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Steppingstone and gateway ideas: A discussion of origins, research challenges, and promising lines of research for the future

James C. Anthony*

Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing, MI 48824, United States

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ABSTRACT

In this discussion of contributed papers for the special issue of DAD, the author draws attention to early American laws concerning cannabis and to statements made about the epidemiology of cannabis smoking and other drug use between 1858 and the contemporary scene, with coverage of opium, heroin, tobacco, alcohol, cocaine, kava, and other drugs. He discusses these steppingstone and gateway processes in relation to political environment and in relation to scientific challenges such as uncontrolled confounding. He provides a critique of between-individual research designs, including co-twin and co-sib designs of behavior genetics, as well as imaging research, where uncontrolled confounding often exists. He highlights the epidemiologic case-crossover design and prevention research experiments as potentially valuable approaches in new directions for research on the steppingstone and gateway processes.

In their introductory overview, Vanyukov and Ridenour (this volume) provide an excellent description of each of the important contributions found in this special issue of *Drug and Alcohol Dependence*, including their own substantial contribution, which provides a brief history of the 'gateway' idea in research on progression from one drug to another, which was pre-dated by a related (but not identical) 'steppingstone' idea. In this essay, I am playing the role of a discussant. By skimming the Vanyukov–Ridenour overview, readers of this essay will gain a view of context, with references to the primary scholarly contributions in the area.

As discussant, I chose to address two tasks. The first task involves setting the context for the scientific investigation of the steppingstone and gateway ideas, from the perspective of a scientist who has lived through most of the history of these ideas. By completing this task, I hope that readers will gain an appreciation that the steppingstone and gateway ideas are fairly modern. I think of these ideas as 'vapors' that emerged from a political cauldron during the middle of the 20th century when it was very difficult to find definitive and convincing evidence of harmful effects of cannabis use–over and above (1) the sometimes extremely severe consequences of criminal penalties for simple cannabis possession and use, and (2) adverse effects on mouth, nose, throat, and lung, as might be traced to smoking cannabis (as opposed to its use by other routes of administration) or to smoking cannabis-tobacco combinations (which is one of the most common cannabis self-administration practices throughout the world). I believe it is impossible to understand the current challenges faced in research on the steppingstone and gateway ideas without an appreciation of the political genesis of these ideas. Focus on links from cannabis smoking to its later suspected harmful effects leads naturally to focus on links from cannabis smoking to later use of opium or opium-related compounds such as heroin and other internationally regulated drugs.

The second task is to sketch some of the challenges in future research on the steppingstone and gateway ideas, with reflection back to the original contributions published in this special issue of *Drug and Alcohol Dependence*, and a consideration of what I think might be the most promising lines of future research on the steppingstone and gateway ideas. Pondering these challenges, I was reminded to look back to opposing views articulated on one side by O'Donnell and Clayton, who maintained that cannabis use was a quite plausible and reasonably well-substantiated cause of later use of internationally regulated drugs (O'Donnell and Clayton, 1982),

* Corresponding author at: Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, 909 Fee Road (B601 West Fee), East Lansing, MI 48824, United States. Tel.: +1 517 353 8623; fax: +1 517 432 1130.
E-mail address: janthony@msu.edu

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and on the other side by Baumrind (1983), who judged the evidence to be insufficient. Readers who are not familiar with the challenges of causal inference in the face of limited evidence will benefit by a look at these two important viewpoints, which include summaries of prior contributions by Weppner and Agar, Kandel, and other notable scientists who have worked on this topic. These initial empirical studies anticipated post-1980 contributions from the Fergusson research group in New Zealand and the research group at RAND Corporation led by Morral, among others.

1. Steppingstone/gateway ideas: vapors from the political cauldron

Cannabis surfaced early in colonial American politics and law. It seems that drafts of the American Declaration of Independence of 1776 were written on paper made from cannabis (hemp). Moreover, years before, early American colonial farmers were required by law to grow it as a cash crop. In some colonies, these 'must grow' cannabis laws were reinforced when the plant was deemed acceptable as a form of 'legal tender' in commercial exchange of goods and services (Ransom, 1999).

