, such an analysis means measuring the number, volume and duration of cigarette puffs. In adults, these puff topography variables are also related to nicotine/cotinine intake (Herning et al., 1983; Zacny et al., 1987; Bridges et al., 1990; Hofer et al., 1992; Rieben, 1992). For SLT, a similarly fine analysis might mean measuring the size of each 'dip' or 'plug' as well as a study of chewing behavior (e.g. time spent 'working' the tobacco). No such detailed microanalysis of SLT use has been reported, though one study has demonstrated that the number of 'dips' per day is correlated with saliva cotinine levels in adult male SLT users (Severson et al., 1990).

Understanding tobacco use onset may involve studying the first several tobacco use episodes, thus a very fine analysis of tobacco use is required. That is, for the first use episode, the relationship between topography of use, nicotine intake, and the resulting subjective/physiological effect may be critical for determining the likelihood and/or frequency of subsequent tobacco use behavior. No such data currently exist. This section first reviews the data that do exist regarding initial use and nicotine exposure and then reviews which topography variables might be most informative for understanding the nicotine exposure that occurs during an initial tobacco use episode.

3.2.1. Initial use topography in children and adolescents

Using retrospective survey methods, three studies have examined the topography of initial smoking episodes in adolescents (Hirschman et al., 1984; Friedman et al., 1985; McNeill et al., 1987a). In one, 183 public school children who had tried cigarettes were asked to recall their first smoking experience (Hirschman et al., 1984). For the first cigarette, 47.2% of these young smokers reported 'inhaling a little', while 16.1% 'inhaled deeply'; 36.7% did not inhale. Only 4.4% of these first time smokers in this sample reported smoking the whole cigarette. Thus the smokers who reported 'inhaling a little' or 'deeply' (63.3%) may have experienced effects that led them to not complete their first cigarette. Similar results regarding probability of inhalation were reported by 157 7–12th grade smokers (Friedman et al., 1985) who described their first

three smoking episodes. Retrospective data from these smokers reveals that the probability of inhalation increased over the first three smoking episodes, from a low of 0.46 for the first cigarette to a high of 0.77 for the third. Self-rated depth of inhalation also changed as a function of cigarette number: subjects were asked 'How deeply did you inhale?' and the proportion that responded with 'lightly' decreased from 0.64 for the first cigarette to 0.21 for the third (Fig. 3). While such retrospective, self-rated data regarding puff topography may have questionable validity, self-reported depth of inhalation has been shown to be well-correlated with expired breath CO and salivary cotinine among adolescents (McNeill et al., 1987a). To the extent that retrospective self-reported data are reliable and valid, adolescent smokers are likely to have been exposed to nicotine early in their smoking careers, perhaps within their first three cigarettes. Little information is currently available on adolescent SLT users and nicotine exposure.

3.2.2. Smoking topography and nicotine exposure in adults

Retrospective data describing tobacco use effects and topography may be influenced by a variety of factors, including poor and/or selective recall. Thus, data suggesting that adolescents' initial tobacco use episodes involve nicotine-like effects and a topography consistent with nicotine self-administration must be interpreted cautiously. However, in adult smokers, actual smoking topography measures such as puff number, volume, and frequency demonstrably influence nicotine exposure (Zacny et al., 1987; no SLT topography data are available). This relationship between tobacco use topography and nicotine exposure in adults is briefly reviewed below in an attempt to determine which topography variables would most likely predict nicotine exposure in future studies of adolescent smokers.

Some puff topography measures (e.g. puff number and duration, inter-puff interval) can be measured by careful observation (Ashton and Watson, 1970; Moody, 1984; Hofer et al., 1992); others (puff volume and peak flow rate) involve one of a variety of computerized measurement systems (Herning et al., 1983; Zacny and Stitzer, 1986; Hofer et al., 1992; Eissenberg et al., 2000). For those measures that may be observed, there is good agreement between observational and computerized measurement (Henningfield et al., 1980; Hofer et al., 1992). Topography measurement can be accomplished in a laboratory (Zacny et al., 1986; Eissenberg et al., 2000) or in a more naturalistic setting (Hatsukami et al., 1987). Current technology allows sophisticated measurement of all topography variables to be accomplished with battery-operated, portable (i.e. laptop) computer systems. Thus topography data can be collected at virtually any location convenient for adolescent smokers (i.e. school, home, shopping mall, etc). Saliva samples can also be collected with similar ease, for later analysis of cotinine.

Data from studies across several laboratories using different measurement devices generally indicate that puff number and volume are important in determining blood nicotine levels (Herning et al., 1983; Zacny et al., 1987; Bridges et al., 1990; Hofer et al., 1992; Rieben, 1992). Puff number may explain more variability in plasma nicotine levels than does puff volume (Rieben, 1992; but see Hofer et al., 1992 for contradictory data), though these data are from adult smokers whose smoking topography patterns may have been well established and thus fairly consistent from one puff to the next (i.e. low between-puff variability). Adolescent smokers may have less well-established topography patterns and, therefore, between-puff variability may be greater. Increases in puff volume influence self-administered nicotine dose by increasing the amount of smoke (Djordjevic et al., 1995, 1997) and blood nicotine concentrations (Zacny et al., 1987). Thus, puff volume may be more influential in determining nicotine exposure in adolescents compared to adults. Laboratory study of the relationship between topography measures and nicotine exposure in adolescent tobacco users will be most helpful in determining which measures best predict nicotine exposure.

3.3. Summary

There is a growing body of literature suggesting that adolescent tobacco users, both smokers and SLT users, are exposed to nicotine early in their tobacco use careers. This conclusion is supported by converging lines of evidence using biological samples from adolescents who smoke regularly, (e.g. saliva cotinine; McNeill et al., 1987b; Bauman et al., 1989), the nature of effects remembered from early use episodes (Friedman et al., 1985; Hahn et al., 1990), reports of withdrawal symptoms during tobacco abstinence (United States Department of Health and Human Services, 1994b; Rojas et al., 1998), and retrospective reports of use topography (Friedman et al., 1985). Other tobacco constituents of tobacco use, such as those that contribute to non-nicotine mediated MAO-B inhibition (Fowler, et al., 1998), may also contribute to the effects of tobacco in young users. Unfortunately, there are no data that reveal conclusively the exposure to nicotine and other tobacco smoke constituents and their resulting physiological and subjective effects in adolescents who use tobacco for the first time. Such data may be essential in understanding and deterring future tobacco use.

4. What research is needed next?

The preceding review has made clear that much remains to be known about initial tobacco use episodes

and the acquisition of tobacco use behavior among children and adolescents. Ideally, learning about the acquisition of tobacco use would include observing the details of this behavior as it emerges among different groups of young people. Such observation would be very informative, especially if it entailed cigarette-by-cigarette, dip-by-dip, or puff-by-puff records of tobacco use in real time. This detailed observation might allow the development of a 'cumulative record' of drug dependence acquisition, akin to the records produced during the acquisition of other learned behaviors. These records do not exist for the acquisition of any drug or alcohol abuse behavior in humans. One likely finding from this line of research might be that early use patterns are highly variable within individuals, but become more stereotyped as addiction develops. Indeed, the speed with which stereotyped use patterns develop may be an early index of dependence and/or dependence liability. Variable early use patterns, prior to stereotyped behavior pattern development, may be the most amenable to behavioral interventions. However, with knowledge of these patterns incomplete, forming empirically derived classifications of the different trajectories, theories as to their determinants, and their susceptibility to intervention is difficult. If such information could be obtained for modal patterns of the acquisition of tobacco abuse, it may also contribute to the understanding of the etiology of drug addictions in general. In this section some potential areas of future research are described that address questions related to the acquisition of tobacco use behavior. Throughout the following section readers should note two important points: (1) the research areas/questions identified here are not intended to be exhaustive, but should be seen as areas of more immediate need, and (2) where possible, comparisons between boys and girls should be made to determine if and how gender plays a role in the acquisition of tobacco use.

