National Institute on Drug Abuse

Research 89

MONOGRAPH SERIES

Biological Vulnerability to Drug Abuse

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

Biological Vulnerability to Drug Abuse

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NIDA Research Monograph 89
1988

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, Maryland 20857

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Editorial Advisors

NIDA Research Monograph Series

Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857

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ACKNOWLEDGMENT

This monograph is based on papers and discussions from a technical review on biological vulnerability to drug abuse held on June 2 and 3, 1986, at Rockville, Maryland. The review meeting was sponsored by the Office of Science and the Division of Clinical Research, National Institute on Drug Abuse.

DHHS Publication No. (ADM)90-1590
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1988, Reprinted 1990

NIDA Research Monographs are indexed in the Index Medicus. They are selectively included in the coverage of American Statistics Index Biosciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.

Preface

Surveys have shown a heterogeneous pattern of illicit drug use by the American public. Fortunately, many people never experiment with illicit drugs and, therefore, avoid the personal tragedy that drug abuse can bring. Others may be enticed into experimenting with drugs but, having done so, refrain from any further drug use. Still others, however, who begin with experimentation, eventually develop a regular pattern of drug use that is difficult to terminate although it may produce severe personal, social, and medical complications. The factors that account for these individual differences in outcome to drug use are largely unknown. They undoubtedly will include a wide range of behavioral, biological, psychosocial, and cultural influences. In addition, the combination of factors that account for drug experimentation may be different from the combination of factors that account for chronic drug abuse/dependence. It is important to understand the factors involved in the etiology of drug abuse for several reasons. Not only will this knowledge expand our scientific knowledge base, but it will hopefully lead to improved strategies for the treatment and prevention of drug abuse as well.

Research findings suggest that genetic factors are involved in the etiology of alcoholism. It is expected that genetic factors may also be involved in the etiology of drug abuse. In an attempt to understand the role of genetic factors in drug abuse, a technical review on "Biological Vulnerability to Drug Abuse" was held on June 2-3, 1986, in Rockville, MD. Researchers from the fields of alcoholism and drug abuse were invited to review the present state of knowledge in the area and to discuss future research directions. This research monograph is based in large part on the proceedings of that review. Included are discussions of strategies for identifying genetic factors in drug abuse, assumptions and methodological issues that underlie each strategy, results of recent investigations in the area, and implications of the findings for treatment and prevention of drug abuse. The technical review and resulting research monograph are intended to stimulate research interest in

the genetics of drug abuse, as well as in other factors that may be involved in the etiology of drug abuse.

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Genetic Vulnerability to Drug Abuse

Roy W. Pickens and Dace S. Svikis

INTRODUCTION

The purpose of this review is to assess the current status of our knowledge regarding genetic factors in drug abuse. That genetic factors may be involved in drug abuse is suggested by several decades of research in the field of alcoholism, where research has strongly implicated a role for genetic factors in the etiology of the disorder. For example, animals can be selectively bred to show alcohol-accepting characteristics (Deitrich and Spuhler 1984). Human family studies have shown that first-degree relatives of alcoholics are more likely to be alcoholic than first-degree relatives of nonalcoholics (Cotton 1979). Adoption studies have found that adopted-away children of alcoholic parents are more likely to develop alcoholism than adopted-away children of nonalcoholic parents (Goodwin et al. 1973). Twin studies have found that monozygotic twins are more likely to be concordant for alcoholism than dizygotic twins (Kaij 1960). Finally, high-risk studies have shown that children of alcoholics differ from children of nonalcoholics in response to alcohol (Schuckit 1985).