By the middle of the 19th century, there was an appreciation of the potential medicinal value of cannabis use (Grinspoon and Bakalar, 1997; Ransom, 1999), but the once positive American political attitudes toward this drug had shifted toward neutrality or negative attitudes, as conveyed in an anonymous contribution to *Harper's New Monthly Magazine* of 1858. The 1858 article has the curious abbreviated title of "Hasheesh and Hasheesh Eaters," and provides an interesting early global view of the epidemiology of drug use. Whereas the article makes use of the term 'narcotic' in a loose and colloquial manner, as opposed to the correct pharmacological or scientific use of this term, the author reminds us that potentially injurious effects of cannabis smoking were identified in the Middle East and the western parts of Asia as early as the 800s (i.e., the 9th century of the modern era):

> The statistics and phenomena of narcotics deserve more attention, as an element of general knowledge, than they have heretofore received. . . Of the minor narcotics Siberia has its narcotic fungus; the Polynesian Islands their ava [kava, sakau]; New Granada and the Himalayas their thornapple; the Florida Indians their emetic holly, and Northern Europe and North America their ledum and sweetgale. The five great narcotics, which are articles of national consumption in different parts of the world, are tobacco, opium, hemp (hasheesh [cannabis]), betel, and coca. Of these, tobacco alone is universal. Opium is consumed by four hundred millions of men; hemp by between two and three hundred millions; betel by one hundred millions; and coca by ten millions (Anonymous, 1858).

This magazine article contains a useful starting point in a discussion of steppingstone and gateway ideas. Namely, it will prompt readers to think that differing effects of cannabis and opioid drugs might tap different segments of the drug-taking consumer base, and might yield inverse, neutral, or weak positive associations, rather than the moderate-strong associations generally observed in research from the later 20th century and in the 2000s. As noted below, one of the steppingstone ideas included the possibility that there might be segregation of drug users according to the pharmacological effects found to be most reinforcing (see Mandel, 1969, discussed in more detail later in this essay). This idea first appeared in this mid-19th century magazine article, and some future detective work may disclose the identity of its now-anonymous author:

> Coca chewed by the couriers of Peru, has the wonderful power of sustaining muscular strength in the absence of food, and of preventing the wasting of the tissues of the body during the greatest and most prolonged fatigues. Betel is an antidote to opium, as tea is to alcohol. Tobacco suspends mental activity, while opium and hasheesh increase it a thousand-fold. The strange illusions produced by opium, and the peculiar effects of that drug upon the system, have been placed on record for us by the most brilliant of modern essayists and metaphysicians, whose accounts of the "happiness that may be purchased for a penny and carried in the waistcoat pocket; the portable ecstasies which may be had corked up in a pint bottle; and the peace of mind that can be sent down in gallons by the mail-coach," are familiar to all who read. Hasheesh has many points in common with opium; but the two drugs are opposite in this, that while opium tends to obliterate all sensitiveness to external impressions, hasheesh increases this to an almost unlimited and most surprising extent. In fact, hasheesh. . .exaggerates rather than perverts the reports of the senses as to external objects.

In the context of contemporary research on the steppingstone and gateway ideas, including research on individual differences in susceptibility and possible heritable traits, it is noteworthy that this anonymous 19th century author decided to draw attention to the possibility of subgroup variations in the effects. He also noted that cannabis use might be quite harmful: "The Arabic physicians [during the 800s]. . .seem early to have awakened to its injurious effects upon mankind. 'The truth is,' says one, 'that there is nothing more injurious to the human constitution than this herb.'" The anonymous author then went on to speculate that the harmful effects due to long-sustained use, observed among the 'Eastern races,' would not be experienced by the 'Anglo-Saxon race':

> We [in the Anglo-Saxon world] are, however, in very little danger of becoming a nation of hasheesh-eaters. A predisposing warmth and activity of imagination – a common quality with Eastern races, but a rare one with us – is absolutely necessary to enable a man to become a hasheesh-eater to any purpose. The vast majority of experiments made by Europeans and Americans resulted in naught but a general and painful disturbance of the nervous system—preceded, in a large number of instances, by a condition of insensibility, lasting from twenty-four to thirty-three hours. The hasheesh fantasia seems physically unattainable to the great majority of the Anglo-Saxon race.

