109

EPIDEMIOLOGY OF DRUG DEPENDENCE

JAMES C. ANTHONY

If one judges solely by the cumulative table of contents of the official journal of the American College of Neuropsychopharmacology, *Neuropsychopharmacology,* the intersection where epidemiology meets neuropsychopharmacology is quite empty. When one looks elsewhere, the traffic becomes visible, with a scope that encompasses topics such as the characteristics of incarcerated drug users, adolescent drug use, epidemics of drug taking, the ''overmedication'' of American society, and postmarketing surveillance of new neuropsychopharmacologic drug products (e.g., see refs. 1–4).

One of the possible reasons that epidemiologic research articles have been seen rarely in *Neuropsychopharmacology* is the generally nonexperimental and observational character of the studies. In this respect, epidemiology shares features of astronomy, geology, ecology, and other sciences in which the evidence comes mainly from field studies, without the benefit of maximal control over experimental error and sometimes with heavy reliance on retrospection. This reliance on retrospection has been a source of considerable criticism, and a countervailing trend has developed toward prospective, longitudinal, and even randomized experimental studies in epidemiology. Nonetheless, the scale and environment of epidemiologic research introduce constraints not seen elsewhere in human biology and the biomedical sciences, even when epidemiology harnesses the power of a randomized trial.

Against a such a background, the primary goal of this chapter is to describe the focus of epidemiologic research in drug dependence and to elucidate the contributions that such research can make when connected with that in other areas of neuropsychopharmacology. A secondary goal is to aid neuropsychopharmacologists who may wish to know more about what can be learned by collaborating with epidemiologists.

For focus, this overview concentrates on the clinical syndromes of drug dependence, as defined in recent diagnostic and statistical manuals of the American Psychiatric Association (e.g., DSM-III, DSM-IIIR, and DSM-IV) and the tenth revision of the World Health Organization International Classification of Disease (ICD-10). The chapter is organized in relation to five main rubrics or subheadings for the subject matter of epidemiologic research. Under each rubric is included a selection of recent examples of epidemiologic evidence regarding drug dependence.

THE FIVE MAIN RUBRICS OF EPIDEMIOLOGY

Morris (5) described seven ''uses'' of epidemiology, which can be simplified in relation to the five ''rubrics'' or main subheadings of epidemiology listed in Table 109.1. These five rubrics offer an easily remembered way of organizing the central research questions and subject matter of this branch of biomedical science (6). Each rubric corresponds to a research question, and each research question demonstrates the substantive research focus of epidemiology and creates an opportunity to explain some of the concepts, principles, and methods that are used to make progress in epidemiology.

To some extent, the progress of an individual epidemiologic investigator can be plotted in relation to a mastery of the concepts, principles, and methods that fall under each rubric listed in Table 109.1. In time, it may prove useful to plot the progress of epidemiology over generations of scientists in terms of the relative balance of attention to the more advanced rubrics. To some extent, progress may be represented by increased attention to issues addressed under the last three rubrics: causal inference, causal mechanisms, and means of prevention and control. As progress is made in future generations, the attention given to estimating how many people are affected and describing how cases are distributed within a population, from place to place or during successive seasons or years, may be correspondingly reduced.

James C. Anthony: Johns Hopkins University, School Of Hygeine And Public Health, Baltimore, Maryland.

TABLE 109.1. THE MAIN RUBRICS AND RESEARCH QUESTIONS OF EPIDEMIOLOGY, AS APPLIED TO CLINICAL SYNDROMES OF DRUG DEPENDENCE

The Rubrics	General Issues	Research Questions Associated with Each Rubric
1. Quantity (Prevalence and incidence)	How many?	"In the population, how many are becoming new cases of drug dependence?" "How many already have become drug-dependent?"
2. Location (variation)	Where?	"In the population, does the frequency or occurrence of drug dependence cases vary from place to place, from time to time, or in relation to individual-level characteristics, conditions, or processes?"
3. Causes (Etiology)	Why?	"In the population, why do some people become drug-dependent while others are spared?"
4. Mechanisms	How?	"What sequences of circumstances, conditions, and processes lead to the development of drug dependence?"
5. Prevention and Control	What can be done?	"What can be done to prevent, reduce, or ameliorate the adverse impact of drug dependence?"

Adapted from Anthony JC, Van Etten ML. Epidemiology and its rubrics. In: Bellock AS, Hersen M, eds. *Comprehensive clinical psychology*, first ed. New York: Pergamon, 1998, with permission.

RUBRIC 1, QUANTITY: ''IN THE POPULATION, HOW MANY ARE BECOMING CASES?''

Concepts and History

The first and most basic of the rubrics of epidemiology involves quantification of the disease burden. Generally, in epidemiologic research on disease states or health events, the main research questions under the rubric of quantity are these: ''In the population of interest, how many people are affected?'' and ''How many people are becoming affected?'' Expressed as a proportion of the total population size, the first question concerns the *prevalence* of the condition. Expressed as a rate, the second question concerns the *incidence* of the condition.

As a concept at the level of individuals within a population, the prevalence of a disease can be discriminated from its incidence. Prevalence relates to ''an individual's probability of *being* a case'' at some point in time or during a specified interval, whereas incidence concerns ''the individual's probability or risk of *becoming* a case for the first time.'' Accordingly, an *incident case* is one that has just become a case (6).

Examples of Epidemiologic Evidence under the Rubric of Quantity

Preclinical research describes a broad range of species that self-administer psychoactive drugs, sometimes to a point of maladaptation and self-harm. These studies have also demonstrated substantial within-species individual differences in predisposition to initiate or sustain drug-taking behavior. Clinical studies under controlled laboratory conditions have clarified that drug self-administration can be shaped by manipulating the profiles of available reinforcers, and by increasing the availability of nondrug reinforcers. Nevertheless, these laboratory studies have not been able to characterize the likelihood of becoming drug-dependent in free-living human populations. At the group level, with population-averaged estimates, this task has been accomplished by means of epidemiologic research in the community. Consider the group of internationally regulated, controlled drugs such as cannabis, cocaine, and heroin, and consider a clinical syndrome defined by the co-occurrence of sustained use of one or more of these drugs with features such as tolerance or withdrawal, with or without signs and symptoms of secondary harm (e.g., loss of a job, recurrent infection or abscess, drug overdose), as encompassed by the DSM-III concept of ''psychoactive drug use disorders.'' The first research to estimate the risk of becoming a DSM-defined case of ''drug use disorder'' was a coordinated set of prospective follow-up studies conducted as part of the National Institute of Mental Health Epidemiologic Catchment Area Program. Case ascertainment was via the diagnostic interview schedule method. Based on field survey evidence from these prospective studies of community-dwelling adults, most never treated for drug problems and studied between 1980 and 1985, the risk for becoming a case of ''drug use disorder'' was estimated at 1.1% per year for a community-dwelling adult in the United States (standard error, 0.4%). In other words, of the literally thousands of adults who did not have drug use disorder at the start of the follow-up interval, drug dependence or a related drug use disorder developed during the 1-year follow-up interval in just over 1% (7).

Ethanol was treated as a separate drug, with ''alcohol use disorder'' defined in terms of sustained use, tolerance or withdrawal, and secondary harms. Based on the Epidemiologic Catchment Area evidence, for a community-dwelling adult in the United States, the risk for becoming a case of alcohol use disorder was estimated at 1.8% per year (standard error, 0.4%), a risk some 70% greater than that for the development of dependence or a related disorder involving an internationally regulated psychoactive drug (7).

Roughly 10 years after the Epidemiology Catchment Area field studies, the National Comorbidity Survey provided new epidemiologic evidence to complement these estimates of the risk for becoming a case of drug use disorder. Although entirely retrospective and cross-sectional in character and lacking the prospective features of the Epidemiologic Catchment Area studies, the National Comorbidity Survey produced useful information necessary to estimate how many users of various classes of drugs had acquired a clinical syndrome of drug dependence, with the syndrome defined and made operational in relation to the DSM-IIIR criteria (8). Based on its nationally representative sample of community-dwelling Americans between 15 and 54 years of age in the early 1990s, the National Comorbidity Survey estimated how many persons had started taking each of several different drugs (e.g., alcohol, cannabis, cocaine), and also how many of them had become dependent on each drug (i.e., alcohol dependence, cannabis dependence, cocaine dependence). On this basis, it was possible to derive a population-average estimate for each drug; once someone had started taking a drug, how likely was it that he or she would have become drug-dependent?

From epidemiologic data derived retrospectively and cross-sectionally in the National Comorbidity Survey, it was determined that for persons who had consumed tobacco on at least once occasion, the probability of having become tobacco-dependent was an estimated 33%. Among persons who had consumed heroin, DSM-IIIR heroin dependence had developed in about 23% (standard error, 5.6%). Among those who had taken cocaine, cocaine dependence had developed in an estimated 16% to 17% (standard error, 1.5%), a value not too distant from that observed for alcohol dependence, 15% (standard error, 0.7%) (8).

The estimated probability that a clinical syndrome of dependence had developed was somewhat lower for users of cannabis, the psychostimulant drugs, anxiolytic–sedative–hypnotic drugs, hallucinogens such as lysergic acid diethylamide (LSD), and inhalant drugs (e.g., glue, gasoline). For example, among stimulant users, the estimate was about 1 in 9 (11%; standard error, 1.6%). For cannabis users, it was 1 in 11 (9%; standard error, 0.7%). Figure 109.1 shows these and other epidemiologic estimates based on the National Comorbidity Survey data (8).

The interpretation of epidemiologic estimates of this type can be tricky. These estimates certainly do not reflect which drugs are associated with a greater potential for dependence than others. In the community at large, exogenous factors, such as the relative availability of a drug (e.g., tobacco vs. cocaine), influence whether drug dependence has a chance to develop once drug use is initiated. In addition, some drug users do not survive from the time of first use to the time of field survey assessment, either dying or disappearing from the sampling frame of the epidemiologic survey before a diagnostic assessment can be completed (see ref. 8). Despite limitations such as these, estimates of this type draw attention to the variability in response to drugs such as nicotine and cocaine, even when laboratory studies demonstrate the robust reinforcing functions served by these drugs. In counterpoint, the laboratory studies demonstrate more limited reinforcing functions served by cannabis and LSD. Nonetheless, DSM-IIIR dependence syndromes appear to have developed in a substantial proportion of alcohol, cannabis, and hallucinogen users (Fig. 109.1).