In contrast to alcoholism, little is known about genetic factors that contribute to other types of drug abuse (e.g., heroin addiction and cocaine abuse). In terms of etiology, most attention in the drug abuse field has been focused on psychosocial factors that contribute to drug experimentation by adolescents (Jones and Battjes 1985). Only limited attention has been paid to the role of genetic and environmental factors in drug abuse, particularly as it relates to the development of compulsive patterns of drug abuse and/or drug dependence. Evidence suggests that the pattern of inheritance for drug abuse may be similar to that for alcoholism. Drug abusers frequently abuse alcohol, and alcoholics often report problematic drug use (Barr and Cohen 1987; Benzer and Cushman 1982; Croughlin et al. 1981). Also, alcoholism and drug abuse tend to run in the same families. Family studies of alcoholism have found increased rates of pyschiatric disorders (including drug abuse) in the relaties of alcoholics (Meyer 1986). High rates of alcoholism

have also been found among the relatives of drug abusers (Smith et al. 1966; Ellinwood et al. 1966).

One reason for the paucity of genetic studies in drug abuse has been the difficulty of obtaining a sufficient number of subjects for research purposes. Compared to alcoholism, drug addiction occurs less frequently in the general population, and drug abusers are more difficult to recruit into research because of the illicit nature of their drug abuse activities. Nevertheless, studies of the role of genetic factors in drug abuse are important for several reasons. First, such studies would extend our scientific knowledge base in the areas of behavioral genetics and behavioral pharmacology. Second, in providing better understanding of the etiology of substance abuse, these studies would complement studies previously conducted in the alcoholism area. In fact, knowledge gained from research with alcoholism should prove useful in directing research in the drug abuse field. Finally, given the high cost of drug abuse to our nation and the growing AIDS problem among intravenous drug abusers, it is essential that we improve our understanding of basic factors underlying drug abuse so that improved methods of treatment and prevention of the disorder can be developed.

GENETIC INFLUENCES IN DRUG ABUSE

If genetic factors are involved in drug abuse, what does this mean? First, we must realize that genes do not directly cause behavior. No gene or set of genes, for example, will directly cause a person to become a drug abuser or to engage in drug-taking behavior. Instead, genes are segments on chromosomes that code for the production of specific proteins (or serve to regulate the activities of other genes) that are important in the control of behavior. If a gene is absent, a protein that controls the development or function of a physiological system may not be produced. In certain cases, the impact may be obvious, as in the case of phenylketonuria, when failure of a gene to code for the enzyme responsible for metabolism of phenylalanine results in development of a severe form of mental retardation. In other cases, however, the impact of genes on behavior may be less obvious but just as real, as when genetic factors produce a tendency or predisposition to respond in a certain manner. Such is believed to be the influence of genes on a number of behavioral traits and disorders, including alcoholism and drug dependence. Thus, genes are not the sole determinant of alcoholism or drug dependence, but their presence (or absence) may increase the likelihood that a person will become alcoholic or drug dependent.

Second, as the above statement indicates, genes do not act alone in determining whether a person will become alcoholic or drug dependent. Our experience in behavioral genetics suggests that both genetic and environmental factors will ultimately be implicated in the etiology of drug abuse. As with alcoholism, simple cause-and-effect models will not be sufficient for explaining vulnerability. Rather, various combinations of biological and environmental factors are likely to be identified that function to attenuate or

exacerbate an individual's likelihood for becoming drug dependent. Just because an individual has a genetic tendency for developing drug dependence does not mean he or she will necessarily develop the disorder. Whether the disorder develops will ultimately depend on environmental influences. Certain types of environmental influences are believed to be necessary for a genetically vulnerable person to develop drug dependence. For example, one environmental influence that is essential to the development of the disorder is that an individual must initially engage in drug-taking behavior. Thus, while a person may be genetically loaded for drug dependence, if drugs are never used, that person will never run the risk of becoming drug dependent. The presence of other environmental factors in the development of drug dependence (e.g., drug availability, the manner in which a person uses drugs) is also suspected. These may include environmental influences that operate within the immediate milieu (e.g., family and peer influences) or more broadly (e.g., cultural factors).