4.1. Definition of the initial tobacco use episode

A clear definition of an initial use episode must be established. Establishing that definition means addressing several difficult questions. In smokers, does the first puff of a cigarette, the first attempted complete cigarette, or the first completed cigarette constitute initial use? How are non-inhaled puffs accounted for in terms of a use episode? In SLT users, is the first placement of a 'dip' in the mouth an initial use or does 'use' imply some elapsed time between placement and removal? Defining characteristics of the initial use episode is critical to understanding the effects of that episode: the effects of the first puff of another child's cigarette may be very different from the effects of the first completed cigarette and/or the first inhaled puffs. The increasing popularity of cigars and the potential for adolescent SLT users to use cigarettes concurrently highlight the need to define initial tobacco use episodes precisely and comprehensively.

4.2. Descriptive information and the relationship between initial and regular use

As described, retrospective accounts of the effects of adolescents' (Friedman et al., 1985; Hahn et al., 1990) and adults' (Pomerleau et al., 1998) initial tobacco use episodes suggest that tobacco use can be accompanied by some drug-like subjective effects (e.g. nausea, dizziness, pleasurable 'rush' or 'buzz'). The importance of these retrospective data might be enhanced if they were supported by prospective data collected from adolescent tobacco users at the beginning of, or at least early in, their tobacco use history. Such prospective data may answer several important questions about the subjective effects of smoking, nicotine intake, etc. Chief among these is a determination of the extent to which the subjective and physiological effects of the first few tobacco use episodes are related to chronic tobacco use. In a related point, knowing the role that nicotine plays in producing subjective and other effects will help to determine if reducing the nicotine content of tobacco products will reduce adolescent smoking behavior.

Descriptions of early use episodes must also take into account the variety of non-pharmacological factors that may influence those episodes. These factors include the setting in which the use occurs, the demographic and socioeconomic characteristics of the users and their peer groups, previous and/or concurrent drug use (e.g. alcohol and/or marijuana use), and the role that social factors play in initiating and maintaining tobacco use. Personality traits, expectancies, and psychopathologies may also influence initial and subsequent tobacco use episodes. There is a growing body of literature that describes how many of these factors relate to current adolescent tobacco use (McAlister et al., 1984; Bauman et al., 1992; Brown et al., 1996; Bachman et al., 1997). The task of future research will be to describe the extent to which these factors interact with initial use episodes to prevent or lead to chronic tobacco use (see articles in this volume by Colby et al., 2000 and Shadel et al., 2000). Results of this research will form the basis for effective prevention and treatment strategies.

4.3. Microanalysis of tobacco use behavior acquisition: progression from initial use to regular use

Progression from initial to regular tobacco use probably involves dramatic changes in behavior. For example, the novice smoker may avoid inhaling cigarette smoke, may take some small and some large puffs, and/or may take very few puffs on each cigarette. In contrast, the experienced smoker almost always inhales,

takes consistently sized puffs, and generally uses the same number of puffs to consume each cigarette. These puff topography variables can influence the amount of nicotine a smoker self-administers. As a smoker learns to control nicotine self-administration through puff topography, variables such as puff volume and puff number likely become more standardized. Thus, increasing standardization of puff topography may be the hallmark of increasing nicotine dependence. Similar factors may be relevant to the development of nicotine dependence in SLT users. A microanalysis of tobacco use behavior may be essential for understanding how novice users become nicotine dependent. Such an analysis may help to establish nicotine exposure in novice tobacco users, the means by which novice users become tolerant to nicotine's aversive effects, and a range of other critical factors concerning the acquisition of tobacco use behavior.

The acquisition of tobacco use behavior is probably dependent on a variety of factors, including tobacco availability, and may be a discontinuous process. Many users may obtain the tobacco for their first use by sampling from a supply provided by their peers, siblings, or parents. Eventually, though, regular use will lead to a purchase for personal use. This purchase may be an important event in the changing pattern of tobacco use. An intense form of research on these critical events in the acquisition process will be important. Analysis of tobacco acquisition may be useful in order to understand important issues such as when users begin to self-identify as tobacco users, how advertising influences tobacco acquisition, and the effects of price and supply on the transition from occasional to regular use. Understanding these issues may lead to interventions that can change the course of this behavior.

4.4. Influence of environmental tobacco smoke and other smoking experiences

Another important issue in understanding the effects of initial tobacco use episodes is the potential influence of environmental tobacco smoke (ETS), also known as 'second hand smoke'. ETS is made up of sidestream smoke (e.g. from the lit end of the cigarette) and the smoke that smokers exhale. ETS can be inhaled by non-smokers; such inhalation is sometimes called 'passive smoking'. Passive smoking can involve nicotine exposure, as indexed by low but measurable urinary cotinine levels (Trout et al., 1998) which are positively correlated with the number of smokers with whom a child has contact (Jarvis et al., 1981; Strachan et al., 1989; Cook et al., 1993; Bono et al., 1996). For example, Italian adolescents who were not exposed to ETS at home had an average urinary cotinine level of 13.4 ng/ml, while those with the most at-home exposure (i.e. mother and other family members who smoked) had an average urinary cotinine level of 28.4 ng/ml (Bono et al., 1996). Similarly, in a sample of 770 children (6.5–7.5 years old) in Scotland, the 405 children with no smokers in their household had median salivary cotinine concentrations of 1.1 nmol/l, as compared to 10.2 nmol/l for the 241 children with one smoker in the household, and 25.0 nmol/l for the 124 children with two or more smokers in the household (Strachan et al., 1989). By way of comparison, smokers' urine can contain over 1000 ng/ml cotinine (Jarvis et al., 1984; Olincey et al., 1997) and salivary cotinine levels greater than or equal to 82 nmol/l generally indicate a regular smoker (Jarvis et al., 1987). Thus ETS may provide a means by which children who live with smokers are exposed to nicotine chronically, though the dosage of that exposure is likely much lower than that of a smoker. Such low-level chronic exposure may induce tolerance to some of nicotine's effects and thus influence the likelihood of positive and/or aversive effects during initial tobacco use episodes. Little is known about the influence of ETS on initial tobacco use episodes, though the presence of smokers in the household, among other factors, has been shown to be a positive predictor of smoking behavior in young smokers (Pederson et al., 1997). It is also likely that some initial tobacco smoking experiences will be preceded by smoking of other materials, including various herbal products that are widely available, marijuana, corn silk, or other products. These experiences too are very likely to diminish the aversiveness of initial tobacco smoking. Systematic information on how the smoking of other materials influences the first tobacco use episode is not currently available.

5. Potential methods for tobacco-related research that includes adolescents and children

One of the reasons why so much remains to be known about tobacco use in children and adolescents is that they are a challenging population to study. For example, most data collection efforts using non-adult populations are limited, and rightly so, by the need for informed parental consent. However, many young tobacco users may not want parents informed about their tobacco use. Also, studying tobacco use behavior in a relatively naïve user (e.g. < 10 episodes of use, lifetime) may be seen as encouraging use, possibly furthering an ongoing addiction process, or both. While these and other challenges have limited research, the eventual cost of tobacco use in children and adolescents has grown. Estimates are that, each day, ~ 6000 American adolescents try their first cigarette and 3000 American adolescents begin to smoke on a daily basis (United States Department of Health and Human Services, 1998a,b,c); one third of these adolescent smokers may prematurely die, given current levels of cessation (Food and Drug

Administration, 1996). Similar or worse mortality rates exist throughout the world. This unacceptably high cost of adolescent tobacco use emphasizes the need for research aimed at understanding the acquisition of tobacco use behavior in children and adolescents, despite the inherent challenges. The purpose of this section is to discuss briefly the ethical rationale for and the risks of tobacco-related research in adolescents, and then to suggest some empirical methods for studying young tobacco users. Readers should note that the proposed methods described in this section are intended as a starting point for informed discussion rather than a blueprint for future research. Some suggested methods will require modification due to important ethical and/or practical concerns. These modifications will reflect the universally recognized need to protect the safety and basic rights of children who participate in this vital research.