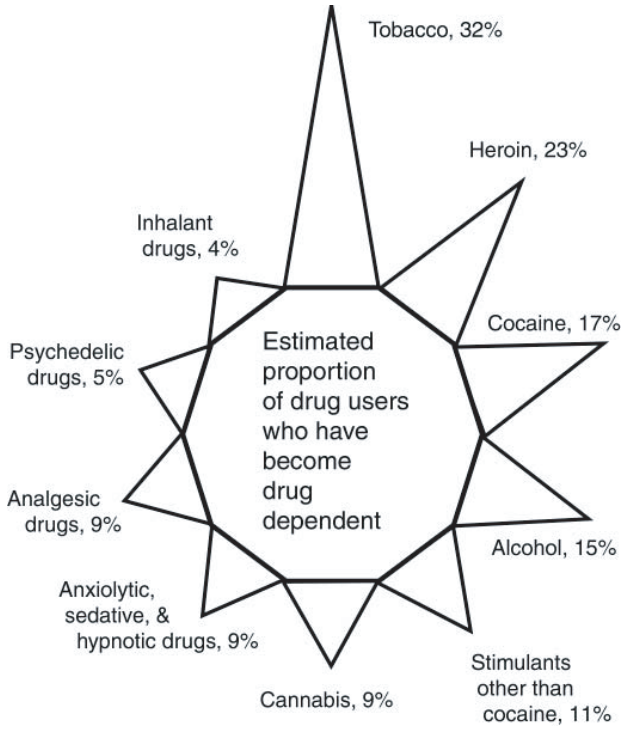

FIGURE 109.1. Estimated probability of drug dependence among drug users, by drug group. (From Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalents: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol* 1994;2:244–268, with permission.)

A slightly different, and more complex, epidemiologic estimate has been derived by dividing the number of currently dependent drug users by the number of currently active drug users (see refs. 9–16). The complexity starts in estimating the numerator of the ratio; here, it is necessary to mix the probability of becoming dependent with the probability of continuing to be dependent. Complexity is sustained in estimating the denominator of the ratio. To focus on currently active drug users, it is necessary to mix the probability of starting to use the drug with the probability of continuing to use the drug. An additional complexity enters the picture because drug dependence, as a process, becomes one of the determinants of whether a person continues to use a drug once drug use has been initiated. Hence, the force of persisting drug dependence is exerted not only in the numerator of this ratio but also in its denominator. In

TABLE 109.2. ESTIMATED PROPORTION OF ACTIVE DRUG USERS WHO REPORT FEATURES OF ACTIVE DRUG DEPENDENCE

Drug or Drug Group	Number of Active Drug Users in the Sample	Estimated Proportion with One or More Clinical Features of Active Drug Dependence (%)	Estimated Proportion with Three or More Clinical Features of Active Drug Dependence (%)
Cocaine	709	38	18
Cannabis	3,444	42	17
Alcohol	14,596	23	8
Tobacco	8,187	60	34

Data from *National household survey on drug abuse: main findings, 1998.* DHHS publication No. (SMA) 00-3381. Rockville, MD: Department of Health and Human Services, Substance abuse and Mental Health Services administration, 2000.

consequence, the resulting estimate cannot be interpreted as a risk for becoming dependent, much less as an indication of relative dependence liability. At best, this estimated ratio reflects the proportion of active drug users who may, in theory, require drug dependence treatment services—that is, it is an indicator of burden. This kind of statistic may be helpful in planning services. Its utility in etiologic studies is compromised by its complexity.

Table 109.2 presents the most recently published drug-specific estimates for the proportion of active drug users who have currently active drug dependence, based on the 1998 National Household Survey on Drug Abuse in the United States (14). Reading the table, one can see that 709 recently active cocaine users were included in the nationally representative survey sample of community-dwelling respondents ages 12 years and older. According to the population estimates, among active cocaine users in the study population, 38% reported at least one of seven active clinical signs or symptoms of cocaine dependence, and an estimated 18% reported at least three active clinical features. Applied in an estimate of burden in the general population, these values indicate that about 0.7% of the study population have a cocaine-related problem and about 0.3% have three or more cocaine-related problems, perhaps meriting treatment or intervention services. By comparison, the corresponding estimates for cannabis, based on 3,444 active cannabis users in the sample, indicate that 42% of active cannabis users reported at least one cannabis dependence problem and 17% reported three or more clinical features of cannabis dependence. In terms of population burden, an estimated 3.6% of the study population have an active cannabis problem and an estimated 1.5% have three or more active features of cannabis dependence. Values for alcohol and for tobacco cigarettes are included in Table 109.2 for comparison with the values for cocaine and cannabis.

An increasing number of epidemiologic studies have started to produce estimates of this type, helping to quantify the number of affected cases in various parts of the world and for selected subgroups of the population, such as young adults. For example, Grant (15,16) estimated that alcohol dependence developed in about 20% of drinkers, that drug dependence developed in about 19% of persons initiating illicit drug use, and that 16% of active illicit drug users were dependent on illicit drugs. In addition to other recent U.S. survey estimates for the number of active dependence cases among active drug users (10,11,13,14,17), estimates have now been made for national populations or subpopulations in Australia, the United Kingdom, Germany, and other countries (18–20).

Against the background of rapidly accumulating prevalence estimates based on cross-sectional epidemiologic surveys, prospective studies and incidence estimates for the drug dependence syndromes have progressed much more slowly. Although prospective studies are much more difficult to complete, they cannot be omitted if we are to understand the force of drug-related morbidity, and distinguish the separate conditions and processes that promote the initiation of drug dependence, as distinct from the conditions and processes that sustain drug dependence once the syndrome has started. In this respect, it is unfortunate that the Epidemiologic Catchment Area estimates, now more than 15 years old, are currently our most authoritative values for the risk for the development of alcohol or other drug dependence in the U.S. adult population (7). Elsewhere in the world, prospectively gathered data on the incidence of clinically defined syndromes of alcohol or other drug dependence (21), sometimes obtained with rigorous methods in quite isolated populations (e.g., 22), are very limited.

Much of the postmarketing surveillance of a population's actual experience with newly distributed medicines falls under the first rubric of epidemiology. Recent efforts to monitor the abuse potential of tramadol (Ultram) demonstrate the utility of epidemiologic concepts, principles, and methods at the intersection of epidemiology with neuropsychopharmacology (23).

Before we leave the rubric of quantity, it may be useful to note that several generations of epidemiologically oriented

scientists have attempted to estimate the number of ''hard-core'' drug users in the United States by extrapolating from the number of cases seen in treatment, law enforcement, or other facilities. In the earliest reports, the approach involved guessing the number of untreated or nonincarcerated drug users for every case registered in treatment or known by law enforcement authorities. Since the 1960s, sophisticated mathematical estimation procedures have been used, with advanced statistical treatments such as projections from truncated Poisson distributions and capture–recapture methods (see ref. 24).

This work is at the margin of the scientific enterprise. It may be understood best for its enduring political popularity. As a source of authoritative scientific evidence, it is of dubious value and based on assumptions that are not well tested and may never be testable. In a brief, pithy article, Newman and Cates (25) made this point 30 years ago, quoting from the classic study by Terry and Pellens (26): ''As a matter of fact, it is not necessary to know the exact number of users or even the minimal extent, to realize that there are a large number [of addicts] and that the problem is serious.'' Newman and Cates also summarized an observation made by the very talented epidemiologist Leon G. Hunt, whose work is mentioned in the next section. Hunt was quoted as saying, ''The question is not whether there are three or four million [addicts], but that the number is several million rather than only several hundred thousand'' (25).

The view espoused by Newman and Cates (25) actually was much more harsh. They wrote, ''The great disparity of the findings of studies using different methods of enumeration generally ensures that data will be found to support any position, and contradictory information is simply ignored.'' They concluded, ''Objectives of studies that are intended to measure the incidence and prevalence of addiction must be reassessed in terms of experience. It is necessary to ask candidly what impact such research has had in the past and to question the premise that knowledge, for its own sake, is sufficient justification [to undertake these studies.]'' This sentiment is especially appropriate in an era of dramatically increased investment by the U.S. government in surveys to estimate the number of active drug users in populations at the state level, with sample sizes for the U.S. National Household Survey on Drug Abuse growing from under 10,000 respondents per year in the early 1990s to more than 70,000 respondents per year in the early twenty-first century.

RUBRIC 2, LOCATION (VARIATION): ''IN THE POPULATION, IS THERE ANY VARIATION IN THE OCCURRENCE OF CASES?''

Concepts and History

The best epidemiologic studies to quantify the occurrence of drug dependence also have had a more general purpose of studying variations in prevalence or incidence in relation to characteristics of place (e.g., geographic variation), time (e.g., from year to year), or person (e.g., male vs. female drug users). Often, the analyses to disclose variation are not intended to produce links in a chain of causal inferences. Rather, the purpose of these analyses is description, as in Fig. 109.2, or they may be a necessary step of clarifying variation before anyone undertakes a more probing causal analysis or new investigation (6).

Examples of Epidemiologic Evidence under the Rubric of Location

Two of the most robust findings from epidemiologic studies on the location of drug dependence cases within population subgroups are a male excess and an excess in the age group 15 to 44 years old, disclosed by both prevalence differences and relative risk estimates (see ref. 7). To be sure, the male excess in the occurrence of drug dependence can be contradicted with certain evidence involving some specific drugs, such as those in the group of anxiolytic, sedative, and hypnotic medicines. In addition, in some places, the use of opium derivatives is commonplace in persons in the later years of middle age and among the elderly, and several studies have noted a slight upturn in the risk for alcohol dependence during the last decades of life, at least among men (27). Nonetheless, these exceptions help prove the more general rule.