Third, genes may influence a person's tendency to develop drug dependence in many ways. Most people believe that genetic influences operate by producing an aberrant or idiosyncratic biological response to drugs. For example, genes may make some people more (or less) sensitive to a drug's effect, or they may produce a qualitatively different drug effect in some people than in others. While this may indeed be the case, it is important to recognize that there are mechanisms other than pharmacological mechanisms that may account for genetic effects. One nonpharmacological mechanism is that genes may determine personality characteristics that increase the probability of drug abuse. For example, a person may inherit a sociopathic personality that increases the likelihood of contact and experimentation with drugs. Cultural factors may in part be genetically determined, which may increase the likelihood of drug use that will eventually lead to increased rates of drug dependence.

For both pharmacological and nonpharmacological factors that influence drug dependence, it is important to determine the level at which genetic factors exert their effects. For example, genes may operate by putting individuals into high-risk situations where drugs are readily available for use, by increasing the likelihood that drug use (experimentation) will occur, or by increasing the probability that initial regular drug use will eventually escalate into drug dependence.

Fourth, genetic influences should not be viewed solely in terms of factors that predispose an individual to drug abuse. Instead, genetic influences can also operate by eliminating factors that protect an individual from drug abuse. If genes serve to eliminate or reduce the intensity of adverse drug effects, then factors that suppress excessive drug use will be removed. This will result in greater drug use than would have occurred had the natural protective factors been present. For example, in the case of alcoholism, genetic influences that reduce severity of hangover symptoms may hypothetically eliminate a mechanism that ordinarily controls

excessive alcohol use. As a result, people with reduced hangover effects from alcohol may engage in more intense drinking behavior, which will increase the likelihood of developing alcoholism. Similar mechanisms may also operate with other forms of drug abuse.

Finally, if genetic factors are involved in drug abuse, it is important to determine whether similar or different genetic factors are involved in alcoholism and drug abuse, as this may guide future research to enhance our understanding of the physiological processes that underlie both disorders. For example, if different genetic factors are found, this suggests that different physiological mechanisms may underlie alcoholism and drug abuse. If similar genetic factors are found, however, this suggests a common mechanism for both types of disorders. If this is the case, then research can focus on physiological or biochemical processes that are common to both disorders, rather than concentrating on processes that are unique to each disorder. The same is also true for genetic factors that may be involved in different forms of drug abuse (e.g., heroin addiction vs. cocaine abuse).

GENETIC RESEARCH STRATEGIES

Five types of research strategies have been employed in the study of genetic factors in alcoholism and therefore have relevance to studies of drug abuse. They are: (1) animal selective-breeding studies, (2) family studies, (3) adoption studies, (4) twin studies, and (5) high-risk studies. The first four of these are employed in establishing whether a genetic influence is involved in alcoholism. Animal selective-breeding studies have attempted to develop strains of animals that show a propensity toward alcohol drinking. The successful breeding of such strains suggests that genetic factors may be involved in human alcohol use. After such strains are developed, further studies can be conducted to determine how these animals differ biologically and behaviorally from animals that do not show this propensity. Additional research is needed to determine if animals can be selectively bred to show a greater propensity for drug taking and to determine the extent to which this characteristic generalizes across drug classes and/or alcohol.

Family studies in humans attempt to determine if a disorder (such as drug abuse) runs in families. A familial pattern is indicated if the disorder occurs more frequently in relatives of affected individuals than in relatives of nonaffected individuals. While evidence of familiality fails to distinguish between genetic and environmental influences, these results are often most useful in establishing the direction of future genetic research. Failure to find familiality suggests that genetic factors are not involved in the etiology of the disorder. While familial patterns of alcohol use have been well established, more research is needed on familial patterns of drug use, including the extent to which drug abuse, alcoholism, and psychopathology co-occur within the same individual and across family members.