It seems that suspected harmful, as well as beneficial, effects of eating and smoking cannabis were covered extensively in the Indian Hemp Drugs Commission Report of 1894, one of the most comprehensive studies of the relationship between cannabis consumption and health outcomes ever conducted (Chandra et al., 2010). As might be expected, in later years, there was an emphasis on the suspected harmful effects of cannabis use during international meetings intended to increase international agreements about regulation of opium and opium-containing products. In the transcripts of these international regulatory meetings, we may find the original foundation stones for contemporary political discussions about cannabis use as a source of variation in harm to the individual and to society (Willoughby, 1925).

Discussions of these adverse effects were centered on disturbances of the mental life and behavior, including the possibility of cannabis-induced psychoses. Reading original source documents as well as histories of these regulations (Ansley, 1959), I have not yet found mention of cannabis use as a steppingstone or its involvement as a gateway toward the use of opioids that were the primary concern of that time. This possibility does not seem to have entered the picture in these early discussions, which had a broad range and included the following two observations about associations linking cannabis to distinctive psychiatric and behavioral conditions,

the first of which has been attributed to M. El Guindy, the Egyptian delegate to the Second Opium Conference:

> [Use of]. . .hashish is the principal cause of most of the cases of insanity occurring in Egypt. In support of this contention, it may be observed that there are three times as many cases of mental alienation among men as among women, and it is an established fact that men are much more addicted to hashish than women. (In Europe, on the contrary, it is significant that a greater proportion of cases of insanity occur among women than among men.)

Without commentary on the fallacies in that argument, let us note the next observation that Willoughby described. From the same opium conference proceedings, and in response to M. El Guindy's testimony, a Mr. Bourgois, from France, made the following assertion:

> Without going into the subject in detail, I may quote the fact that in the Congo, for example, there are several tribes of savages and even cannibals among whom the [cannabis] habit is very prevalent.

I do not wish to leave the reader with the impression that Mr. Bourgois imagined cannabis as a cause of cannibalism. In context, this observation was presented as an objection to the proposed international regulation of cannabis trafficking. It seems that Mr. Bourgois simply was trying to draw attention to the possibility that cannibalism might make it difficult for the police forces of his country to enforce cannabis trafficking regulations in parts of French colonial Congo inhabited by cannibals (Willoughby, 1925).

Be that as it may, at present, the origins of the steppingstone and gateway ideas linking cannabis and the opioids or other internationally regulated drugs seem to be attempts by American law enforcement authorities to link cannabis smoking with other illegal behavior or violations of social norms. Legal historians Mandel (1969), as well as Bonnie and Whitebread (1970), share a general consensus on this matter.

From Mandel (1969), we have the following opinion:

> As the consensus among experts that marijuana leads to heroin use gets weaker and weaker, [US] federal drug-enforcement officials seem to be emphasizing the steppingstone theory. So Harry Giordano, Commissioner of the FBN [Federal Bureau of Narcotics], stressed the steppingstone argument above all others in arguing the dangers of marijuana before congressional committees in 1967 and 1968 (Mandel, 1969, pp. 995–996).

Bonnie and Whitebread (1970) concurred, at least in part:

> The 1950's [sic] witnessed the advent of an extremist legislative policy with respect to drugs generally and marijuana in particular. For the first time in our national history, there was public interest in narcotic drugs. Apparently there had been an increase in narcotic drug abuse in the late 40's, and the public mind was ripe for the FBN propaganda. In the paranoid atmosphere of the times, the call for harsher penalties was soothing. Unfortunately, marijuana was caught in the turbulence of this era. Although the pharmacological facts about the drug were beginning to emerge, congressional furor was aroused by the novel assertion, rejected by [FBN] Commissioner Anslinger in 1937, that use of marijuana led to use of harder drugs. This new plateau of misinformation was to provide the base for continual escalation of penalties and proliferation of offenses throughout the decade (Bonnie and Whitebread, 1970, Chapter VI).