A recent intriguing discovery about male–female differences in drug use within the United States is that a male excess is found at the earliest stages of drug involvement; boys are more likely than girls to be exposed to opportunities to try illicit drugs. However, once presented with the opportunity, they are equally likely to try a drug (28). Furthermore, once drug use has started, women are almost as likely as men to become drug-dependent (12.6% vs. 16.4%), alcohol and cannabis being two noteworthy exceptions (8).

When cases are located in relation to time, the past 35 years have seen a marked increase in the prevalence of illicit drug use, mainly between 1965 and 1980, as illustrated for the United States in Table 109.3. Analyses of retrospective data from the Epidemiologic Catchment Area studies and the National Comorbidity Survey have highlighted corresponding differences in the experiences of successive birth cohorts born during the first two-thirds of the twentieth century. According to this evidence, the risk for drug dependence has been markedly greater in persons born since World War II than in prior birth cohorts (17,29–31).

The location of cases in relation to geography also has been scrutinized in descriptive epidemiologic studies. Figure 109.2 provides a cartoon summary of an apparently epidemic spread of heroin use in the United States during the Vietnam War era, based on the analyses of Hunt (24) of heroin-dependent persons entering treatment and their age at onset of heroin use. Figure 109.3 pertains to the more recent outbreaks of cocaine involvement among young peo-

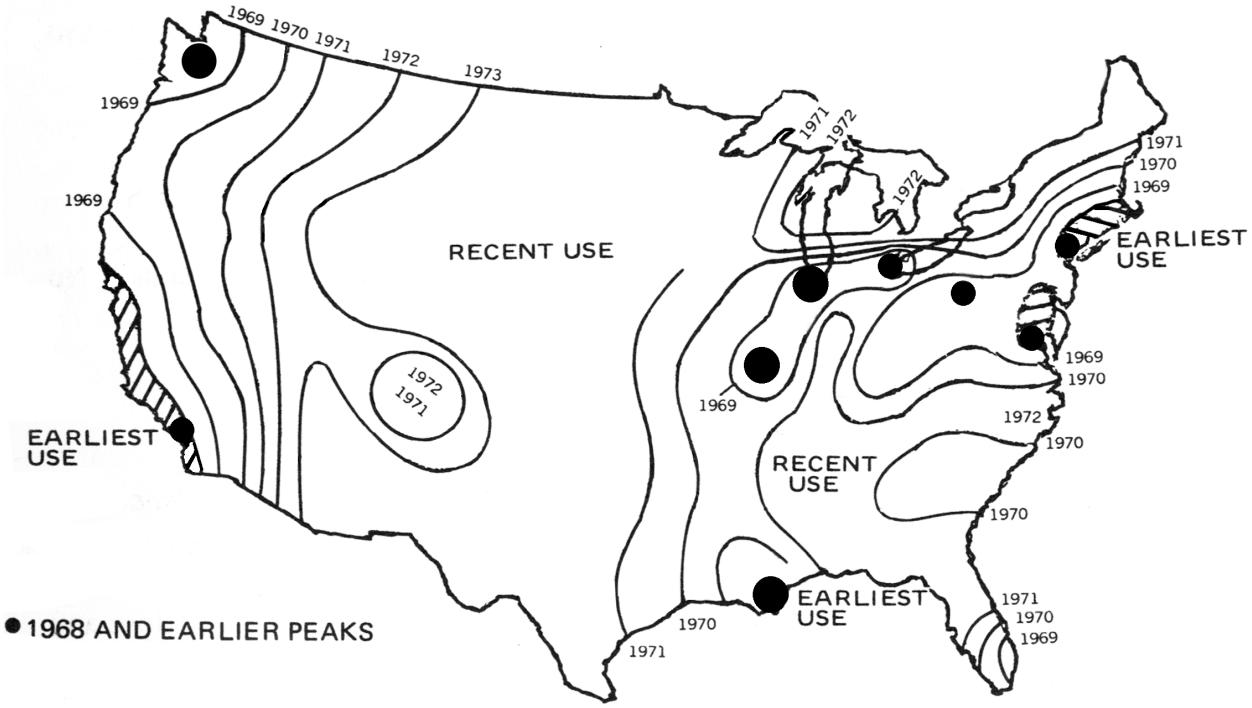

FIGURE 109.2. Retrospectively constructed geographic spread of the epidemic of heroin use in the United States during the Vietnam War era. Data from age at onset of cases admitted to treatment facilities. (From Greene MH, Kozel NJ , Hunt LG, et al. An assessment of the diffusion of heroin abuse to medium-sized American cities. Washington, DC: Special Action Office for Drug Abuse Prevention, 1974, with permission.)

TABLE 109.3. ESTIMATED PREVALENCE OF ILLICIT DRUG USE IN THE UNITED STATES

Survey Year	Number of Survey Respondents	Estimated Proportion with a History of Illicit Drug Use (%)	Estimated Prevalence of Recent Illicit Drug Use (%)
1971–72	3,760[a]	15–22[a]	N/A[a]
1979	7,224	31.3	17.5
1985	8,021	34.4	16.3
1991	32,594	34.1	11.1
1992	28,832	33.3	9.7
1993	26,489	34.2	10.3
1994	17,809	34.4	10.8
1995	17,747	34.2	10.7
1996	18,269	34.8	10.8
1997	24,505	35.6	11.2
1998	25,500	35.8	10.6

[a]Data from the *National household servey on drug abuse: main findings, 1998.* DHHS publication No. (SMA) 00-3381. Rockville, MD: Department of Health and Human Services, substance abuse and Mental Health Services administration, 2000.

FIGURE 109.3. Estimated geographic distribution of coca paste smoking among Chilean youth, 1999. (From Dormitzer C, Caris L, Anthony JC. Parental attention and risk of coca paste smoking in Chile: preliminary data from the 1999 national school survey in Chile. Rockville, MD: Department of Health and Human Services, 2000, with permission.)

ple living in Chile and shows a substantially greater prevalence of coca paste (''pasta base'') smoking in areas in the north of the country, near the borders with coca-producing countries, than in the south of the country (32).

What is common to all these epidemiologic observations is that they describe, but do not explain or account for, the observed variation. We know that men have been more likely to become drug-dependent than women, but the studies that produced solid evidence on this variation have not helped us explain why this is so. The same is true for the epidemiologic observations of birth cohort differences, which prompt speculation about the greater availability of illicit drugs but then beg the question of what prompted the greater availability. The patterns of epidemic spread of heroin use in the United States remain unexplained, and it is possible that the exclusive attention to treated cases in the study of Hunt (24) may have produced a biased impression of the temporal sequencing of spread through different areas. Finally, at one level, the north–south pattern of coca paste smoking in Chile may be interpreted as a manifestation of proximity to the coca-producing countries, but no probing analysis has confirmed the impression that coca paste is substantially more available in the north. More probing epidemiologic analyses are required to confirm the impression left by initial descriptive observations of this type.

RUBRIC 3, CAUSES: ''IN THE POPULATION, WHY DO SOME BECOME AFFECTED WHILE OTHERS ARE SPARED?''

Concepts and History

What differentiates the rubric of ''causes'' from the rubric of ''location'' is the degree to which the analysis is oriented toward explaining and accounting for the observed phenomena, rather than merely describing the patterns of occurrence. To the extent that the search for causes can lead us toward more effective intervention maneuvers, work under this rubric merits a special status; many regard this search as one of the highest callings of epidemiology (33). Nonetheless, numerous examples show that epidemiologic research can have a considerable impact on the health of a population even before the search for causes is complete. John Snow's effective demonstration that proper water sanitation can reduce or prevent outbreaks of cholera anticipated Robert Koch's identification of *Vibrio cholerae* by several decades. Epidemiologic evidence plotting an offspring's risk for Down syndrome by age of the mother at the time of delivery created one pathway toward effective prevention of trisomy 21 and associated conditions, although we still do not know the causes of the trisomies. HIV prevention efforts directed toward the unsafe sex practices of gay men in the United States helped to change the dynamics of the HIV/AIDS epidemic in the early 1980s, when many believed AIDS to be caused by inhalant drug use (''poppers'') and before isolation and identification of the AIDS-causing virus (6).

In some instances, weak links in the chains of disease causation have been spotted by epidemiologists working with basic quantitative methods, such as cross-tabulation or plotting of incidence estimates, as was done for maternal age and risk for Down syndrome. Complex diseases and conditions such as the drug dependence syndromes do not yield so readily; what might seem to be an apparently simple ''chain'' of causation actually turns out to be a complex ''web'' of causation of multifactorial origin.

As in the other sciences allied with neuropsychopharmacology, epidemiology sometimes can turn to the power of randomized, controlled trials and multiple replications for definitive evidence of the web of causation. However, a great many of the important questions in the intersection between epidemiology and neuropsychopharmacology cannot be answered with randomized, controlled trials; in some instances of ''natural experiments,'' the concept of replication leaves much to be desired.

With respect to a ''natural experiment'' that may never be repeated, we have the experience of members of the U.S. Armed Forces who served in Vietnam. Virtually all Vietnam veterans were exposed to the opportunity to try heroin within a span of a few months in-country; many (but not all) tried heroin when the opportunity arose (34). When diagnostic interview schedule field study methods were used to assess a large representative sample of Vietnam returnees, almost 20% of the study sample qualified as cases of active heroin dependence during the tour of duty. Nevertheless, no more than a fraction continued to use heroin or remained heroin-dependent once they returned stateside to home. O'Brien et al. (35) have suggested that heroin availability had much to do with this situation. Studying Vietnam veterans who came home to urban areas known for heroin availability, they found substantially higher fractions returning to heroin use. Nonetheless, even in this study sample, a great many heroin users did not come back from Vietnam to the United States and return to heroin dependence once they had settled in urban areas. These results challenge conventional notions of any inherent addictive quality, abuse potential, or dependence liability of heroin as a chemical substance. During an era of discovery that genetic predispositions are prominent among causes of drug dependence, these ''subject as own control'' results from once-in-a-lifetime natural experiments demonstrate that environmental contingencies also are important (36,37).