In contrast to family studies, adoption and twin studies permit an estimate of the relative influences of genetic and environmental factors in the etiology of a disorder. In adoption studies, the influence of rearing environment can be largely separated from that of genetics by use of children born of affected biological parents but adopted out early in life and raised by nonaffected foster parents. Prevalence of the disorder is determined in this group of adoptees as adults and compared to that of a control group of adoptees born of nonaffected biological parents but also raised by nonalcoholic foster parents. While several adoption studies of alcoholism have been conducted, only one adoption study of drug abuse has recently been reported (Cadoret et al. 1986). Because of the strict adoption confidentiality laws that exist in the United States, most of this research is expected to be conducted elsewhere.

Twin studies compare concordance for a disorder in monozygotic and dizygotic twins. Because monozygotic twins have all common genes, any difference in monozygotic twin pairs must be due to environmental factors. However, since dizygotic twins have only 50 percent common genes, any difference in dizygotic twin pairs may be due to either genetic or environmental influences, or both. By comparing the concordance for a disorder in monozygotic and dizygotic twins, the relative influences of genetic and environmental factors in the etiology of a disorder can be determined. While there have been several twin studies of quantity and frequency of alcohol drinking, only three twin studies of alcoholism (or the alcohol dependence syndrome) have been reported. Except for studies of quantity and frequency of smoking and coffee drinking, only a limited number of twin studies of quantity and frequency of other drug use have been reported. To our knowledge, no twin study of drug dependence has been reported.

The final strategy, the high-risk paradigm, is employed to determine possible mechanisms that may underlie an obtained genetic effect. High-risk studies attempt to identify factors that contribute to the etiology of a disorder by comparing individuals at high risk for later developing a disorder to individuals without such risk. When a disorder is familially linked, children of affected individuals are known to have a greater risk of developing the disorder than children of nonaffected individuals. Therefore, responses of such children may be compared to identify factors that contribute to development of the disorder. In the case of alcoholism, children of alcoholics are known to be at higher risk for later developing alcoholism than children of nonalcoholics. In high-risk studies, these children are frequently compared at early ages to determine possible differences in behavioral and physiological responses, including their response to alcohol. Since children of alcoholics also have a higher risk for drug abuse than children of nonalcoholics (Cadoret et al. 1986), children of alcoholics may also be employed in studies to identify factors that contribute to drug abuse. To our knowledge, however, no high-risk studies of drug abuse have been reported to date.

ORGANIZATION OF THE MONOGRAPH

This monograph reviews research on genetic factors in alcoholism and drug abuse. The review is conducted for the purpose of better understanding the possible role of genetic factors in drug abuse and for stimulating research in the drug abuse field. The first section is a basic review of the research strategies that have been employed in determining genetic influences in alcoholism. In each case, the authors were asked to review the available information concerning the role of genetic factors in alcoholism and to make extensions whenever possible to the use of the strategies to study the genetics of drug abuse. In this section, MEISCH and GEORGE examine the self-administration of drugs by animals selectively bred for different responses to alcohol. STABENAU reviews the family pedigree method as a strategy for examining vulnerability to alcoholism and drug dependence. PICKENS and SVIKIS describe the twin study method and summarize preliminary findings from a new twin study of alcoholism and drug abuse. Finally, CLONINGER reports the results of adoption studies of alcoholism and discusses possible biochemical correlates of different types of alcoholism.

The next section examines possible mechanisms for inheritance of a tendency toward alcoholism or drug abuse. Participants were asked to review either a strategy for identifying specific characteristics that may predispose an individual to drug abuse or to discuss some of the frequently posited mechanisms for inheritance of a biological vulnerability to alcoholism or drug abuse. The use of the high-risk strategy to identify possible mechanisms in the inheritance of alcoholism is discussed by TARTER. Personality factors that may mediate a predisposition to drug abuse are discussed by BUTCHER. WILSON discusses individual differences in drug response by humans and presents preliminary data from individuals with different degrees of genetic and environmental similarity. Finally, ROUNSAVILLE discusses the role of psychopathology in the transmission of substance abuse.