5.1. Ethical rationale for tobacco-related research in children

Medical research involving children as research participants has been a subject of recent discussion (Grodin and Alpert, 1988; Arnold et al., 1995; Levine, 1995; Vitiello and Jensen, 1997). One product of this discussion is the current National Institutes of Health (NIH) guideline requiring that "children (i.e. individuals under the age of 21) must be included in all human subjects research conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them" (National Institutes of Health, 1998). Part of the rationale for this guideline is the growing realization that pediatricians and parents are frequently required to make decisions in the treatment of sick children without the benefit of well-controlled, population-specific research. This lack of research is particularly noticeable in medications development, where physical, metabolic, hormonal, and other developmental factors can make a pharmacotherapy that is safe and effective in adults unsafe and/or ineffective in children (Arnold, 1993; Rudorfer, 1993; Arnold et al., 1995). Thus, advocates of children as participants in clinical research have focussed on the short- and long-term therapeutic benefits of that participation. They note that encouraging children to participate in research, including healthy normal children, may well help to determine the etiology of childhood disorders and will likely improve how those disorders are treated (Arnold et al., 1995). This same logic supports the involvement of children in tobacco-related research.

First, the growing realization that tobacco use has a pediatric age of onset (Kessler et al., 1997; Najem et al., 1997) clearly indicates that studying children will be necessary for a full understanding of the etiology of this disorder. Most tobacco-related research has focused on subjects in whom the disease has progressed in full: dependent smokers or SLT users. Such research is valuable, and is most appropriate for the development of effective therapies for this population. However, understanding how disease states begin is an important component of medicine that can inform and strengthen existing treatment and prevention strategies. The preceding literature review makes clear that little is known about initial tobacco use episodes in children. Involving children as participants in safe, well-controlled, carefully monitored studies designed to increase understanding of the etiology of tobacco use is likely to contribute meaningfully to the prevention of tobacco use in a way that studying adult, experienced tobacco users cannot. Thus, the moral imperative for conducting these studies is compelling (Klin and Cohen, 1994) while the argument for continuing to avoid all such studies because they are challenging practically is difficult to justify ethically.

Second, including children as participants in tobacco-related research is necessary to determine how best to treat young tobacco users. Little is known about the pharmacodynamic and pharmacokinetic profile of nicotine in children. This lack of information potentially increases a child's risk of toxic effects from tobacco dependence pharmacotherapies and may invalidate measures of nicotine dependence (Fagerstrom, 1978) that have been tested primarily in adults. The unknown efficacy and toxicity of nicotine replacement medications in children is especially disconcerting, considering that nicotine gum and/or patch are available over-the-counter. These readily available medications are likely to be a first-line treatment to which parents and/or children turn when a child attempts tobacco cessation, and warnings indicating that children should not use these products may not dissuade motivated individuals. Involving children as participants in safe, well-controlled, carefully monitored studies designed to establish the safety and efficacy of tobacco cessation treatments is likely to contribute meaningfully to the reduction of childhood tobacco use by establishing if and how these treatments can be used in a population that is so clearly different from adult tobacco users. Further, interventions targeting the early acquisition of this behavior will necessarily be studied in relatively inexperienced users.

In summary, there is a growing recognition that the research needs of children must be addressed in all areas of pediatric medicine. Meeting these needs will require an honest assessment of the special challenges and risks associated with this vulnerable population. The costs of not meeting these needs, however, may far outweigh the risks, as Arnold et al., 1995 (p. 931), states:

> The consequences of not conducting research in children and adolescents might include the perpetuation or introduction of harmful practices, failure to dis-

> cover etiology of illnesses, and failure to develop new treatments for… disorders of childhood and adolescence. Any risk assessment must include the risk of not having data for clinical decisions.

In the past, avoidance of children as research participants may have resulted in overprotection that led to less-than-optimal treatment. In the future, careful and constant evaluation of studies that include children will help to ensure that participant protection is balanced with concern for prevention and treatment of childhood disease, including tobacco use.

5.2. Minimizing the risks associated with tobacco-related research in children

The preceding discussion makes clear that tobacco-related research in children is ethically justifiable only when the benefits of that research outweigh the risks. To a large extent, risks associated with a child's participation in tobacco-related research depend upon the individual project. Observational studies where the behavior of children who use tobacco is monitored and recorded may be associated with minimal risk, whereas intensive laboratory studies involving administration of a pharmacologically active compound (i.e. nicotine) pose greater risks. For example, nicotine doses that are well-tolerated by adults (i.e. one piece of 4-mg nicotine gum) may cause nausea and vomiting in younger subjects. In many cases, these risks can be reduced substantially by monitoring research subjects carefully, designing studies cautiously (e.g. ascending rather than random dose ordering in initial projects), and maintaining good laboratory practices. Importantly, several safe and non-invasive methods of nicotine delivery (gum, nasal spray, vapor inhaler) allow investigators to administer very small doses of nicotine in a highly controlled manner. This fine control over nicotine delivery allows instantaneous termination of nicotine dosing if unwanted nicotine-related side-effects such as nausea, jitteriness, and/or dizziness, become apparent. Thus, many risks inherent in laboratory-based research can be minimized with a combination of precise control over drug delivery and careful monitoring of drug effects.

Other potential risks of child participation in tobacco-related research are less easily managed but nevertheless must be addressed fully before an informed judgement as to the risk/benefit ratio can be made. One such potential risk is that participation may initiate or maintain tobacco use in research subjects that otherwise would not have occurred. Experimentally-induced tobacco use may seem unlikely, especially considering the data reviewed above suggesting that initial tobacco use episodes can be aversive. Nonetheless, the possibility that any exposure to tobacco or nicotine may kindle interest in continued use or help to express a genetic predisposition to nicotine dependence (Sullivan and Kendlar, 2000) must be considered. Fortunately, there are several safeguards that may reduce the likelihood of this occurrence, including: (1) studying products with low abuse potential (i.e. nicotine patch or vapor inhaler) as opposed to commonly abused products such as cigarettes or smokeless tobacco; (2) presenting nicotine and/or tobacco in a sterile, laboratory setting rather than a social environment where peer influence may work to reduce unpleasant aspects of tobacco/nicotine administration; and (3) ending studies with a comprehensive, informative, and non-threatening debriefing regarding the dangers associated with tobacco use. These and other strategies may be combined to make laboratory study an effective means of preventing future tobacco use in child participants. Whatever the strategy chosen to minimize risks, ensuring the full protection of child participants is a challenge that will require researchers and Institutional Review Boards to work together closely as they identify and address completely the risks of individual research studies.

5.3. Critical challenges

There are at least three critical challenges that must be faced if a research agenda aimed at understanding the acquisition of tobacco use behavior in non-adult smokers is to be successful. Researchers must:

1. identify subjects before they begin a tobacco use career or at critical early periods of acquisition of tobacco use behavior,
2. attain informed consent, and
3. observe subjects and collect data.

Some suggestions for meeting each of these three challenges will be discussed below.

5.3.1. Identification of subjects as they acquire tobacco use behavior

To study the acquisition of tobacco use behavior in children and adolescents completely, subjects must be identified before they start using tobacco and before their tobacco use patterns have been acquired. Identifying tobacco users before they use tobacco is challenging, but possible. Strategies might include longitudinal surveys with periodic assessments of smoking behavior and/or identification and/or detailed study of 'at-risk' children. Indeed, these two approaches might be combined by identifying a study population where future tobacco use is highly likely and beginning a longitudinal program of universal study within that population.

5.3.1.1. Longitudinal surveys with periodic assessments. One strategy for identifying subjects who have recently begun or who are very likely to begin to use tobacco is to implement a detailed longitudinal survey of adolescent tobacco use; the survey would incorporate frequent objective assessments or 'probes' of tobacco use

behavior. Such a strategy has been implemented in the past with some success. For example, 194 girls aged 11–14 years were followed longitudinally for 3 consecutive years and 12 girls who switched from non-smokers to smokers over the course of the first year were identified (McNeill et al., 1989). Also, in a study of 1267 7th grade boys and girls, 836 were identified as non-users of tobacco (had never tried any tobacco product; Simon et al., 1995). Of these never-triers, 155 had tried tobacco products 1 year later. While these studies demonstrate that longitudinal methods can be used to identify individuals who change their smoking status, they also highlight some of the limitations of this method. Specifically, the low percentage of subjects who became smokers (6–19%) over a 1-year period suggests that large groups must be studied to identify a meaningful sample of interest. Also, the fact that these smokers were identified only after a period of as much as 1 year of smoking suggests that more frequent probes are required if many subjects are to be identified during the active acquisition of their tobacco use behavior. Thus, longitudinal methods will require large samples and frequent probes of smoking behavior. Use of questionnaires purporting to assess stages of adolescent tobacco-use acquisition (Elder et al., 1990) may be one method to limit the number of subjects and/or probes needed in such studies. Another method might be to reinforce subjects to identify themselves once tobacco use has occurred, although such reinforcement must be structured to preclude being an inducement to initiate tobacco use. Finally, large, longitudinal studies unrelated to tobacco use that are already underway might be used to identify individuals who have transitioned into tobacco use since their enrollment. Frequency of data collection and intensity of observation of this subset of initial users could then be increased while, at the same time, introducing additional measures relevant to tobacco use behavior. Thus, a study that might have no immediate tobacco-related goals could be extended to increase our understanding of the importance of initial tobacco use episodes.