The Vietnam era research also highlights the necessarily observational character of much epidemiologic work; no responsible investigator would undertake a randomized, controlled trial of exposure to heroin in otherwise drug-naïve young adults. Recent evidence on the early onset of drug use raises similar issues. Since the 1960s, epidemiologic evidence from observational studies has accumulated about

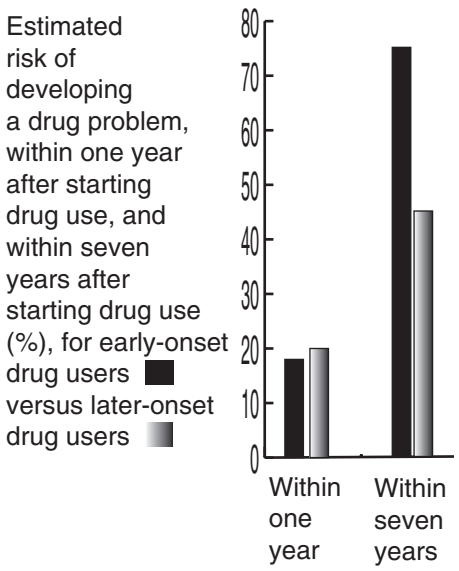

FIGURE 109.4. Estimated risk for the development of a drug problem 1 year after the start of illicit drug use and 7 years after the start of illicit drug use, by age at onset of illicit drug use. Data from National Institute of Mental Health Epidemiologic Catchment Area Program, 1980–1984. (From Anthony JC, Petronis KR. Early-onset drug use and risk of later drug problems. *Drug Alcohol Depend* 1995;40:9–15, with permission.)

age at first illicit drug use and the subsequent risk for drug problems, including drug dependence, as illustrated in Fig. 109.4. Very simple cross-tabulations of study data were enough to bring this association to light (38–42).

Many observers have been convinced by this cross-tabular evidence and have inferred that drug dependence can be prevented by delaying the onset of illicit drug use. Nonetheless, some observers have noted that persons who start using drugs at an early age have more time to experience the hazards of drug use (38) or have other characteristics that make it seem that early age at onset is to blame for the excess when alternative explanations are more plausible (43,44). In addition, basic cross-tabulations typically cannot rule out the possibility of an underlying common predisposition, laid down at conception or later in development, that manifests itself not only in an earlier age at onset of drug use but also in a greater risk for becoming drug-dependent. If some predisposition regulates both age at onset and risk for drug dependence (e.g., something linked to a predisposition toward anxiety disorders or antisocial behavior), then efforts to delay age at onset of drug use may have a limited effect on risk for drug dependence.

In this type of context, a direct randomized, controlled trial is out of the question; no one would deliberately expose children to illicit drugs for the sake of experimental confirmation of the observational evidence. Instead, epidemiologists have turned to alternative approaches. First, the life table method developed by Edmund Halley (of comet fame) was used to clarify that the risk for drug problems is not simply a consequence of the fact that early-onset drug users have more time to experience drug problems (Fig. 109.4). Then, "survival analyses" were completed for different strata of the population (e.g., males vs. females) to rule out some of the worrisome predispositions that might lead to a distorted and imperfect view of causal relationships (38). Whereas a randomized, controlled trial may call on randomization to bring distorting predispositions into balance, epidemiologists seek an approximation of this balance via stratified analyses of observational study data or by "matching." Just as a clinical researcher may match subjects by age or sex, epidemiologists create more homogeneity within "risk sets" by matching subjects on measured variables thought to represent confounding predispositions. Some of these confounding predispositions are genetic and can be matched within monozygotic twin pairs, or they are environmental and can be matched within neighborhoods of residence (6). Second, over and above stratification and matching, multiple regression methods and other forms of the generalized linear model have been used to make statistical adjustments for an array of suspected confounding variables, too many to control via matching or stratification. Finally, indirect randomized, controlled trials are being undertaken in a final push to challenge the belief that the early onset of drug use causes drug dependence. These indirect trials involve the random allocation of preventive interventions intended to delay the onset of drug use; subsequent post-intervention follow-up tests whether delayed onset of drug use is followed by a reduced risk for drug dependence.

In summary, whereas trialists may use a direct randomized, controlled trial to probe suspected causal relationships in the setting of a laboratory or experimental clinic, in the context of population research, epidemiology turns to tools such as stratification, matching, statistical modeling, and the indirect randomized, controlled trial, in which the causal factor is a proximal target for intervention and the condition to be prevented is a more distal outcome (6). Of course, many trialists also make use of stratification, matching, and statistical models—for example, when they anticipate that randomization will not yield completely balanced distributions or when randomization has failed to bring suspected confounding variables into balance. In this sense, a methodologic intersection exists between epidemiology and neuropsychopharmacology, the epidemiologist typically working with larger and less restricted samples at the population level rather than the smaller samples of patients seeking help seen in most clinical trials.

Examples of Epidemiologic Evidence under the Rubric of Causes

Challenging epidemiologic problems have surfaced in research on the suspected hazards of illicit drug use and neuropsychopharmacologic drug products. For example, during

the height of the cocaine epidemic in the late twentieth century in the United States, ethnographic studies of cocaine users and a limited number of case reports from psychiatrists drew attention to symptoms of panic anxiety, experienced not only during episodes of cocaine intoxication but also afterward. Because of some resonance with pharmacology and neurobiological theory, several clinicians inferred that cocaine use was precipitating panic attacks and panic disorder in persons who had not experienced them previously (45,46). Nonetheless, the ethnographic study samples were small (e.g., see ref. 47), and the research was based on relatively uncontrolled study designs (e.g., assessors were not blinded with respect to the suspected causal hypothesis).

In addition, it may not come as a surprise that cocaine users visiting psychiatrists had an apparent excess of a psychiatric condition. The well-known Berkson's bias (48) can account for a false appearance of comorbidity when samples are clinical rather than epidemiologic.

With Berkson's bias in mind, several epidemiologists investigated the suspected causal link of cocaine use to panic attack and panic disorder, each with the strengths of study methods that involved double-blinding with respect to the causal hypotheses (i.e., neither the clinical assessors nor the study participants knew that the hypotheses would be tested). One community sample study of young adults was oriented to anxiety in general rather than to discrete panic attacks specifically, and its general evidence about anxiety did not support the published clinical observations (49). However, drawing prospectively ascertained incident cases of first-time panic attack from within the Epidemiologic Catchment Area study sample, and using multiple regression methods to constrain a range of suspected confounding variables, another epidemiologic study produced statistically robust evidence that cocaine users in the community are about three times more likely to experience panic attacks than are age- and neighborhood-matched nonusers (46). A third study, which applied a new case-crossover research design for epidemiology to data from the National Household Survey on Drug Abuse, produced an estimated relative risk not too distant from the one observed in the prospective Epidemiologic Catchment Area studies (RR = 3) (50).

This example of a suspected psychiatric hazard of cocaine use illustrates how epidemiology makes use of study procedures such as standardized diagnostic assessment, double-blinding, matching, and multiple regression to strengthen the basis for causal inference from evidence based on nonrandomized observational studies. Nevertheless, more work has actually been done and the history of epidemiologic research is longer on the "other side" of co-occurring psychiatric disturbances and drug dependence, where the observed "comorbidity" is thought to arise because the psychiatric disturbance leads to drug dependence. Perhaps the oldest tradition of this type of comorbidity research started with clinical observations about sociopathy and criminal backgrounds in drug dependence cases sent to federal narcotics farms. For example, clinical investigators such as Kolb and Pescor (51) estimated that as many as 50% to 60% of incarcerated cases qualified as antisocial or socially maladapted, with evidence of social maladaption generally predating drug use.

The potential for a type of Berkson's bias is ripe in this context; one should not be too surprised to find an excess of socially maladapted persons among incarcerated prisoners of any stripe. Even so, it was more than 25 years after the initial observations before a proper epidemiologic investigation of this relationship was undertaken. This investigation was a "nonconcurrent prospective study" of children seen in child guidance clinics of the 1920s, some with record-based evidence of childhood rule breaking and deviance, and others without such evidence. The research team secured old child guidance records in the 1950s, and by the early 1960s they had successfully traced, reengaged, and used standardized diagnostic survey methods to assess the vast majority of the sample, who were then well into adulthood, mostly within or beyond the end of the effective period of risk for the development of drug dependence. To the extent that any single study can do so, this classic epidemiologic investigation set to rest most of the concerns about Berkson's bias and showed that prior childhood deviance is linked to a subsequent risk for dependence on heroin and other "narcotic" drugs, with the evidence tending to support a causal inference linking earlier deviance with later drug problems (52,53).

Numerous subsequent observational studies followed along this path, with the strength of community samples outside clinics and prisons, but generally with cross-sectional and retrospective research designs (53). One noteworthy exception was the Woodlawn Project "concurrent prospective study" of a large sample of first-graders recruited in the mid-1960s and followed later as teenagers and then as young adults. The teenage follow-up study produced evidence that resonated with the nonconcurrent prospective evidence from the child guidance study sample. Namely, an excess occurrence of "heavy" drug use was noted among teenage boys whose first-grade teachers had rated them as "aggressive" rule-breakers in the classroom (54; M. Ensminger, *personal communication*). Subsequent follow-up, when the teens had matured to adulthood and entered the fourth decade of their lives, showed an excess occurrence of cocaine use in association with teacher-rated aggression measured more than 20 years beforehand.

It is difficult to imagine a direct randomized, controlled trial to test the causal influence of antisocial, deviant, or aggressive behavior on later risk for drug dependence. Regrettably, the observational studies described to this point do not rule out the possibility of an underlying diathesis or predisposition that gives rise both to unruly behavior and to drug dependence, the first coming developmentally earlier in the expression of the diathesis, and the second devel-

opmentally later (see ref. 55 for a recent discussion). This, of course, is one of the main problems of causal inference in contemporary ''psychiatric comorbidity'' research. Other problems include ''shared methods covariation'' resulting from heavy reliance on self-report and recall in the measurement of drug dependence and other psychiatric disturbances, and problems associated with an assumption that coarse-grained age-of-onset data can illuminate which condition came first, even when the prodrome of the conditions is known to develop insidiously, often over a span of years (56).