The third section concerns methodological issues in biological vulnerability research. SVIKIS and PICKENS discuss assumptions underlying family, adoption, and twin studies, as well as methodological issues that must be considered in conducting such research. Statistical approaches to analyzing twin and family data are discussed by MCGUE, and special problems in drug abuse research are reviewed by GOTTESMAN.

The last section is a discussion of the practical implications of research on biological vulnerability to drug abuse. Implications for the treatment of drug abuse are discussed by BIGELOW, BROONER, MCCAUL, and SVIKIS, and implications for the prevention of drug abuse are considered by KAUFMAN.

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Influence of Genetic Factors on Drug-Reinforced Behavior in Animals

Richard A. Meisch and Frank R. George

INTRODUCTION

This paper provides an overview of genetic effects on drug-reinforced behavior. It is limited to animal studies, and since the majority of research has focused on one drug, namely ethanol, much of this review concerns ethanol studies. The influences of genetic factors on drug-reinforced behavior are considered within the larger context of pharmacogenetic influences on behavior. The conclusion of this survey of studies can be anticipated by noting that genetic factors are important determinants of many effects of abused drugs including their reinforcing effects.

STRAIN DIFFERENCES IN DRUG EFFECTS

Inbred Strains

There are many reports of inbred strains of rats and mice differing in their acute response to drugs (Broadhurst 1978). One advantage of these studies is the ability to perform correlations between behavioral and biochemical variables across strains, and this use of correlations is a powerful means of testing mechanistic hypotheses. One example is that the locomotor effects of morphine vary with the strain of mouse studied (Castellano and Oliverio 1975; Brase et al. 1977; Moskowitz et al. 1985). This effect has been analyzed in a series of experiments and has been attributed to differences between strains in stimulation of dopaminergic systems by morphine (Oliverio et al. 1983). Another example is the variation in analgesic response to opiates among strains, and this variation is significantly correlated with differences in mu opiate receptor binding (Reith et al. 1981; Moskowitz and Goodman 1985). An important general finding from studies with inbred strains is that the various behavioral and physiological effects of drugs (e.g., locomotor and analgesic responses) do not necessarily covary across strains, and the direction and magnitude of response are dependent on the specific behavior measured.

Selective Breeding

It has been possible to go beyond the simple demonstration of strain differences in drug effects by showing selective breeding for certain drug effects. One of the best known examples is that of the short (SS) and long (LS) sleep mice. Starting from a genetically heterogeneous stock of mice, McClearn and Kakihana 1973) successfully conducted a bidirectional selective breeding study. They selectively bred mice for both short and long durations of loss of the righting reflex following an intraperitoneal injection of ethanol. There was a rapid separation of the two lines. Other lines of animals have been selectively bred for differences in ethanol effects, such as the most affected (MA) and least affected (LA) rat lines (Riley et al. 1976; Riley et al. 1977) and the alcohol-tolerant (AT) and alcohol-nontolerant (ANT) rats (Eriksson and Rusi 1981). As Crabbe and Belknap (1980) note, the successful selection for these characters provides ipso facto evidence for genetic control.

STRAIN DIFFERENCES IN ETHANOL AND DRUG DRINKING

Measurement of Ethanol Drinking

Rat and mouse strains differ in the amount of ethanol they drink. However, before these findings can be critically discussed, it is necessary to describe the most commonly used technique for measuring ethanol drinking. This technique is the two bottle choice procedure, introduced by Richter and Campbell (1940). In this procedure, two bottles are attached to the side of an animal's home cage. One bottle is filled with an ethanol solution and the other, with water. The amount of ethanol solution and water consumed is measured once every 24 hours. This technique and variants on it have been used in hundreds of subsequent studies. The basic findings suggest that rats and mice prefer dilute solutions of ethanol to water. Neither intoxication nor physical dependence are reliably observed, which is not surprising given that the rats and mice do not consume enough ethanol to maintain high sustained blood ethanol levels (Cicero 1979; Cicero 1980; Meisch 1977; Meisch 1981; Meisch 1984; Mello 1976; Myers 1978; Pohorecky 1981).