5.3.1.2. Identification of at-risk children. Another strategy that might be used to identify children and/or adolescents when they initiate tobacco use is to choose a subject population that is at high risk for tobacco use behavior. A number of risk factors for tobacco use have been identified, including sociodemographic status (Escobedo et al., 1990), education (Escobedo et al., 1990), and family member tobacco use (Burchfiel et al., 1989). Other factors that might be expected to play a role in predicting tobacco use behavior include cultural (Wiecha, 1996) and/or regional differences (Tomar and Giovino, 1998) and participation in certain sports (Davis et al., 1997; Tomar and Giovino, 1998). These risk factors can be used, perhaps in combination, to select subjects for studies aimed at determining the effects of tobacco use acquisition behavior. Using risk factors as selection criteria for subjects who might participate in either naturalistic or laboratory studies has the advantage of limiting the subject population to those children who are most likely to use tobacco on their own. It presents the ethical challenge of studying a population known to be vulnerable to a disorder (i.e. tobacco use) and, potentially, failing to intervene once that disorder becomes manifest.

5.3.1.3. Longitudinal study within a specific at-risk population. A combination of longitudinal methods and risk factor selection might present the greatest chance for the identification and eventual observation of children as they acquire tobacco use behavior. That is, a population of subjects might be identified who all are at risk for tobacco use: for example, baseball playing male children in rural tobacco-producing regions of Virginia, Kentucky, or North Carolina. Such children might be identified well before tobacco use occurs (i.e. through little league baseball participation) and then studied longitudinally, using a combination of naturalistic and laboratory methods, for several years. As subjects would be recruited into the study before tobacco use occurs, parental informed consent need not imply that children are engaging in any behavior that parents might deem unacceptable. Also, subjects who are thus selected and who do not become tobacco users, a potentially valuable sub-population of resistant individuals, will be identified. Laboratory measurement (see below) might be included early in the study to determine if predictors of subsequent regular tobacco use could be identified (i.e. physiological or behavioral responses to specific challenges). Identifying predictors of subsequent regular tobacco use is an important ethical rationale for the study, as it provides justification for failing to intervene once initial tobacco use episodes are reported/detected. Such a study might be more ethically sound if study participants are given the option of accessing tobacco use cessation aids at no cost, if desired.

5.3.1.4. Longitudinal study of tobacco use in older subjects. Not all tobacco users begin to use tobacco as children, thus longitudinal study of the acquisition of tobacco use may be possible in young adults (i.e. individuals who are at least 18 years old). An advantage of recruiting these subjects is that, as adults, they are not considered a vulnerable population and can provide informed consent. Identifying these subjects may be easier if recruitment efforts focus on at-risk populations such as young adults entering the military or first entering college. The paucity of data related to the acquisition of tobacco use challenges researchers to identify this and other novel strategies for placing this behavior under scientific scrutiny.

5.3.2. Attainment of informed consent

One of the most perplexing problems regarding the study of the acquisition of tobacco use behavior in children is how to attain, ethically and legally, the informed consent of a minor to participate in a research study. Under current US regulations, informed consent from a parent or legal guardian must be obtained before a minor may participate as a research subject. However, adolescents who use tobacco may want to participate as research subjects, but choose not to do so if their guardians are to be notified of their tobacco use. Thus, there may be special challenges inherent in recruitment of the subjects who are of most interest. These challenges may be met using several strategies, including:

1. Obtaining a blanket consent for all adolescents within a group, such as a school or school district. This blanket consent might include language such as, 'If your child already uses tobacco, we will study their continued tobacco use as part of their study participation. If your child does not use tobacco, they will not be asked to use it as part of this study. At the end of their participation, all children will be informed of the dangers of tobacco use and will be given the opportunity of entering programs designed to reduce or eliminate their tobacco use'.
2. Identification of a subject population of children whose tobacco use is neither illegal nor actively discouraged by parental and societal influences.
3. Alteration of federal regulations so that underage tobacco users may participate in certain types of tobacco-related research without parental consent (cf. Levine, 1995). Given the immediate and long-term costs of continued tobacco use among children and adolescents, current regulations that restrict clinical research efforts may do more harm than would less restrictive regulations that do not require parental consent in every case.

A broad discussion of human subjects concerns is likely to enhance any dialogue about novel scientific strategies for studying the onset of tobacco use in children and adolescents. This discussion may be most informative if it involves a joint effort by tobacco researchers and others with a stake in developmental research and human subjects protection.

5.3.3. Observation of subjects/data collection

Identifying potential study subjects/populations and obtaining informed consent has little utility if ethically acceptable and practically feasible methods for observing these subjects and collecting data regarding their initial tobacco use episodes have not been identified. Observation of tobacco use behavior can be at various levels, ranging from naturalistic observation to in-depth laboratory evaluation of tobacco use topography and/or response to pharmacological (e.g. nicotine) challenge. Several approaches, each at a different level of detail, have merit.

5.3.3.1. Naturalistic observation. Naturalistic observation consists of observing behavior as and where it occurs naturally. Such observation might include monitoring and/or surveying subjects and might also involve the analysis of the remains of used tobacco products.

The simplest and least invasive form of naturalistic observation involves detailed monitoring of adolescent tobacco use behavior from a distance (Sussman et al., 1993). If adolescent tobacco use occurs in a public area, and subjects' names are not recorded, monitoring of that use is likely to be exempt from informed consent requirements, though the protocol is not exempt from review by an Institutional Review Board (IRB: 45CFR46.101[b]). As has been discussed, valuable information, including some topography variables, can be obtained from naturalistic observation (Ashton and Watson, 1970; Moody, 1984; Hofer et al., 1992). This information can be collected by trained observers, but might also be collected using electronic recording devices, including video cameras mounted in public locations.

The technologies available for unobtrusive observation are rapidly improving and some of these technologies may be useful in research efforts. For example, monitoring or taping of public areas to aid law enforcement agencies and deter crime is gaining acceptance and has been in wide use for several years. Observing or taping (video or audio) public areas to collect scientific data may or may not be acceptable to subjects, IRBs, or the public at large. Detailed monitoring, either by trained observer or recording technology, has several advantages: a large number of subjects can be observed in their natural setting, monitoring can be accomplished without altering subject behavior, and information regarding the social parameters of tobacco use behaviors can be recorded. There are also several disadvantages, including problems of determining individual tobacco use history and a lack of information regarding subjective effects of observed tobacco use. There may be conditions under which observed subjects might be contacted immediately after the observation period so that they can be asked to participate in more detailed data collection efforts (i.e. provide informed consent) in order to gain this valuable information.

One method of naturalistic observation that allows collection of information related to individual tobacco use history and subjective effects of tobacco use involves detailed surveys. As previously reviewed, detailed surveys have been used to collect retrospective accounts of initial tobacco use episodes in adolescents (Bewley et al., 1974; Friedman et al., 1985; Hahn et al., 1990). Structured survey methods might be used prospectively in an effort to:

- identify potential subjects prior to initiation of tobacco use,
- determine when subjects first initiate use,
- probe the effects of initial use episodes as they occur, and
- track the acquisition of regular tobacco use behavior.