Fortunately, some twin and adoption paradigm research has clarified the issue of shared genetic and environmental predispositions toward antisocial behavior and the problems associated with drug dependence (57,58). In addition, an indirect randomized, controlled trial has been completed to evaluate a new developmentally sensitive modality of drug prevention programming and to shed new light on the suspected causal influence of early deviance, aggression, and rule breaking. A detailed description of the indirect randomized, controlled trial is beyond the scope of this chapter and can be read elsewhere (59,60). Nevertheless, in brief, the research design involved a repetition of the Woodlawn Project recruitment of a large sample of first-graders (n = 2,311), but with random assignment of the children to a ''good behavior game'' condition, which involved a teacher-led classroom-based intervention designed to improve the behavior and rule abidance of children and promote their social interactions, versus control conditions (either the standard curriculum or a ''mastery learning'' curriculum designed to improve reading achievement). The children assigned to the experimental interventions were kept in the same primary school classrooms and the same conditions for 2 years, during which they received increasing ''doses'' of the behavior and reading curriculum. The children assigned to the ''standard-setting'' or control classrooms also were kept together for 2 years and received just the usual and customary curriculum of the local public school system.

Follow-up assessment of the children who grew up and went to school in this urban public school system occurred on an annual basis from grades 3 to 4 of primary school to grades 7 to 8 of middle school. These assessments involved private face-to-face interviews with each child, in which standardized survey research methods with blinding (assessors did not know which children had received which intervention) and teacher ratings were used. Once the children were old enough, they were allowed to mark their answers on an answer sheet that could not be read by the assessor and was sealed in an envelope for later data entry. The assessments also involved ratings by the teachers in these later grades; the middle school teachers knew that the children had been in a prevention experiment, but they did not know which of the three conditions the child might have received during the first 2 years of primary school.

Life table and regression analyses of the follow-up teacher ratings and self-reported age at first use of tobacco provided evidence consistent with the preventive hypotheses; (a) boys who had received the good behavior game intervention were rated as better-behaved than their counterparts in the other study conditions ($p < .05$), and (b) the risk of starting to smoke tobacco by age 13 or 14 years was substantially greater for boys in the ''standard-setting'' control classrooms than in those who had spent first and second grades in the ''good behavior game'' classrooms (RR = 2.0; $p < .05$). Consistent with the observational evidence suggesting that deviant or aggressive behavior is a stronger determinant of drug use for boys than for girls, the ''good behavior game'' effect was less pronounced among the girls (59). Current continuing follow-up of these study participants into their young adult years, supported by the National Institute of Mental Health and the National Institute of Drug Abuse, will reveal whether the apparent intervention effects are long-lasting and influence the risk for the use of other drugs and the development of drug dependence.

Whereas an indirect randomized, controlled trial of this type is a challenge and requires follow-up over spans of time that exceed typical durations of National Institutes of Health grant awards, this type of experimental investigation of the suspected causal link of early deviance or aggression to later drug use and dependence is indispensable when the task is causal inference. Random assignment of the children to different intervention conditions helps to bring into balance an array of suspected confounding variables. Thereafter, careful measurement and regression modeling help to constrain what randomization has not constrained. Although it is not possible to make a random assignment of children to higher or lower levels of rule breaking and aggressive behavior, it is possible to assign them at random to interventions designed to reduce these levels.

Of course, no single indirect randomized, controlled trial will settle the outstanding issues about this form of psychiatric comorbidity. The case for causal inference will depend on completion of more indirect trials along these lines, with each replication adding strength to the chain of inference and web of causation.

Other forms of ''comorbidity'' with drug dependence have come under scrutiny in epidemiologic research, most recently an observed co-occurrence involving the anxiety disorders, especially phobic disorders (61). One can expect a more rapid acceleration of epidemiologic attention to the link of anxiety disorders to alcohol or other drug dependence, with time from the first nonexperimental observations to the first indirect randomized, controlled trial measured in years rather than in decades, as was the case for the link of childhood deviance and antisocial behavior to drug dependence. In this context, it may be important to note another feature of the Woodlawn Project findings, which drew attention to the combination of shyness and aggression or rule breaking among boys. The Woodlawn Project report noted an interaction of shyness and aggres-

sion, directing attention mainly to the excess risk for heavy drug use among boys who were rated in first grade as being both shy and aggressive. However, careful inspection of the Woodlawn Project study data indicated that the observed interaction depended heavily on a quite low occurrence of drug use among the boys who were shy but not aggressive. In other words, in the absence of aggression, being shy and not having many friends may help protect an inner city youth against the risks of illicit drug use. The link to current anxiety disorders and comorbidity research involves the prominence of phobias in the observed association with alcohol and other drug dependence, and the Woodlawn Project measurement of shyness as a trait that encompasses not having very many friends, being socially withdrawn, and staying on the fringes of or outside social groups (54).

Before we leave the rubric of causes, several recent studies merit special mention because of their pertinence in the genetic epidemiology of drug dependence. The Vietnam Veteran twin study is especially noteworthy because it is seeking to partition genetic, shared and nonshared environmental influences across a sequence of transitions leading to drug dependence. Unique to this study is its attention to the transition from before to after the first exposure to opportunities to try drugs (62). The importance of this transition in etiologic research on drug dependence is discussed in the next section, under the heading of causal mechanisms.

The work of Kendler and colleagues (63,64) is noteworthy for its initial focus on female twins and its spotlight on gene–environment interactions. This work is leading us to a better understanding of how genetic predispositions may have an important influence on entry into risk-laden environments, where exposure to drugs and drug taking becomes more likely, over and above any influence of inherited characteristics on responses to drug exposure. In a related line of work on parent–child interactions, Kendler et al. (65) have recently added new evidence that parental coldness or aloofness may affect the occurrence of alcohol or other drug dependence, but the evidence is not generally supportive of an influence of active parenting styles (e.g., authoritarianism). Of course, evidence to the contrary exists, including some new evidence on how children shape the parenting behaviors displayed by their mothers and fathers (66). Soon, results will be available from indirect randomized, controlled trials in which interventions have been used to increase the aspects of parenting behavior suspected of being most influential in early drug involvement (e.g., supervision and monitoring). Here, the causal inference is supported by a fairly solid body of observational evidence contributed by many different research groups (67–71). Nonetheless, as in the link between sociopathy and drug dependence, replications from indirect randomized, controlled trials are apt to provide the most definitive evidence regarding these issues of causal inference. In time, indirect randomized, controlled trials with large epidemiologic samples will probably be performed, possibly with specific targets identified and characterized through elaborations of the human genome project. For example, one can imagine research on parental influences on drug taking that includes measurement of parenting behaviors in addition to inherited determinants of persistent drug use, such as the alleles controlling the cytochrome P-450 enzyme, which is important in nicotine metabolism (72).

RUBRIC 4, MECHANISMS: ''HOW DO SEQUENCES OF CIRCUMSTANCES, CONDITIONS, AND PROCESSES LEAD TO DISEASE?''

Epidemiology as a discipline places emphasis on studies of the ''natural history'' of disease, in part because of its early confluence with clinical medicine, bacteriology, and virology. Here, natural history may be understood as the outward manifestations of an evolving causal process and the expression of causal mechanisms that lead toward the fatal or nonfatal resolution of the condition under study. In the study of diseases, ''clinical course'' can be differentiated from ''natural history'' once clinical attention can make a fundamental difference. Before then, what we see is natural history. Once effective treatment maneuvers have been started, what we see is the clinical course, or natural history modified by clinical attention.

Until recently, when the concept of natural history was applied in the epidemiology of drug dependence, most attention was given to observable ''stages'' and ''developmental sequences.'' For example, Robins (73) and Winick (74) advocated decomposition of the addiction process into stages. They specified a pre-initiation stage that involved first exposure to an opportunity to try a drug. Thereafter, some presented with an opportunity go on to try the drug, whereas others do not. Among those who actually try the drug, the drug-using stage may or may not be followed by another stage—transition into drug dependence. Some users actually ''mature out'' of stages of very serious drug use (e.g., see ref. 74).

In the work of Kandel and Davies (75), the natural history of drug involvement is conveyed as a stage developmental sequence in which different drugs are tried, first legally available beer or wine, then hard liquor or tobacco, then marijuana as the first ''illicit'' drug in the sequence, then other illicit drugs. The last development in Kandel's sequence is use of prescription psychotherapeutic medicines (Fig. 109.5) (85); others have confirmed this position for prescription drug use (86).

Nonetheless, some observers have argued that this ''gateway description'' of sequences from drug to drug may rest solely on different levels of availability or opportunity to use different drugs. Other investigators have challenged the stage transition concept as applied to drug dependence and youthful tobacco smoking (77). They have advocated an

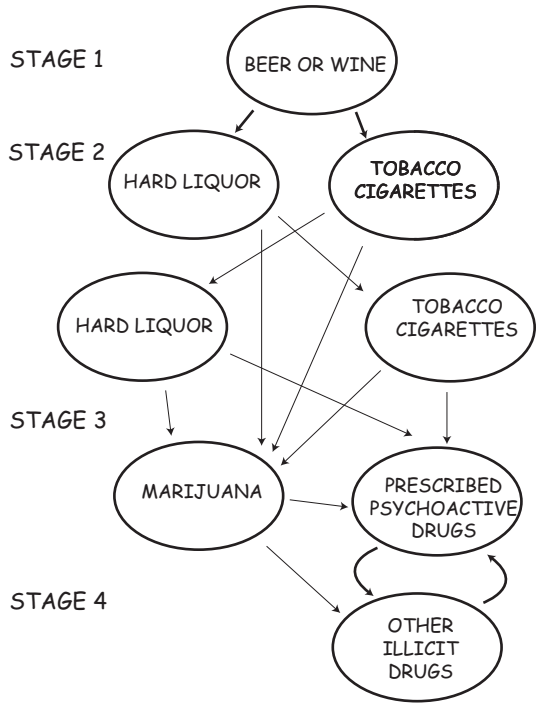

FIGURE 109.5. Stages in the developmental sequence of adolescent drug involvement. (Adapted from Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *J Stud Alcohol* 1992;53:447–57, with permission.)

analysis of levels of drug involvement in terms of a hybrid concept that allows for discrete stage transitions, but with dimensional movement within each stage (e.g., see ref. 27). Statistical methods for studying this hybrid transition progression model are being developed for epidemiologic research (e.g., see refs. 78,79).