Mandel (1969) actually laid forth some of the arguments in favor of the steppingstone and gateway ideas as they were understood at that time. His description from the late-1960s stresses the role of the 'pusher' and illegal traffickers seeking to make a profit, although subsequent research in the mid-1970s made it clear that for most users a non-capitalistic sharing of cannabis within social groups was the occasion of the first chance to try cannabis for most prevailing users of the drug (O'Donnell et al., 1976). Nonetheless, here is what Mandel had to say, which includes an echo of the mid-19th century idea that drug users might segregate into subgroups based upon which pharmacological effects are found to be most reinforcing:

> One view is that the drug user is a kick-seeker who will try anything. He moves from one drug to another, seeking stronger and more "way out" thrills. Thus, the traffickers handle a wide variety of drugs and it is in their interest to move their clientele up the ladder to stronger and more expensive drugs. In the competing view, drugs are differentiated according to their effects. Drugs can be classified as "uppers" or "downers," consciousness expanders or dullers, those that facilitate hallucinations and those that fix one in a 'here and now reality." Drugs, or at least various classes of drugs, are competitors. If the user tries one drug, he might follow a path away from the life-style engendered by the use of some other drug. Pushers, like users, usually specialize in two or three related drugs (Mandel, 1969, pp. 996–997).

Earlier in this essay, I drew attention to opposing viewpoints offered by O'Donnell and Clayton (1982) and by Baumrind (1983), whose task was to judge whether the accumulating observations amounted to definitive evidence in favor of the idea that cannabis smoking might be a cause of later use of internationally regulated drugs. By now, I hope that I have helped draw the reader's attention to the political origins of these ideas, which continue to influence scientific investigation. I do not wish to convey that scientists should ignore ideas that arise as vapors from the political cauldron. I hold the opposite perspective that many of the most significant public health research challenges have origins in the imaginations of politicians and policy makers, whose discussions bring to light potentially soluble research problems that deserve investigation when the result is definitive evidence to guide subsequent policy-making and programmatic investments. This work represents the 'soluble and possible' cell of a 2×2 contingency table where Medawar's concept of science as 'the art of the soluble' intersects with Aristotle's view of politics as 'the art of the possible,' whereas many of the policy analysis questions about what might be possible actually turn out to be insoluble, unless we are satisfied with crude approximations (e.g., estimating the 'true' number of 'cocaine addicts' in the US population, and gauging whether that number rises or falls based upon choice of policy instruments). Nevertheless, as I see it, the nub of our present and future challenges in research on the steppingstone and gateway ideas is that we will not achieve definitive evidence on the steppingstone or gateway issues when or where the use of these drugs is pre-conditioned by a legal structure that helps account for the last important fact stated by Mandel in 1968—namely, 'Pushers [by which he meant illegal vendors], like users, usually specialize in two or three related drugs."

At the end of the day, we may be confronted with a problem of consumer choice, and a sequence of states and processes that have their origins in early consumer choices. True, it is possible to posit an individual-level susceptibility trait that prompts some young people to make an early choice in favor of drug use of a specific type whereas others do not make that choice. Nevertheless, an appeal to that kind of susceptibility trait is one that ultimately can confound any investigation of the suspected causal linkage from the first use of one drug compound to the later use of other drug compounds.

2. Toward more definitive evidence on these topics

This brief essay is not a place to describe a full program of research as will be required to produce definitive evidence on the suspected causal association that links earlier cannabis use to later use of heroin, cocaine, or other internationally regulated drugs, nor the suspected causal association that might link use of tobacco or alcohol to the use of cannabis or other internationally regulated drugs. What follows is a sketch of ideas in that direction.

Elsewhere, with others in my research group (Anthony, 2002; Wagner and Anthony, 2002; Wilcox et al., 2002; Chen et al., 2004; Storr et al., 2011; Wells et al., 2011), I have sketched out ideas for an elaboration of the steppingstone and gateway research. These studies are centered on the concept of drug exposure opportunities—i.e., the environmental circumstances that might set the stage for the first chance to try each drug. The logic here is that scientific problems in epidemiology are most soluble when we try to estimate the effects of causes, and they are less soluble when we try to study the causes of effects. This approach does not deny possibilities that genetic or other individual susceptibility traits help to influence whether someone does or does not experience the first chance to try a drug at any given age or point in development. The approach merely simplifies the problem via a focus on readily measured environmental conditions and processes that represent plausible causal mechanisms that might account for the sequence from one drug to the next.