Thus, survey methods could be used to elicit information from children and adolescents as they progress from non-users to regular users of tobacco. Such a study would necessarily be longitudinal and may also be labor intensive. Use of technological tools, such as the world wide web and hand-held personal data collection devices (Shiffman et al., 1997), may help to decrease laborious data collection efforts while maintaining subject interest. Certainly, the success of survey methods in collecting retrospective data regarding initial use episodes highlights the potential advantages of using similar methods prospectively.

An innovative and potentially valuable method of naturalistic observation involves the analysis of used tobacco products. At one level, collection of remnants of used tobacco products may provide an estimate of adolescent tobacco use in a given area, such as a school or club (Charlin et al., 1990; Chan et al., 1994). At another level, analysis of used tobacco products can provide an estimate of the amount of nicotine consumed during product use. In terms of cigarette smokers, such an analysis might be performed on cigarette butts; for SLT the analysis would be performed on used 'dips'. This strategy has already been used with some success in cigarette smokers (Moody, 1984). If nicotine dose can be determined from used tobacco products, this method may decrease the need for biochemical measures of nicotine consumption, such as saliva, urine, or blood samples. Collection of biochemical samples may be problematic in children or adolescents due to ethical and/or practical constraints (such as identifying who was the actual user) and subjects' fears of illicit drug use detection.

As with identification, a combined approach to naturalistic observation, using detailed monitoring, intensive questionnaire, and used product analysis methodology may well be the most revealing. For example, careful observation (or video taped monitoring) of known tobacco use locations (e.g. near a junior high school) might be used to identify apparent first-time tobacco users. Obviously, observers must adhere to a strict operational definition of an apparent first-time user. For example, one definition might involve an observed use after several non-use episodes when in the company of other tobacco users. These apparent first-time users might be approached and recruited to respond to questionnaires regarding this tobacco use episode. Items might address previous use episodes, subjective effects, motivation for use, inhalation depth and frequency, etc. Used tobacco products could be collected for later analysis and non-invasive biochemical samples (saliva, breath CO) might also be collected. After participating, these subjects might be given an internet address where they could respond to questionnaires assessing the effects of future tobacco use episodes. Undoubtedly other innovative strategies for combining observation and survey research methodologies could be imagined.

5.3.3.2. Rigorous laboratory evaluation. Laboratory-based evaluation of early tobacco use episodes provides rigorous control over many variables present in the natural environment. Some variables that are easily controlled in a laboratory setting include the influence of tobacco-using and non-using peers, the type and duration of tobacco use, and the concurrent use of other pharmacologically active substances (e.g. caffeine). Laboratory evaluation also allows for more detailed measurement of the effects of tobacco use, including physiological and behavioral measures. Thus, in the laboratory, the effects of initial use episodes on variables such as heart rate, blood pressure, and saturated oxygen level can be determined. Concurrently, topography variables such as puff volume, number, and intensity in cigarette users can also be assessed. With the addition of non-invasive biochemical measures (saliva cotinine, breath CO levels), the level of nicotine exposure produced by these initial use episodes can be determined and then correlated with subjective and physiological responses. If these measures are taken with each successive tobacco use episode, they might lead to a complete characterization of the transition from first-time to regular tobacco user. Thus laboratory evaluation of initial tobacco use episodes can be a powerful tool to aid the understanding of the acquisition of tobacco use behavior.

Despite some important strengths, laboratory evaluation of initial tobacco use behavior involves some difficult challenges, especially when children or adolescents are to be recruited as laboratory subjects. Even assuming subjects can be identified and informed consent attained, substantial challenges remain. Chief among these challenges is the potential for encouragement of the acquisition of a dangerous and addictive behavior (i.e. tobacco use) that is inherent in asking children to use tobacco in the laboratory. The following discussion focuses on some methods that might be used to address that challenge. These methods involve recruiting child/adolescent subjects and presenting them with pure pharmacological substances or pharmacologically inactive tobacco. They might also include recruiting 18-year-old never smokers and presenting these subjects with tobacco, pure pharmacological substances, or both. These methods are elaborated upon below, in the context of how potential risks to subjects might be minimized.

One method of laboratory evaluation that might yield valuable information without encouraging tobacco use in young people would be to investigate the effects of non-tobacco-delivered nicotine. The goals of this research are twofold: to determine non-smoking children's or adolescents' response to nicotine and, through careful follow-up, to determine if their response to nicotine in the laboratory predicts future smoking behavior. There are at least three advantages to examining the response to non-tobacco-delivered nicotine in young people. First, nicotine's abuse potential depends upon the route of administration: some routes, such as buccal, transdermal, or nasal are generally considered to limit nicotine's abuse liability (Henningfield and Keenan, 1993; Pickworth et al., 1994; Schuh et al., 1997). Thus, children can be exposed to nicotine in the laboratory using gum, inhaler, patch, or nasal spray with minimal risk of reinforcing future nicotine/tobacco use in these subjects. Second, FDA-approved nicotine delivery systems (i.e. nicotine gum, inhaler, patch, or nasal spray) are much safer for research subjects than is tobacco. Third, delivering nicotine in these systems rather than tobacco allows nicotine administration without teaching children how to use cigarettes or SLT. In the short-term, valuable information can be gained from determining the effects of acute nicotine administration in children. This information includes the pharmacokinetic and pharmacodynamic profile of nicotine's effect in tobacco-naïve children. In the long term, valuable information can be gained by correlating nicotine's effects with future tobacco use.

Well-controlled investigations of the effects of psychoactive compounds in young people may be challenging, but they can be accomplished. For example, one recent placebo controlled study safely examined the effects of double-blind caffeine administration (2.5 and 5.0 mg/kg, p.o.) in 8–12 year olds (Bernstein et al., 1994). In this study, informed consent was obtained from both parent and child, and subjective, performance, psychometric, and biochemical measures were recorded. Indeed, this study suggests another potential strategy in the study of tobacco use behavior: rather than administering nicotine to children, other more commonly used stimulants, such as caffeine, might serve as the pharmacologic probe. Longitudinal survey results might reveal a relationship between response to the acute administration of a stimulant and subsequent tobacco use. Thus caffeine or other safe pharmacologic probes might be used to identify children who are at risk for later tobacco use.

Another potentially valuable laboratory strategy that may not encourage further tobacco use in adolescent subjects involves nicotine-free tobacco administration. Ultra-low nicotine cigarettes have been used in research for several years (Butschky et al., 1994; Baldinger et al., 1995). Commercially available tobacco cigarettes with 0.06 mg nicotine are now available along with matching controls (UltraTech, NJ); these tobacco cigarettes are intended to be as similar as possible to normally marketed cigarettes. At least one commercially available, nicotine free SLT-like product has been reported, though this product contains no tobacco leaf (Fant et al., 2000). Nicotine-free tobacco products could be used to determine what effects of initial use episodes are due to self-administration of other tobacco constituents, such as CO. Indeed, studies with these products might be informative even if non-tobacco using adults were used as subjects, rather than children or adolescents. In either case, particular attention must be paid to the topography of use, as non-tobacco users might inhale or chew less than experienced tobacco users. One method for controlling topography, especially smoking topography, would be to have non-smokers' topography yoked to that of an age-matched control. Thus, for example, the non-smoker would be asked to inhale puffs of the same size as the average puff volume produced by their matched control.

Finally, there may be some value and fewer ethical challenges in comparing the effects of controlled tobacco use in tobacco-naive and -experienced young adults (i.e. 18–19 year olds). In one such study (Silverstein et al., 1982), 18-year-old subjects with little smoking experience (mean 6.85 cigarettes lifetime) inhaled eight, 2-s puffs of a commercial tobacco cigarette. Results of this report indicated that urinary pH may influence non-smokers' desire to smoke. A similar recruitment strategy might be used to investigate the effects of normal and nicotine-free tobacco in tobacco-naïve and -experienced young adults. Indeed, this same type of experimental design might be used to advantage to investigate how smoking status influences response to a variety of stimuli, including exposure to CO and pharmacologically pure nicotine, in young adult subjects. Whatever the study design, use of young adult subjects may provide a means of studying initial tobacco use behavior that is less challenging than using children or adolescent subjects.