A recent development has been epidemiologic research on the natural history and clinical course of the various clinical features of alcohol dependence (e.g., see refs. 80–82). Separate lines of clinical and epidemiologic research on the natural history of dependence on drugs other than alcohol have also been initiated (e.g., see refs. 83,84).

RUBRIC 5, PREVENTION AND CONTROL: ''WHAT CAN BE DONE TO PREVENT, REDUCE, OR AMELIORATE THE ADVERSE IMPACT?''

The central position of prevention in epidemiology already has been mentioned in this chapter, although many epidemiologists' careers are devoted to observational studies, with little attention to intervention research. ''Control'' is also a key concept in epidemiology, referring to maneuvers such as quarantine or the effective treatment of active cases to limit spread to other persons.

During the evolution of epidemiology in the nineteenth century, a new type of professional emerged—a public health officer equipped with newly found knowledge of epidemiology and armed with police powers necessary to protect the larger population from the threat of infectious diseases. In twentieth century efforts to mount an effective societal response to drug dependence, the police authority was split from the public health authority. As a result, when most people now think of the prevention of drug dependence, what comes to mind are health education classes for young people of school age or mass media campaigns to publicize the hazards one faces once drug use starts. We do not tend to think of the international, federal, state, and local laws or police actions as societal instruments for prevention. Nor do we tend to think of early interventions for drug-dependent cases, tracing of secondary contacts who may be sources of sustained outbreaks, or effective treatment of active cases as a means of preventing new cases. Indeed, in some quarters, the opinion has been expressed that concepts of epidemiology and public health should not be applied to drug dependence because these concepts are tied inherently to coercive actions, such as quarantine (85).

Notwithstanding these concerns, during the past quarter-century, some epidemiologists have directed attention to the evaluation of laws and regulatory activities thought to prevent and control drug dependence and associated hazards. Starting in the 1960s, de Alarcon (86) and Hughes et al. (87) refined methods of tracing secondary cases and of street outreach to curb urban outbreaks of heroin dependence. Figure 109.6 shows the pattern of spread of heroin injection that was central to de Alarcon's work on epidemiology and the prevention of heroin epidemics.

It may come as a surprise that epidemiologists have not been the ones to sustain this work or build on it. For example, the most advanced efforts to evaluate drug policy have come from systems research models that make use of epidemiologic data but are based more on econometrics and operations research than on epidemiologic principles, concepts, and methods (e.g., see refs. 88–90). Indeed, more epidemiologic attention and evaluative research have been devoted to community mobilization to prevent HIV infection and AIDS than to the prevention and control of drug dependence, although a new impetus for community mobilization is coming from drug treatment researchers (e.g., see refs. 91,92).

Noteworthy exceptions to this generalization about drug prevention research do exist. As examples, the work of Pentz and Perry and their colleagues (93–97) involves the mobilization of communities to shape policy and procedures, with a core of interventions directed toward young persons of school age. Gutman and Clayton (98) have recently urged that greater attention be paid to ''upstream'' prevention maneuvers that affect large aggregations of communities, such as state, federal, and even international policy initiatives. In alcohol and tobacco research, some noteworthy examples can be found of the evaluation of ''upstream'' interventions

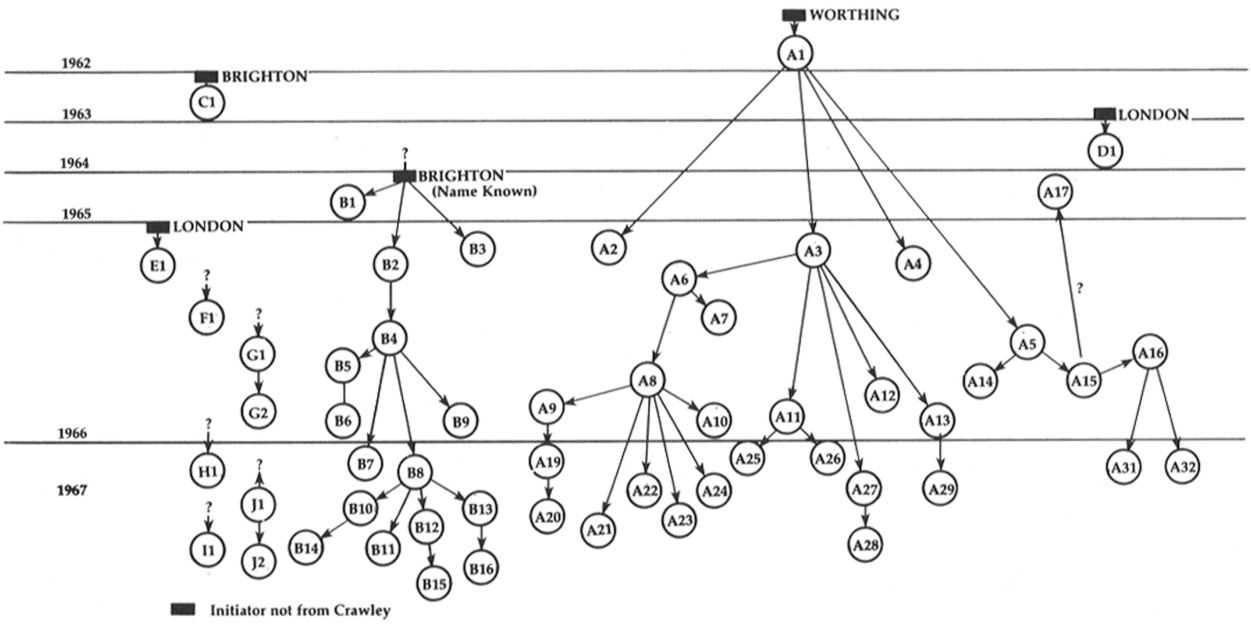

FIGURE 109.6. The person-to-person spread of heroin injection across time and space in the United Kingdom in the 1960s. (From De Alarcon R. The spread of heroin abuse in a community. *Community Health (Bristol)* 1969;1:155–161, with permission.)

(e.g., see refs. 99–102), in addition to evaluations of ''downstream'' maneuvers, such as limiting tobacco sales to minors (103).

Recently, interest has been renewed in ''multilevel'' statistical models that take into account different levels of organization, from the community at large to the local neighborhood to the household or individual, and in models of ''dependent happenings,'' such as are seen when innovations (e.g., drug use) diffuse from one person or group to the next (104–106). A carryover into the domain of prevention research has been expressed in recent articles and a textbook (107). These developments, coupled with a greater appreciation of gene–environment transactions or reciprocities, rather than gene–environment competition, promise to transform and sharpen the focus of prevention research during future decades as the human genome project yields new targets (108–110).

CONCLUSION AND FORECAST

It is possible to make an optimistic forecast regarding the application of epidemiology to the study of drug dependence. Under the rubric of ''quantity,'' sustained growth in the number of cross-sectional ''prevalence surveys'' that estimate the frequency of drug dependence in various populations and subpopulations of the world is apparent. Diagnostically oriented national surveys, such as the National Comorbidity Survey and the National Household Survey on Drug Abuse in the United States, will continue to be at center stage. The ''World Mental Health 2000'' surveys, organized by Professor Ronald Kessler of Harvard University and Dr. Bedirhan Ustun of the World Health Organization, will enlarge these national perspectives and offer epidemiologic data on the prevalence of drug dependence in more than 15 different participating countries. Because of the greater difficulty and complexity of the Epidemiologic Catchment Area studies, it is less likely that we will see similar growth in prospectively derived estimates of the incidence of drug dependence and the risk for becoming drug-dependent. Most likely, we will have to make do with approximate estimates of risk based on retrospective data from the cross-sectional surveys.

The sustained attention given to determining the prevalence of drug dependence within the context of more general surveys of psychiatric disturbances essentially guarantees a raft of new findings on the location of cases and ''psychiatric comorbidity'' within the populations of the world. We are likely to see more and more data on the male excess in drug dependence cases, although in some countries, because of the use of psychotherapeutic medicines, a female excess may be shown for some drug categories. Similarly, the excess occurrence among 15- to 44-year-olds in comparison with other age groups may prove to be a general rule via excep-

tions, such as the high prevalence of heroin or opium dependence among elderly persons living in the opium-growing regions of the world. Nonetheless, it seems that new findings from these cross-sectional surveys will be most useful in confirming past observations. One may hope for transformative evidence, but the work is not likely to be groundbreaking.

Under the rubric of "causes," the intersection of epidemiology intersects with the human genome project provides a basis for optimism. As discussed elsewhere, epidemiology has a special capacity to discover environmental circumstances, conditions, and processes that modify inherited predispositions. To the extent that epidemiologic studies are able to incorporate measurements of genetic polymorphisms and to characterize participants as heterozygotes and homozygotes, they will disclose variations in the expression of risk. These variations, linked to environmental conditions or processes, will clarify the webs of causation leading to drug dependence.

The capacity of epidemiology to yield definitive evidence regarding macrosocial causes of drug dependence, such living within an inner city community or being of low socioeconomic status (e.g., see ref. 111), is less of a reason for optimism. The definitive quality of research on these topics will remain limited without a truly massive investment in prospective studies within urban areas, and without levels of subject cooperation and participation far in excess of what is now achieved in these areas.

Under the rubric of "mechanisms," the above-mentioned statistical advances will bear fruit once investments have been made in longitudinal studies designed to make the measurements required to characterize the hybrid sequences of transitions and progressions. Linked with advances in human genetics and the measurement of environmental conditions and processes, these longitudinal studies promise advances in our understanding, but as a "basic science" initiative, the clinical application of this new understanding is not immediately clear.