In this context, our research group has raised the possibility that early childhood intervention experiments might help us achieve increasingly definitive evidence about whether an early experimentally induced disruption of drug involvement (e.g., delay in first chance to try a drug) can have a lasting impact on longitudinal trajectories of drug use of the type described by Vanyukov et al. (this issue of *Drug and Alcohol Dependence*). The types of interventions range from the Good Behavior Game in group settings such as the first and second grade classrooms of primary school (e.g., see Kellam and Anthony, 1998), parenting interventions (e.g., see Furr-Holden et al., 2004), as well as programs not yet evaluated in relation to drug outcomes (e.g., efforts to promote sustained religious activity, as suggested in Chen et al., 2004). Here also the focus is on environmental conditions or circumstances, experimentally assigned at random so as to bring suspected confounding variables into balance—in lieu of a focus on individual-level differences that may never be understood with any completeness. In this context, it is important to note a just-published study suggesting early impact of a primary prevention program on the timing of the first chance to try tobacco, with no additional impact on the actual first tobacco smoking experience—i.e., impact via 'exposure opportunity' circumstances (Wang et al., 2012).

At the start of a consideration of new lines of research on these issues, we must confront a problem with any evidence coming from jurisdictions where the legal structure imposes criminal, civil, or informal social sanctions for simple possession and use of alcohol, tobacco, or other drugs. The problem is faced when and where there are legal minimum ages for drinking alcohol or smoking tobacco (or cannabis). This problem is more prominent when and where the sanctions include serious criminal penalties. Namely, any co-occurrence or patterning in the use of these drug compounds must address a potential individual-level variation in likelihood of engaging in such use, given the environmental background of social sanctions. To put this problem in another way, even when we hold constant similar levels of background social sanctions, what individual level characteristics influence who will or will not use the first drug specified in the sequence under study?

In this special issue of *Drug and Alcohol Dependence*, and in prior contributions, the use of a between-individual observation research design to study these sources of variation is faced with the problem that we do not yet have excellent predictive models to account for the sources of variation in who will or will not engage in socially sanctioned drug use of any form. Once we have excellent predictive models, it may become possible to apply propensity scoring approaches of a type that have become more common in recent epidemiological and clinical services research of an observational character, and in experiments as well (e.g., see Harder et al., 2008, 2010). The need for special approaches of this type in a randomized experiment can be traced to our uncertainties about whether, in each individual trial, the randomization scheme has produced completely balanced distributions of all 'third variables' of importance (i.e., the challenge of 'uncontrolled confounding').

It probably goes without saying that observational research in the domain of imaging genetics is affected by this challenge as well, not only in the between-individual research designs used for this area of science, but also in the longitudinal within-individual research designs that start with young people before any drug use and follow them forward in time to the post-drug imaging sessions. We still must account for the possibility that something happened just before the first occasion of drug use that might account for both the occurrence of the drug use and the brain imaging parameters observed after drug use. One possibility involves the use of single polymorphism nucleotides or other genetic markers as instrumental variables in this context of observational research (i.e., 'Mendelian randomization' in the unfortunate jargon of epidemiology). Nonetheless, one suspects that the sample sizes obtained in imaging genetics never will be sufficient to overcome concerns about falsely positive signals and spurious gene-image associations, even if the samples are large enough to fit instrumental variable models.

At first blush, one might posit that behavioral genetics research designs such as co-sib or co-twin designs of the type included in this volume serve to address sources of these potential individual-level variations. After all, for the most part, social sanctions against drug use might be considered to be shared aspects of the co-twin environment. Nonetheless, as noted elsewhere (O'Brien et al., 2012), even in research on cannabis-related outcomes of discordant monozygotic (MZ) co-twins, one must explain why one member of twin pair has consumed cannabis (or has consumed it earlier than the other co-twin) and why the other member of the twin pair has a different cannabis exposure history. These observational designs also are subject to the challenge of uncontrolled confounding.