5.3.3.3. Detailed observation in a non-laboratory setting. Observation of early tobacco use episodes might benefit from a combination of naturalistic and laboratory methods. For example, laptop and handheld computers make possible the detailed field observation of variables such as subjective effect and use topography. By collecting data in the field, some practical and ethical challenges may be minimized. Practically, bringing laboratory equipment to adolescent tobacco users would likely increase participation relative to asking these same subjects to come to the laboratory. Ethically, issues such as encouraging tobacco use might be of reduced importance if users were recruited as they

began a self-initiated use episode. If a non-laboratory observation strategy were adopted, it may even be possible to involve adolescents in the data collection process, perhaps by supplying them with subjective effect and topography measurement equipment. Involving adolescents in data collection may increase subject participation, though it may also decrease the reliability of the resulting data. In any case, the use of new technologies and methods that can be applied to enhance understanding of initial tobacco use episodes should be encouraged.

There are many observational strategies that might be useful in studying initial tobacco use episodes. Some strategies might be more or less acceptable depending upon the culture or setting in which that strategy were employed. For example, measuring the effects of a child's first tobacco use episode would present fewer challenges in cultures where childhood tobacco use is legal and commonplace. Similarly, laboratory measurement of tobacco use and nicotine's effects in children might face few ethical challenges if it were done in the context of tobacco use cessation. For example, an argument might be made that any cessation effort aimed at children must begin with a detailed examination of the patients' level of tobacco and nicotine dependence. The results of detailed laboratory measurement of tobacco use topography, complete with blood nicotine levels, would be used to enhance treatment outcomes. Generally, providing help with tobacco cessation may strengthen the ethical rationale of virtually any evaluation of tobacco use in children and/or adolescents.

6. Conclusion

Tobacco abuse is a disease with a pediatric age of onset (Kessler et al., 1997; Najem et al., 1997). As with any disease, researchers interested in treating tobacco abuse must understand each stage of this disease's progression, from first exposure to final outcome. Over the previous several decades much research effort and resources have been focused on tobacco abuse and dependence in those who suffer from its later stages: adult tobacco users with well-developed tobacco use patterns and lengthy tobacco use histories. This important and generally successful research effort has resulted in the development of several treatments for adult tobacco users who would like to stop their tobacco use. When successful, these treatments 'cure' adult tobacco users by helping them become tobacco abstinent, thereby dramatically decreasing the likelihood of their early death from tobacco-related cancer, emphysema, etc.

There would be no need to cure adult tobacco abusers if their disease were prevented. Prevention will likely involve research with individuals who are in the early stages of the disease. Those individuals are the 6000 children in the United States who use tobacco for the first time each day. One of the keys to preventing tobacco abuse in children may be understanding why initial tobacco use episodes sometimes lead to continued tobacco use and sometimes do not. Understanding how initial use episodes influence later use may lead to identification of at-risk children, successful prevention of regular use, and development of tobacco products and/or regulations that protect children from continued use.

This review has revealed that there is much to be learned about the effects of initial tobacco use episodes. We do not know exactly how children use tobacco, if early tobacco use delivers pharmacologically active nicotine doses, if tobacco-delivered nicotine reinforces tobacco use in children, or what factors determine the effects of these early uses of tobacco. These issues may be critical to understanding the effects of initial use episodes and their influence on later continued use. Despite the ethical and practical challenges involved in studying tobacco use in children, systematic study of initial tobacco use episodes may well be the key to guiding effective prevention efforts.

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References

Arnold, L.E., 1993. A comparative overview of treatment research methodology: adult versus child and adolescent, psychopharmacological versus psychosocial treatments. Psychopharmacol. Bull. 29, 5–17.

Arnold, L.E., Stoff, D.M., Cook, E. Jr, Cohen, D.J., Kruesi, M., Wright, C., Hattab, J., Graham, P., Zametkin, A., Castellanos, F.X., McMahon, W., Leckman, J.F., 1995. Ethical issues in biological and psychiatric research with children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 34, 929–939.

Ashton, H., Watson, D.W., 1970. Puffing frequency and nicotine intake in cigarette smokers. Br. Med. J. 3, 679–681.

Bachman, J.G., Wadsworth, K.N., O'Malley, P.M., Johnston, L.D., Schulenberg, J.E., 1997. Smoking, Drinking, and Drug Use in Young Adulthood: The Impacts of New Freedoms and New Responsibilities. Lawrence Erlbaum, New Jersey.

Baldinger, B., Hasenfratz, M., Battig, K., 1995. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field condition. Hum. Psychopharmacol. 10, 127–136.

Bauman, K.E., Koch, G.G., Bryan, E.S., Haley, N.J., Downton, M.I., Orlandi, M.A., 1989. On the measurement of tobacco use in

adolescents. Validity of self-reports of smokeless tobacco use and validity of cotinine as an indicator of cigarette smoking. Am. J. Epidemiol. 130, 327–337.

Bauman, K.E., Foshee, V.A., Haley, N.J., 1992. The interaction of sociological and biological factors in adolescent cigarette smoking. Addict. Behav. 17, 459–467.

Benowitz, N.L., 1997. Systemic absorption and effects of nicotine from smokeless tobacco. Adv. Dental Res. 11, 336–341.

Benowitz, N.L., Hall, S.M., Herning, R.I., Jacob, P. III, Jones, R.T., Osman, A.-L., 1983. Smokers of low-yield cigarettes do not consume less nicotine. New Engl. J. Med. 309, 139–142.

Benowitz, N.L., Porchet, H., Sheiner, L., Jacob, P., 1988. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin. Pharmacol. Ther. 44, 23–28.

Bernstein, G.A., Carroll, M.E., Crosby, R.D., Perwien, A.R., Go, F.S., Benowitz, N.L., 1994. Caffeine effects in learning, performance, and anxiety in normal school-age children. J. Am. Acad. Child Adolesc. Psychiatry 33, 407–415.

Bewley, B.R., Bland, J.M., Harris, R., 1974. Factors associated with the starting of cigarette smoking by primary school children. Br. J. Prev. Soc. Med. 28, 37–44.

Bono, R., Russo, R., Arossa, W., Scursatone, E., Gilli, G., 1996. Involuntary exposure to tobacco smoke in adolescents: urinary cotinine and environmental factors. Arch. Environ. Health 51, 127–131.

Boyle, R.G., Jensen, J., Hatsukami, D.K., Severson, H.H., 1995. Measuring dependence in smokeless tobacco users. Addict. Behav. 20, 443–450.

Bridges, R.B., Combs, J.G., Humble, J.W., Turbek, J.A., Rehm, S.R., Haley, N.J., 1990. Puffing topography as a determinant of smoke exposure. Pharmacol. Biochem. Behav. 37, 29–39.

Brown, R.A., Lewinsohn, P.M., Seeley, J.R., Wagner, E.F., 1996. Cigarette smoking, major depression, and other psychiatric disorders among adolescents. J. Am. Acad. Child Adolesc. Psychiatry 35, 1602–1610.

Burchfiel, C.M., Higgins, M.W., Kellar, J.B., Butler, W.J., Donahue, R.P., 1989. Initiation of cigarette smoking in children and adolescents of Tecumseh, Michigan. Am. J. Epidemiol. 130, 410–415.

Butschky, M.F., Bailey, D., Henningfield, J.E., Pickworth, W.B., 1994. Smoking without nicotine delivery decreases withdrawal in 12-h abstinent smokers. Pharmacol. Biochem. Behav. 50, 91–96.

Chan, C.-C., Chen, Y.-C., Wang, J.-D., 1994. Comparison of questionnaires, cigarette butt counts, and nicotine concentration measurements in predicting schoolchildren nicotine exposure. Bull. Environ. Contam. Toxicol. 53, 524–528.

Charlin, V.L., Sussman, S., Dent, C.W., Stacy, A.W., Graham, J.W., Baravich, M., Hahn, G., Burton, D., Flay, B.R., 1990. Three methods of assessing adolescent school-level experimentation of tobacco products. Eval. Rev. 14, 297–307.

Chassin, L., Presson, C.C., Sherman, S.J., Edwards, D.A., 1990. The natural history of cigarette smoking: predicting young-adult smoking outcomes from adolescent smoking patterns. Health Psychol. 9, 701–716.