Under the rubric of "prevention and control," we will begin to see long-term results from rigorous drug prevention research during the first decade of the twenty-first century. This evidence should help us to clarify central issues, such as whether preventing the onset of illicit drug use in the early teenage years will be followed by a reduced risk for drug dependence in later adolescence and early adulthood. One may hope for an intersection of etiologic research and prevention research, but any new gains in understanding the genetics of drug dependence may not yield practical preventive interventions for a half-century or more.

The recently developed systems research models suffer mainly from inadequate epidemiologic and law enforcement data (e.g., see ref. 90). However, having forged these systems research models, the policy analysts should provoke epidemiologists to improve the data, and it is hoped that the societal investment in improved data will lead to more compelling evaluations of drug policies and societal responses to drug dependence and illicit drug use.

Under this same rubric, a ray of light has begun to shine forth from the National Institute of Drug Abuse in the United States, where a new unit has been established to promote research on community mobilization and efforts at the community level to curb outbreaks of drug taking and drug dependence. Coupled with continuing progress in the ongoing evaluation of school-based prevention programs and mass media campaigns, this initiative represents an important step in the next generation of progress in epidemiologic research on drug dependence.

ACKNOWLEDGMENT

Some of the material in this chapter overlaps with material and ideas presented in other review articles and chapters written by the author. For example, the concepts associated with the rubrics of epidemiology originally were presented in a chapter by Anthony and Van Etten (6); concepts on the hybrid transition–progression model were presented by Anthony and Helzer (27). The appropriate work has been cited, and the editors have been notified of the circumstances.

REFERENCES

1. Leighton AH, Clausen JA, Wilson RN. *Explorations in social psychiatry.* New York: Basic Books, 1958.
2. Ball JC, Chambers CD. *The epidemiology of opiate addiction in the United States.* Springfield, IL: Charles C Thomas Publisher, 1970.
3. Terry CE, Pellens M. *The opium problem.* New York: Bureau of Social Hygiene, 1928.
4. Parry H, Balter MB, Mellinger GD, et al. National patterns of psychotherapeutic drug use. *Arch Gen Psychiatry* 1973;28: 18–74.
5. Morris JN. *Uses of epidemiology.* London: Livingstone, 1957.
6. Anthony JC, Van Etten ML. Epidemiology and its rubrics. In: Bellack AS, Hersen M, eds. *Comprehensive clinical psychology,* first ed. New York: Pergamon, 1998.
7. Eaton WW, Kramer M, Anthony JC, et al. The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program. *Acta Psychiatr Scand* 1989;79:163–178.
8. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalents: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol* 1994;2:244–268.
9. Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch Gen Psychiatry* 1997;54:313–321.
10. Kandel D, Chen K, Warner LA, et al. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. *Drug Alcohol Depend* 1997;44:11–29.
11. Chen K, Kandel DB, Davies M. Relationships between fre-

quency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. *Drug Alcohol Depend* 1997;46:53–67.
12. Hall W, Teesson M, Lynskey M, et al. The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: findings from the National Survey of Mental Health and Well-Being. *Addiction* 1999;94:1541–1550.
13. Caetano R, Tam T, Greenfield T, et al. DSM-IV alcohol dependence and drinking in the U.S. population: a risk analysis. *Ann Epidemiol* 1997;7:542–549.
14. *National household survey on drug abuse: main findings, 1998.* DHHS publication No. (SMA) 00-3381. Rockville, MD: Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, 2000.
15. Grant BF. Prevalence and correlates of drug use and DSM-IV drug dependence in the United States: results of the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse* 1996;8:195–210.
16. Grant BF. The relationship between ethanol intake and DSM-III-R alcohol dependence: results of a national survey. *J Subst Abuse* 1993;5:257–267.
17. Warner LA, Kessler RC, Hughes M, et al. Prevalence and correlates of drug use and dependence in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;52:219–229.
18. Hall W, Teesson M, Lynskey M, et al. The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: findings from the National Survey of Mental Health and Well-Being. *Addiction* 1999;94:1541–1550.
19. Meltzer H, Jenkins R. The national survey of psychiatric morbidity in Great Britain. *Int Rev Psychiatry* 1994;6:349–356.
20. Nelson CB, Wittchen HU. DSM-IV alcohol disorders in a general population sample of adolescents and young adults. *Addiction* 1998;93:1065–1077.
21. Hagnell O, Lanke J, Rorsman B, et al. Predictors of alcoholism in the Lundby Study. I. Material and methods. *Eur Arch Psychiatry Neurol Sci* 1986;235:187–191.
22. Chen WJ, Cheng AT. Incidence of first onset alcoholism among Taiwanese aborigines. *Psychol Med* 1997;27:1363–1371.
23. Cicero TJ, Adams EH, Geller A, et al. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend* 1999;57:7–22.
24. Hunt LG. Prevalence of active heroin use in the United States. In: Rittenhouse JD, ed. *Report of the task force on the epidemiology of heroin and other narcotics.* Menlo Park, CA: Stanford Research Institute, 1976:35–52.
25. Newman RG, Cates MS. Estimating the incidence and prevalence of addiction: Why? In: Rittenhouse JD, ed. *Report of the task force on the epidemiology of heroin and other narcotics.* Menlo Park, CA: Stanford Research Institute, 1976:71–72.
26. Terry CE, Pellens M. *The opium problem.* New York: Bureau of Social Hygiene, 1928.
27. Anthony JC, Helzer JE. Epidemiology of drug dependence. In: Tsuang TZ, ed. *Textbook of epidemiology.* New York: Wiley-Liss, 1995:361–406.
28. Van Etten ML, Neumark YD, Anthony JC. Male–female differences in the earliest stages of drug involvement. *Addiction* 1999; 94:1413–1419.
29. Anthony JC, Helzer JE. Syndromes of drug abuse and dependence. In: Robins LN, Regier DA, eds. *Psychiatric disorders in America: the Epidemiologic Catchment Study.* New York: The Free Press, 1991:116–154.
30. Johnson RA, Gerstein DR. Initiation of use of alcohol, cigarettes, marijuana, cocaine, and other substances in U.S. birth cohorts since 1919. *Am J Public Health* 1998;88:27–33.
31. Johnson RA, Gerstein DR. Age, period, and cohort effects in marijuana and alcohol incidence: United States females and males, 1961–1990. *Subst Use Misuse* 2000;35:925–948.
32. Dormitzer C, Caris L, Anthony JC. Parental attention and risk of coca paste smoking in Chile: preliminary data from the 1999 national school survey in Chile. 2000.
33. Morris JN. *Uses of epidemiology.* London: Livingstone, 1957.
34. Robins LN. Estimating addiction rates and locating target populations. How decomposition into stages helps. *NIDA Res Monogr* 1977;16:25–39.
35. O'Brien CP, Nace EP, Mintz J, et al. Follow-up of Vietnam veterans. I. Relapse to drug use after Vietnam service. *Drug Alcohol Depend* 1980;5:333–340.
36. Robins LN, Davis DH, Goodwin DW. Drug use by U.S. Army enlisted men in Vietnam: a follow-up on their return home. *Am J Epidemiol* 1974;99:235–249.
37. Robins LN, Helzer JE, Davis DH. Narcotic use in southeast Asia and afterward. An interview study of 898 Vietnam returnees. *Arch Gen Psychiatry* 1975;32:955–961.
38. Anthony JC, Petronis KR. Early-onset drug use and risk of later drug problems. *Drug Alcohol Depend* 1995;40:9–15.
39. Tennant FS Jr, Detels R, Clark V. Some childhood antecedents of drug and alcohol abuse. *Am J Epidemiol* 1975;102:377–385.
40. Margulies RZ, Kessler RC, Kandel DB. A longitudinal study of onset of drinking among high-school students. *J Stud Alcohol* 1977;38:897–912.
41. Robins LN, Przybeck TR. Age of onset of drug use as a factor in drug and other disorders. In: Jones CL, Battjes RL, eds. *Etiology of drug abuse: implications for prevention.* NIDA Research Monograph No 56. Rockville, MD: National Institute on Drug Abuse, 1985:178–192..
42. Grant BF, Dawson DA. Age of onset of drug use and its association with DSM-IV drug abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse* 1998;10:163–173.
43. Kandel DB, Chen K. Types of marijuana users by longitudinal course. *J Stud Alcohol* 2000;61:367–378.
44. Prescott CA, Kendler KS. Age at first drink and risk for alcoholism: a noncausal association. *Alcohol Clin Exp Res* 1999;23: 101–107.
45. Aronson TA, Craig TJ. Cocaine precipitation of panic disorder. *Am J Psychiatry* 1986;143:643–645.
46. Anthony JC, Tien AY, Petronis KR. Epidemiologic evidence on cocaine use and panic attacks. *Am J Epidemiol* 1989;129: 543–549.
47. Chitwood DD. Patterns and consequences of cocaine use. *NIDA Res Monogr* 1985;61:111–129.
48. Berkson J. Limitations of the application of fourfold table analysis to hospital data. *Biometrics* 1946;2:47–53.
49. Newcomb MD, Bentler PM, Fahy B. Cocaine use and psychopathology: associations among young adults. *Int J Addict* 1987; 22:1167–1188.
50. Wu LT, Anthony JC. The use of the case-crossover design in studying illicit drug use. *Subst Use Misuse* 2000;35:1035–1050.
51. Pescor MJ. The Kolb classification of drug addicts. *Public Health Rep* 1939; [Suppl 55].
52. Robins LN. *Deviant children grown up.* Baltimore: Williams & Wilkins, 1966.
53. Robins LN. The intimate connection between antisocial personality and substance abuse. *Soc Psychiatry Psychiatr Epidemiol* 1998;33:393–399.
54. Kellam SG, Brown CH, Rubin BR, et al. Paths leading to teenage psychiatric symptoms and substance use: developmental epidemiologic studies in Woodlawn. In: Guze SB, Earls FJ, Barrett JE, eds. *Childhood psychopathology and development.* New York: Raven Press, 1983:17–51.
55. Limosin F, Ades J, Gorwood P. Relationships between antisocial