In some of our group's work, and O'Brien et al. (2012) have raised the possibility that the subject-as-own-control case-crossover design with epidemiological samples of individuals studied before and after onset of first drug use might help constrain the sources of individual-level variation more than would be the case in MZ co-twin designs of behavioral genetics. This point is made explicit in O'Brien et al. (2012), where we go so far as to indicate that the epidemiological case-crossover design should be included more generally in any comprehensive coverage of informative behavioral genetics research approaches, designs, and methodology.

Nonetheless, the case-crossover design has limits. For example, Wu and Anthony (2000) used this subject-as-own-control design to clear away individual-level confounding variables in order to derive a more definitive estimate in their attempt to study cocaine use as a precipitating cause of panic attacks. O'Brien et al. (2012) used the design in a similar fashion to derive a more definitive estimate in an attempt to study cannabis onset as a precipitating cause of cocaine onset. Cocaine users were found to be at increased risk of a panic attack shortly after onset of cocaine use (Wu and Anthony, 2000). Newly incident cannabis users were found to be at increased risk of starting to use cocaine shortly after onset of cannabis use (O'Brien et al., 2012).

In each of these examples, the results were statistically robust estimates balanced against the null hypotheses (i.e., favoring

the hypothesized cocaine-panic and the cannabis-cocaine links). Nonetheless, in these papers there is a clear statement of limitations of this approach to observational research on suspected causal associations. Even with the strength of the within-subject observational design, the threat of uncontrolled confounding variables remains.

Optimism must be expressed that new evidence of an increasingly definitive character might be found in observational studies conducted in jurisdictions where there are no social sanctions prohibiting drug involvement by young people–although the sampling frames might have to be restricted to individuals who have reached the normative mean or median age for onset of drug use in these places. One imagines that even in places where young people are allowed to smoke tobacco or drink alcohol in early–mid adolescence, there might be prohibitions against use of these drugs in childhood. With careful consideration to these issues, some good progress can be made, building toward more definitive evidence on the steppingstone and gateway ideas.

I think that a more fruitful line of investigation has been launched in prevention research experiments (Furr-Holden et al., 2004; Wang et al., 2012) when randomization has been used to study sequential drug outcomes. Furr-Holden et al. (2004) worked from experimental evidence on prevention of tobacco smoking reported by Kellam and Anthony (1998), and completed a partial replication study. In the partial replication, a randomly assigned intervention design was used to quantify suspected beneficial intervention effects on initiation of tobacco and other drug outcomes, with apparent benefit in relation to delay or possibly prevention of onset of tobacco smoking. Nevertheless, there was no statistically robust effect on cannabis or other drug involvement. Whereas a larger sample size or longer follow-up might be required to achieve sufficient statistical power to detect the later effects of the intervention, this study can give the reader an idea of how experimentation might be used to achieve more definitive evidence about the steppingstone and gateway ideas. To wit, if the steppingstone or gateway ideas have merit, and when a randomly assigned program achieves prevention or delay in the use of the first drug in a sequence, then the most parsimonious ideas about causal mechanism leads to an implication that there should be later congruent prevention or delay in the use of subsequent drugs in the sequence, all else being equal.

Of course, the phrase 'all else being equal' encompasses a lot of territory, and any single experiment is going to be subject to the possibility that randomization has failed to produce balance in the background confounding variables, as noted above. In light of this possibility of error in any single experiment, replication becomes of special importance.

It is noteworthy that both clinical intervention services experiments, as well as primary prevention experiments, can be useful in this line of extended research on the steppingstone or gateway sequences. For example, there is a growing number of tobacco smoking cessation experiments with adolescent smokers as participants. With proper follow-up of those samples into early adulthood, in contrasts of groups with and without the benefit of efficacious smoking cessation interventions, there should be program-associated reductions in risk of starting to use internationally regulated drugs–at least under some models of causal mechanisms that link smoking and later drug use. Of course, there are some models of the causal mechanisms that might be at play even if these experiments do not show reduced cannabis or other drug involvement. For example, if nicotine 'kindles' or otherwise provokes neurobiological lesions that subserve an enduring vulnerability, the smoking might stop, but the vulnerability from 'nicotine pre-treatment' might persist, and excess risk of later drug involvement might be seen (e.g., see Levine et al., 2011). Nonetheless, meta-analytic research along these lines would be meritorious, at least in my own view.