Cohen, S.J., Katz, D.P., Drook, C.A., Christen, A.G., McDonald, J.L., Olson, B.L., Cloys, L.A., Stookey, G.K., 1988. Overreporting of smokeless tobacco use by adolescent males. J. Behav. Med. 11, 383–393.

Colby, S.M., Tiffany, S.T., Shiffman, S., Niaura, R.S., 2000. Measuring nicotine dependence among youth: a review of available approaches and instruments. Drug Alcohol Depend. (in press).

Cook, D.G., Whincup, P.H., Papacosta, O., Strachan, D.P., Jarvis, M.J., Bryant, A., 1993. Relation of passive smoking as assessed by salivary cotinine concentration and questionnaire to spirometric indices in children. Thorax 48, 14–20.

Curry, S.J., Peterson, A.V. Jr, Mann, S.L., 1989. Investigation of first opportunities to use cigarettes and smokeless tobacco. Health Educ. Res. 4, 27–34.

Davis, T.C., Arnold, C., Nandy, I., Bocchini, J.A., Gottlieb, A., George, R.B., Berkel, H., 1997. Tobacco use among male high school athletes. J. Adolesc. Health 21, 97–101.

Djordjevic, M.V., Fan, J., Ferguson, S., Hoffman, D., 1995. Self-regulation of smoking intensity. Smoke yields of the low-nicotine, low-'tar' cigarettes. Carcinogenesis 16, 2015–2021.

Djordjevic, M.V., Hoffman, D., Hoffmann, I., 1997. Nicotine regulates smoking patterns. Prevent. Med. 26, 435–440.

Eissenberg, T., Adams, C., Riggins, E.C.R. III, Likness, M., 2000. Smokers' sex and the effects of tobacco cigarettes: subject-rated and physiological measures. Nicotine Tobacco Res. (in press).

Elder, J.P., De Moor, C., Young, R.L., Wildey, M.B., Molgaard, C.A., Golbeck, A.L., Sallis, J.F., Stern, R.A., 1990. Stages of adolescent tobacco-use acquisition. Addict. Behav. 15, 449–454.

Ershler, J., Leventhal, H., Fleming, R., Glynn, K., 1989. The quitting experience for smokers in sixth through twelfth grades. Addict. Behav. 14, 365–378.

Escobedo, L.G., Anda, R.F., Smith, P.F., Remington, P.L., Mast, E.E., 1990. Sociodemographic characteristics of cigarette smoking initiation in the United States. Implications for smoking prevention policy. J. Am. Med. Assoc. 264, 1550–1555.

Fagerstrom, K.O., 1978. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3, 235–241.

Fant, R.V., Henningfield, J.E., Nelson, R.A., Pickworth, W.B., 2000. Pharmacokinetics and pharmacodynamics of moist snuff in humans. Tobacco Control (in press).

Food and Drug Administration, 1996. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco products to protect children and adolescents: final rule. Fed. Reg. 61, 44396–45318 August 28, 21 CFR Part 801, et al.

Foulds, J., Stapelton, J.A., Bell, N., Swettenham, J., Jarvis, M., Russell, M.A.H., 1997. Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. Drug Alcohol Depend. 44, 105–115.

Fowler, J.S., Volkow, N.D., Wang, G.J., Pappas, N., Logan, J., MacGregor, R., Alexoff, D., Wolf, A.P., Warner, D., Cilento, R., Zezulkova, I., 1998. Neuropharmacological actions of cigarette smoke: brain monoamine oxidase B (MAO B) inhibition. J. Addict. Dis. 17, 23–34.

Friedman, L.S., Lichtenstein, E., Biglan, A., 1985. Smoking onset among teens, an empirical analysis of initial situations. Addict. Behav. 10, 1–13.

Gorsuch, R.L., Butler, M.C., 1976. Initial drug abuse: a review of social predisposing psychological factors. Psychol. Bull. 83, 120–137.

Gritz, E.R., Baer-Weiss, V., Benowitz, N.L., Van Vunakis, H., Jarvik, M.E., 1981. Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. Clin. Pharmacol. Ther. 30, 201–209.

Grodin, M.A., Alpert, J.J., 1988. Children as participants in medical research. Pediatr. Clin. North Am. 35, 1389–1401.

Hahn, G., Charlin, V.L., Sussman, S., Dent, C.W., Flay, B., Hansen, W.B., Burton, D., 1990. Adolescents' first and most recent use situations of smokeless tobacco and cigarettes: similarities and differences. Addict. Behav. 15, 439–448.

Hatsukami, D., Morgan, S.F., Pickens, R.W., Hughes, J.R., 1987. Smoking topography in a non-laboratory environment. Int. J. Addict. 22, 719–725.

Hatsukami, D., Anton, D., Keenan, R., Callies, A., 1992. Smokeless tobacco abstinence effects and nicotine gum dose. Psychopharmacology 106, 60–66.

Henningfield, J.E., Keenan, R.M., 1993. Nicotine delivery kinetics and abuse liability. J. Consult. Clin. Psychol. 61, 743–750.

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

Henningfield, J.E., Yingling, J., Griffiths, R.R., Pickens, R., 1980. An inexpensive portable device for measuring puffing behavior by cigarette smokers. Pharmacol. Biochem. Behav. 12, 811–813.

Henningfield, J.E., Fant, R.V., Tomar, S.L., 1997. Smokeless tobacco: an addictive drug. Adv. Dental Res. 11 (3), 330–335.

Herning, R.I., Jones, R.T., Benowitz, N.L., Mines, A.H., 1983. How a cigarette is smoked determines blood nicotine levels. Clin. Pharmacol. Ther. 33, 84–90.

Hirschman, R.S., Leventhal, H., Glynn, K., 1984. The development of smoking behavior: conceptualization and supportive cross-sectional survey data. J. Appl. Soc. Psychol. 14, 184–206.

Hofer, I., Nil, R., Wyss, F., Battig, K., 1992. The contribution of cigarette yield, consumption, inhalation and puffing behaviour to the prediction of smoke exposure. Clin. Invest. 70, 343–351.

Jarvis, M.J., McNeill, A.D., Bryant, A., Russell, M.A.H., 1981. Factors determining exposure to passive smoking in young adults living at home: quantitative analysis using saliva cotinine concentrations. Int. J. Epidemiol. 20, 126–131.

Jarvis, M.J., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C., Salloojee, Y., 1984. Biochemical markers of smoke absorption and self reported exposure to passive smoking. J. Epidemiol. Community Health 38, 335–339.

Jarvis, M.J., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C., Salloojee, Y., 1987. Comparison of tests used to distinguish smokers from non-smokers. Am. J. Public Health 77, 1435–1438.

Kessler, D.A., Natanblut, S.L., Wilkenfeld, J.P., Lorraine, C.C., Mayl, S.L., Bernstein, I.B.G., Thompson, L., 1997. Nicotine addiction, a pediatric disease. J. Pediatr. 130, 518–524.

Klin, A., Cohen, D.J., 1994. The immorality of not knowing: the ethical imperative to conduct research in child and adolescent psychiatry. In: Hattab, J. (Ed.), Ethics in Child Psychiatry. Gelfen, Jerusalem, Israel.

Kozlowski, L.T., Harford, M.R., 1976. On the significance of never using a drug: an example from cigarette smoking. J. Abnorm. Psychol. 85, 433–434.

Levine, R.J., 1995. Adolescents as research subjects without permission of their parents or guardians: ethical considerations. J. Adolesc. Health 17, 287–297.

McAlister, A.L., Krosnick, J.A., Milburn, M.A., 1984. Causes of adolescent cigarette smoking: tests of a structural equation model. Soc. Psychol. Q. 47, 24–36.

McNeill, A.D., 1991. The development of dependence on smoking in children. Br. J. Addict. 86, 589–592.

McNeill, A.D., West, R.J., Jarvis, M., Jackson, P., Bryant, A., 1986. Cigarette withdrawal symptoms in adolescent smokers. Psychopharmacology 90, 533–536.

McNeill, A.D., Jarvis, M., West, R., 1987a. Subjective effects of cigarette smoking in adolescents. Psychopharmacology 92, 115–117.

McNeill, A.D., Jarvis, M.J., West, R., Russell, M.A.H., Bryant, A., 1987b. Saliva cotinine as an indicator of cigarette smoking in adolescents. Br. J. Addict. 82, 1355–1360.