personality and alcoholism: genetic hypotheses. *Eur Psychiatry* 2000;15:123–128.
56. Wu LT, Anthony JC. Tobacco smoking and depressed mood in late childhood and early adolescence. *Am J Public Health* 1999;89:1837–1840.
57. Cadoret RJ, Yates WR, Troughton E, et al. Adoption study demonstrating two genetic pathways to drug abuse. *Arch Gen Psychiatry* 1995;52:42–52.
58. van den Bree MB, Svikis DS, Pickens RW. Genetic influences in antisocial personality and drug use disorders. *Drug Alcohol Depend* 1998;49:177–187.
59. Kellam SG, Ling X, Merisca R, et al. The effect of the level of aggression in the first grade classroom on the course and malleability of aggressive behavior into middle school. *Dev Psychopathol* 1998;10:165–185.
60. Kellam SG, Anthony JC. Targeting early antecedents to prevent tobacco smoking: findings from an epidemiologically based randomized field trial. *Am J Public Health* 1998;88:1490–1495.
61. Merikangas KR, Risch NJ, Weissman MM. Comorbidity and co-transmission of alcoholism, anxiety and depression. *Psychol Med* 1994;24:69–80.
62. Tsuang MT, Lyons MJ, Harley RM, et al. Genetic and environmental influences on transitions in drug use. *Behav Genet* 1999; 29:473–479.
63. Kendler KS, Prescott CA. Cocaine use, abuse and dependence in a population-based sample of female twins. *Br J Psychiatry* 1998;173:345–350.
64. Straub RE, Sullivan PF, Ma Y, et al. Susceptibility genes for nicotine dependence: a genome scan and follow-up in an independent sample suggest that regions on chromosomes 2, 4, 10, 16, 17 and 18 merit further study. *Mol Psychiatry* 1999;4: 129–144.
65. Kendler KS, Myers J, Prescott CA. Parenting and adult mood, anxiety and substance use disorders in female twins: an epidemiological, multi-informant, retrospective study. *Psychol Med* 2000;30:281–294.
66. Collins WA, Maccoby EE, Steinberg L, et al. Contemporary research on parenting. The case for nature and nurture. *Am Psychol* 2000;55:218–232.
67. Patterson GR, Stouthamer-Loeber M. The correlation of family management practices and delinquency. *Child Dev* 1984;55: 1299–1307.
68. Curran PJ, Chassin L. A longitudinal study of parenting as a protective factor for children of alcoholics. *J Stud Alcohol* 1996; 57:305–313.
69. Chilcoat HD, Dishion TJ, Anthony JC. Parent monitoring and the incidence of drug sampling in urban elementary school children. *Am J Epidemiol* 1995;141:25–31.
70. Chilcoat HD, Anthony JC. Impact of parent monitoring on initiation of drug use through late childhood. *J Am Acad Child Adolesc Psychiatry* 1996;35:91–100.
71. Chilcoat HD, Breslau N, Anthony JC. Potential barriers to parent monitoring: social disadvantage, marital status, and maternal psychiatric disorder. *J Am Acad Child Adolesc Psychiatry* 1996;35:1673–1682.
72. Pianezza ML, Sellers EM, Tyndale RF. Nicotine metabolism defect reduces smoking. *Nature* 1998;393:750.
73. Robins LN, Helzer JE, Davis DH. Narcotic use in southeast Asia and afterward. An interview study of 898 Vietnam returnees. *Arch Gen Psychiatry* 1975;32:955–961.
74. Winick CS. Maturing out of narcotic addiction. *Bull Narc* 1962; 14:1–7.
75. Kandel DB, Davies M. Progression to regular marijuana involvement: phenomenology and risk factors for near-daily use. In: Glantz M, Pickens R, eds. *Vulnerability to drug abuse.* Washington, DC: American Psychological Association, 1992: 211–254.
76. Trinkoff AM, Anthony JC, Munoz A. Predictors of the initiation of psychotherapeutic medicine use. *Am J Public Health* 1990;80:61–65.
77. Mayhew KP, Flay BR, Mott JA. Stages in the development of adolescent smoking. *Drug Alcohol Depend* 2000;59[Suppl 1]: S61–S81.
78. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 2000;24:882–891.
79. Reboussin BA, Anthony JC. Latent class marginal regression models for modelling youthful drug involvement and its suspected influences. *Stat Med* 2001;20:623–639
80. Langenbucher JW, Chung T. Onset and staging of DSM-IV alcohol dependence using mean age and survival-hazard methods. *J Abnorm Psychol* 1995;104:346–354.
81. Schuckit MA, Anthenelli RM, Bucholz KK, et al. The time course of development of alcohol-related problems in men and women. *J Stud Alcohol* 1995;56:218–225.
82. Schuckit MA, Daeppen JB, Tipp JE, et al. The clinical course of alcohol-related problems in alcohol dependent and nonalcohol dependent drinking women and men. *J Stud Alcohol* 1998;59: 581–590.
83. Anglin MD, Hser YI, McGlothlin WH. Sex differences in addict careers. 2. Becoming addicted. *Am J Drug Alcohol Abuse* 1987;13:59–71.
84. Rosenberg M, Anthony JC. Early clinical manifestations of cannabis dependence in a community sample. *Drug Alcohol Depend* 2001;64:123–131.
85. Sidel VW, Drucker E. Further comments on the communicable disease model of heroin addiction. *Am J Drug Alcohol Abuse* 1976;3:369–372.
86. De Alarcon R. The spread of heroin abuse in a community. *Community Health (Bristol)* 1969;1:155–161.
87. Hughes PH, Barker NW, Crawford GA, et al. The natural history of a heroin epidemic. *Am J Public Health* 1972;62: 995–1001.
88. Rydell CP, Everingham SS. *Controlling cocaine: supply versus demand programs.* Santa Monica, CA: Drug Policy Research Center: RAND, 1994.
89. Behrens DA, Caulkins JP, Tragler G, et al. A dynamic model of drug initiation: implications for treatment and drug control. *Math Biosci* 1999;159:1–20.
90. Manski CF, Pepper JV, Thomas YF. *Assesment of two cost-effectiveness studies on cocaine control policy.* Washington, DC: National Academy Press, 1999.
91. Belding MA, Iguchi MY, Morral AR, et al. Assessing the helping alliance and its impact in the treatment of opiate dependence. *Drug Alcohol Depend* 1997;48:51–59.
92. Abbott PJ, Weller SB, Delaney HD, et al. Community reinforcement approach in the treatment of opiate addicts. *Am J Drug Alcohol Abuse* 1998;24:17–30.
93. Pentz MA, MacKinnon DP, Flay BR, et al. Primary prevention of chronic diseases in adolescence: effects of the Midwestern Prevention Project on tobacco use. *Am J Epidemiol* 1989;130: 713–724.
94. Chou CP, Montgomery S, Pentz MA, et al. Effects of a community-based prevention program on decreasing drug use in high-risk adolescents. *Am J Public Health* 1998;88:944–948.
95. Perry CL, Williams CL, Veblen-Mortenson S, et al. Project Northland: outcomes of a community-wide alcohol use prevention program during early adolescence. *Am J Public Health* 1996;86:956–965. [Comment appears in *Am J Public Health* 1996;86:923–924.]

96. Perry CL, Williams CL, Komro KA, et al. Project Northland high school interventions: community action to reduce adolescent alcohol use. *Health Educ Behav* 2000;27:29–49.
97. Wynn SR, Schulenberg J, Maggs JL, et al. Preventing alcohol misuse: the impact of refusal skills and norms. *Psychol Addict Behav* 2000;14:36–47.
98. Gutman M, Clayton R. Treatment and prevention of use and abuse of illegal drugs: progress on interventions and future directions. *Am J Health Promot* 1999;14:92–97.
99. Allamani A, Casswell S, Graham K, et al. Introduction: community action research and the prevention of alcohol problems at the local level. *Subst Use Misuse* 2000;35:1–10.
100. Toomey TL, Wagenaar AC. Policy options for prevention: the case of alcohol. *J Public Health Policy* 1999;20:192–213.
101. Lantz PM, Jacobson PD, Warner KE, et al. Investing in youth tobacco control: a review of smoking prevention and control strategies. *Tobacco Control* 2000;9:47–63.
102. Gratias EJ, Krowchuk DP, Lawless MR, et al. Middle school students' sources of acquiring cigarettes and requests for proof of age. *J Adolesc Health* 1999;25:276–283.
103. Minozzi S, Grilli R. The systematic review of studies on the efficacy of interventions for the primary prevention of alcohol abuse among adolescents. *Epidemiol Prev* 1997;21:180–188.
104. Duncan TE, Duncan SC, Hops H. Latent variable modeling of longitudinal and multilevel alcohol use data. *J Stud Alcohol* 1998;59:399–408.
105. Bobashev GV, Anthony JC. Clusters of marijuana use in the United States. *Am J Epidemiol* 1998;148:1168–1174.
106. Petronis KR, Anthony JC. Perceived risk of cocaine use and experience with cocaine: do they cluster within U.S. neighborhoods and cities? *Drug Alcohol Depend* 2000;57:183–192.
107. Murray DM. *Design and analysis of group-randomized trials.* New York: Oxford University Press, 1998.
108. Neiderhiser JM, Reiss D, Hetherington EM, et al. Relationships between parenting and adolescent adjustment over time: genetic and environmental contributions. *Dev Psychol* 1999;35:680–692.
109. Anthony JC. The promise of psychiatric enviromics. *Br J Psychiatry* 2001;178(Suppl 40): S8–S11.
110. O'Connor TG, Deater-Deckard K, Fulker D, et al. Genotype-environment correlations in late childhood and early adolescence: antisocial behavioral problems and coercive parenting. *Dev Psychol* 1998;34:970–981.
111. Dohrenwend BP, Levav I, Shrout PE, et al. Socioeconomic status and psychiatric disorders: the causation–selection issue. *Science* 1992;255:946–952.