Pursuit of this line of research in the United States will be difficult, especially within the present framework of NIH impact priority scoring, which gives priority to research designs in which there are essentially no weaknesses, and tends to yield unfundable priority scores when the design involves only one 'minor' weakness. Necessarily, definitive prevention and intervention experiments on this topic will require epidemiologically credible samples and long-term longitudinal follow-up. As contrasted with observational studies that propose small samples with no pre-defined source population, and with little or no longitudinal follow-up, the relatively larger scale of these experiments fosters relative weaknesses in the form of higher non-participation at baseline (often associated with human subjects' reticence to be 'guinea pigs' in randomized trials), and in the form of greater sample attrition during long-term follow-up as compared to short-term follow-up. In consequence, one might suspect that it will take a decade or more before we have a sufficient number of these experiments to produce meta-analyses of a definitive character. Until then, we must satisfy ourselves with an inhalation of vapors from the political cauldron, watching with interest for increasingly definitive evidence on the steppingstone and gateway ideas, as we can see represented in the important original contributions written for this special issue of *Drug and Alcohol Dependence*.

In closing, I should repeat my assertion that there is nothing inherently wrong with scientific investigation of ideas that originate or that gain momentum primarily as vapors from the cauldron of politics, particularly when the work is at that intersection of the 'art of the soluble' with the 'art of the possible.' Regrettably, the political environment is one that may stack the deck against scientists who challenge politically popular views. It never has been especially difficult to secure governmental support for research that seeks to estimate the harmful effects of cannabis use, hallucinogen use, or other illegal drug use, once details of a robust research approach have been specified. In contrast, it has been difficult to secure governmental support for research that advances the null hypothesis of no effect when policy makers believe there is a harmful effect. It has been even more difficult to secure governmental support for research that seeks to estimate potential beneficial effects of using these drugs outside the context of governmentally approved indications for medical prescriptions–particularly when a drug has a history of description as a social menace.

Nevertheless, times change, and perhaps we have entered a new century when it has become more feasible to pursue governmentally funded research into the potential benefits of drugs formerly (or currently) thought to be a social menace. If so, our societies will be turning an important corner.

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References

Anonymous, April 1858. Hasheesh and hasheesh eaters (the hasheesh eater: being passages from the life of a pythagorean). Harper's New Monthly Magazine. Number XCV. Volume XVI (pagination not available in online version: http://www.druglibrary.org/schaffer/hemp/history/eaters.htm).

Ansley, N., 1959. International efforts to control narcotics. J. Crim. Law Criminol. Police Sci. 50, 105–113.

Anthony, J.C., 2002. Epidemiology of drug dependence. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. , 5th ed. Lippincott, William and Wilkins, Philadelphia, pp. 1557–1573 (Chapter 109).

Baumrind, D., 1983. Specious causal attributions in the social sciences: the reformulated stepping-stone theory of heroin use as exemplar. J. Pers. Soc. Psychol. 45, 1289–1298.

Bonnie, R.J., Whitebread, C.H., 1970. The forbidden fruit and the tree of knowledge: an inquiry into the legal history of American marijuana prohibition. VA Law Rev. 56, 971–1203.

Chandra, S., Barondess, D., Anthony, J.C., 2010. Is cannabis an aphrodisiac or sexual suppressant? A view from the past. In: Online Abstract presented at the Annual Scientific Meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, http://www.cpdd.vcu.edu/Pages/Meetings/Meetings_PDFs/2010Programbook.pdf, last accessed 29.03.12.

Chen, C.Y., Dormitzer, C.M., Bejarano, J., Anthony, J.C., 2004. Religiosity and the earliest stages of adolescent drug involvement in seven countries of Latin America. Am. J. Epidemiol. 159, 1180–1188, http://dx.doi.org/10.1093/aje/kwh151.

Furr-Holden, C.D.M., Ialongo, N.S., Anthony, J.C., Petras, H., Kellam, S.G., 2004. Developmentally inspired drug prevention: middle school outcomes in a school-based randomized prevention trial. Drug Alcohol Depend. 73, 149–158.