McNeill, A.D., Jarvis, M.J., Stapleton, J.A., West, R.J., Bryant, A., 1989. Nicotine intake in young smokers: longitudinal study of saliva cotinine concentrations. Am. J. Public Health 79, 172–175.

Moody, P.M., 1984. Human smoking patterns and smoke deliveries. Int. J. Addict. 19, 431–439.

Najem, G.R., Batuman, F., Smith, A.M., Feuerman, M., 1997. Patterns of smoking among inner-city teenagers: smoking has a pediatric age of onset. J. Adolesc. Health 20, 226–231.

National Institutes of Health, 1998. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. NIH, Washington, DC NIH Guide, March 6.

Noland, M.P., Kryscio, R.J., Riggs, R.S., Linville, L.H., Perritt, L.J., Tucker, T.C., 1988. Saliva cotinine and thiocyanate: chemical indicators of smokeless tobacco use and cigarette use in adolescents. J. Behav. Med. 11, 423–433.

Olincey, A., Young, D.A., Freedman, R., 1997. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biol. Psychiatr. 42, 1–5.

Pederson, L.L., Koval, J.J., O'Connor, K., 1997. Are psychosocial factors related to smoking in grade-6 students? Addict. Behav. 22, 169–181.

Perkins, K.A., Grobe, J.E., Fonte, C., Goettler, J., Caggiula, A.R., Reynolds, W.A., Stiller, R.L., Scierka, A., Jacob, R.G., 1994. Chronic and acute tolerance to subjective, behavioral, and cardiovascular effects of nicotine in humans. J. Pharmacol. Exp. Ther. 270, 628–638.

Pershagen, G., 1996. Smokeless tobacco. Br. Med. Bull. 52, 50–57.

Pickworth, W.B., Bunker, E.B., Henningfield, J.E., 1994. Transdermal nicotine: reduction of smoking with minimal abuse liability. Psychopharmacology 115, 9–14.

Pomerleau, O.F., Collins, A.C., Shiffman, S., Pomerleau, C.S., 1993. Why some people smoke and others do not: new perspectives. J. Consult. Clin. Psychol. 61, 723–731.

Pomerleau, O.F., Pomerleau, C.S., Namenek, R.J., 1998. Early experiences with tobacco among women smokers, ex-smokers, and never-smokers. Addiction 93, 595–599.

Prokhorov, A.V., Pallonen, U.E., Fava, J.L., Ding, L., Niaura, R., 1996. Measuring nicotine dependence among high-risk adolescent smokers. Addict. Behav. 21, 117–127.

Rieben, F.W., 1992. Smoking behaviour and increase in nicotine and carboxyhaemoglobin in venous blood. Clin. Invest. 70, 335–342.

Riley, W.T., Kaugers, G.E., Grisius, T.M., Page, D.G., Burns, J.C., Svirsky, J.A., 1996. Adult smokeless tobacco use and age of onset. Addict. Behav. 21, 135–138.

Rojas, N.L., Killen, J.D., Haydel, K.F., Robinson, T.N., 1998. Nicotine dependence among adolescent smokers. Arch. Pediatr. Adolesc. Med. 152, 151–156.

Rudorfer, M.V., 1993. Challenges in medication clinical trials. Psychopharmacol. Bull. 29, 35–44.

Russell, M.A.H., 1990. The nicotine addiction trap: a 40-year sentence for four cigarettes. Br. J. Addict. 85, 293–300.

Russell, M.A.H., Jarvis, M.J., Devitt, G., Feyerabend, C., 1981. Nicotine intake in snuff users. Br. Med. J. Clin. Res. Ed. 283, 814–817.

Schuh, K.J., Schuh, L.M., Henningfield, J.E., Stitzer, M.L., 1997. Nicotine nasal spray and vapor inhaler: abuse liability assessment. Psychopharmacology 130, 352–361.

Severson, H.H., Eakin, E.G., Lichtenstein, E., Stevens, V.J., 1990. The inside scoop on the stuff called snuff: an interview study of 94 adult male smokeless tobacco users. J. Subst. Abuse 2, 77–85.

Shadel, W.G., Shiffman, S., Niaura, R., Nichter, M., Abrams, D.B., 2000. Current models of nicotine dependence: what is known and what is needed to advance understanding of tobacco etiology among youth. Drug Alcohol Depend. (in press).

Shiffman, S., Hickcox, M., Paty, J.A., Gnys, M., Richards, T., Kassel, J.D., 1997. Individual differences in the context of smoking lapse episodes. Addict. Behav. 22, 797–811.

Silverstein, B., Feld, S., Kozlowski, L.T., 1980. The availability of low-nicotine cigarettes as a cause of cigarette smoking among teenage females. J. Health Soc. Behav. 21, 383–388.

Silverstein, B., Kelly, E., Swan, J., Kozlowski, L.T., 1982. Physiological predisposition toward becoming a cigarette smoker: experimental evidence for a sex difference. J. Health Soc. Behav. 21, 383–388.

Simon, T.R., Sussman, S., Dent, C.W., Burton, D., Flay, B.R., 1995. Prospective correlates of exclusive or combined adolescent use of cigarettes and smokeless tobacco: a replication-extension. Addict. Behav. 20, 517–524.

Soria, R., Stapleton, J.M., Gilson, S.F., Sampson-Cone, A., Henningfield, J.E., London, E.D., 1996. Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers. Psychopharmacology 128, 221–226.

Stanton, W.R., 1995. DSM-III-R tobacco dependence and quitting during late adolescence. Addict. Behav. 20, 595–603.

Strachan, D.P., Jarvis, M.J., Feyerabend, C., 1989. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7-year-old children. Br. Med. J. 298, 1549–1552.

Sullivan, P.F., Kendlar, K.S., 2000. The genetic epidemiology of smoking. Nicotine Tobacco Res. (in press).

Sussman, S., Hahn, G., Dent, C.W., Stacy, A.W., Burton, D., Flay, B.R., 1993. Naturalistic observation of adolescent tobacco use. Int. J. Addict. 28, 803–811.

Tomar, S.L., Giovino, G.A., 1998. Incidence and predictors of smokeless tobacco use among US youth. Am. J. Public Health 88, 20–26.

Trout, D., Decker, J., Mueller, C., Bernert, J.T., Pirkle, J., 1998. Exposure of casino employees to environmental tobacco smoke. J. Occup. Environ. Med. 40, 270–276.

United States Department of Health and Human Services, 1994a. Preventing Tobacco Use Among Young People: A Report to the Surgeon General. US Department of Health and Human Services, Public Health Service, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA.

United States Department of Health and Human Services, 1994b. Reasons for tobacco use and symptoms of nicotine withdrawal among adolescent and young adult tobacco users — United States, 1993. Morbidity Mortality Weekly Rep. 43, 745–750.

United States Department of Health and Human Services, 1998a. Incidence of initiation of cigarette smoking — United States, 1965–1996. Morbidity Mortality Weekly Rep. 47, 837–840.

United States Department of Health and Human Services, 1998b. Tobacco use among high school students — United States, 1997. Morbidity Mortality Weekly Rep. 47, 229–233.

United States Department of Health and Human Services, 1998c. Selected cigarette smoking initiation and quitting behaviors among high school students — United States, 1997, 1998. Morbidity Mortality Weekly Rep. 47, 386–389.

Vitiello, B., Jensen, P.S., 1997. Medications development and testing in children and adolescents. Arch. Gen. Psychiatry 54, 871–876.

Wiecha, J.M., 1996. Differences in patterns of tobacco use in Vietnamese, African-American, Hispanic, And Caucasian adolescents in Worcester, Massachusetts. Am. J. Prev. Med. 12, 29–37.

Zacny, J.P., Stitzer, M.L., 1986. Effect of puff size instructions on puff volume. Addict. Behav. 11, 17–23.

Zacny, J.P., Stitzer, M.L., Brown, F.J., Yingling, J.E., Griffiths, R.R., 1987. Human cigarette smoking: effects of puff and inhalation parameters on smoke exposure. J. Pharmacol. Exp. Ther. 240, 554–564.