Grinspoon, L., Bakalar, J.B., 1997. Marihuana, The Forbidden Medicine. Yale University Press, New Haven.

Harder, V.S., Stuart, E.A., Anthony, J.C., 2008. Adolescent cannabis problems and young adult depression: male–female stratified propensity score analyses. Am. J. Epidemiol. 168 (6), 592–601, http://dx.doi.org/10.1093/aje/kwn184.

Harder, V.S., Stuart, E.A., Anthony, J.C., 2010. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol. Methods 15, 234–249, http://dx.doi.org/10.1037/a0019623.

Kellam, S.G., Anthony, J.C., 1998. Targeting early antecedents to prevent tobacco smoking: findings from an epidemiologically based randomized field trial. Am. J. Public Health 88, 1490–1495.

Levine, A., Huang, Y., Drisaldi, B., Griffin Jr., E.A., Pollak, D.D., Xu, S., Yin, D., Schaffran, C., Kandel, D.B., Kandel, E.R., 2011. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. Sci. Transl. Med. 3, 107–109.

Mandel, J., 1969. Problems with official drug statistics. Stanford Law Rev. 21, 991–1040.

O'Brien, M., Comment, L.A., Liang, K.Y., Anthony, J.C., 2012. Does cannabis onset trigger cocaine onset? A case-crossover approach. Int. J. Methods Psychiatr. Res. 21, 66–75.

O'Donnell, J.A., Voss, H.L., Clayton, R.R., Slatin, G.T., Room, R.G., 1976. Young men and drugs—a nationwide survey. NIDA Res. Monogr. 5, i–xiv, 1–144.

O'Donnell, J.A., Clayton, R.R., 1982. The stepping-stone hypothesis: a reappraisal. Chem. Depend. 4, 229–241.

Ransom, J.J., 1999. Anslingerian Politics: The History of Anti-marijuana Sentiment in Federal Law and how Harry Anslinger's Anti-marijuana Politics Continue to Prevent the FDA and Other Medical Experts from Studying Marijuana's Medical Utility, http://www.leda.law.harvard.edu/leda/data/352/Ransom.html, last accessed 29.03.12.

Storr, C.L., Wagner, F.A., Chen, C.Y., Anthony, J.C., 2011. Childhood predictors of first chance to use and use of cannabis by young adulthood. Drug Alcohol Depend. 117 (1), 7–15.

Wagner, F.A., Anthony, J.C., 2002. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. Am. J. Epidemiol. 155, 918–925, http://dx.doi.org/10.1093/aje/155.10.918.

Wang, Y., Storr, C.L., Green, K.M., Zhu, S., Stuart, E.A., Lynne-Landsman, S.D., Clemans, K.H., Petras, H., Kellam, S.G., Ialongo, N.S., 2012. The effect of two elementary school-based prevention interventions on being offered tobacco and the transition to smoking. Drug Alcohol Depend. 120, 202–208.

Wells, J.E., Haro, J.M., Karam, E., Lee, S., Lepine, J.P., Medina-Mora, M.E., Nakane, H., Posada, J., Anthony, J.C., Cheng, H., Degenhardt, L., Angermeyer, M., Bruffaerts, R., de Girolamo, G., de Graaf, R., Glantz, M., Gureje, O., 2011. Cross-national comparisons of sex differences in opportunities to use alcohol or drugs, and the transitions to use. Subst. Use Misuse 46, 1169–1178, PMID: 21417555.

Wilcox, H.C., Wagner, F.A., Anthony, J.C., 2002. Exposure opportunity as a mechanism linking youth marijuana use to hallucinogen use. Drug Alcohol Depend. 66, 127–135.

Willoughby, W.W., 1925. Opium as an International Problem, The Geneva Conferences. The Johns Hopkins Press, Baltimore, Chapter XIX, http://www.druglibrary.org/schaffer/history/e1920/willoughby.htm, last accessed 29.03.12.

Wu, L.T., Anthony, J.C., 2000. The use of the case-crossover design in studying illicit drug use. Subst. Use Misuse 35, 1035–1050.