Many attempts have been made to increase ethanol drinking in rats, including exposure to different types of stress and injection with a very broad range of drugs. No consistent progress has emerged from this research, and often findings reported by one laboratory have not been replicated in other laboratories. In summary, little progress has been made in generating high levels of elective ethanol intake.

This lack of progress has been attributed in part to the persistent use of the two bottle choice technique (Cicero 1979). For example, low levels of intake and preference for only low concentrations may indicate that the behavior is controlled by taste factors rather than by effects that ethanol produces once it is absorbed. Moreover, it is not clear that the results from

preference studies of ethanol-drinking behavior of rats and mice are generalizable to the ethanol-drinking behavior of humans.

The two bottle choice technique has also been used in studies of genetic differences in ethanol drinking. The first study, conducted by Mardones and colleagues (1953), selectively bred rats for high and low ethanol drinking. Large differences in ethanol intake are also found among inbred mouse strains (McClearn and Rodgers 1959; McClearn and Rodgers 1961). Differences in ethanol drinking among selected lines and inbred strains of rats and mice are well documented, and a large body of literature exists (Deitrich and Spuhler 1984).

Although strain differences in ethanol drinking have been examined in many studies, far fewer studies have been carried out with other drugs (Crabbe and Belknap 1980). In several of these studies, oral morphine consumption was examined. Rats were selectively bred for high and low morphine solution intake (Nichols and Hsiao 1967). A difference between high and low drinkers rapidly emerged, and by the third generation there was a fourfold difference in intake. These differences are not due to a more general selection for acceptance or rejection of aversive-tasting solutions, since the two lines did not differ in their intake of a quinine solution. Differences in morphine intake, however, have also been reported for rats selectively bred for high and low open-field emotional reactivity and for high and low rates of avoidance learning (Satinder 1977).

Several studies have been conducted with inbred mouse strains (Eriksson and Kiianmaa 1971; Horowitz et al. 1977). In one study, C57BL/6 mice consumed more morphine solution than did CBA mice (Eriksson and Kiianmaa 1971). In another study, C57BL/6 mice consumed large quantities of a morphine-saccharin solution, whereas DBA/2 mice consumed little (Horowitz et al. 1977). It is interesting that these findings parallel results with ethanol studies: C57BL/6 mice display high intakes , and CBA and DBA/2 mice show low intakes.

Several studies have been conducted with etonitazene, a potent opioid that is pharmacoloically similar to morphine and is effective when taken by mouth (Wikler et al. 1963). In one experiment, C57BL/6J and DBA/2J mice were restricted to a 5 µg/ml solution (George and Meisch 1984). While C57BL/6J mice consumed slightly more drug solution than water, the DBA/2J mice generally avoided the drug solution. When both strains were deprived of food and maintained at reduced body weights, the C57BL/6J mice substantially increased their intake, while the DBA/2J mice decreased their drug intake. Similar findings were obtained with Wistar and Sprague-Dawley rats (Carroll et al. 1986). Initially both groups of rats consumed similar quantities of etonitazene. However, food deprivation increased the etonitazene intake of Wistar rats but decreased the drug intake of Sprague-Dawley rats. The decreases in drug intake during food deprivation are unusual in that food deprivation usually enhances the reinforcing effects of drugs

(Carroll and Meisch 1984). These findings emphasize the degree to which genotype and environment interact and stress the need to examine genetically different groups over a range of conditions.

DRUG-REINFORCED BEHAVIOR

Intravenous Drug Self-Administration

In contrast to studies of ethanol drinking, other investigators have used operant conditioning techniques and concepts to study drug self-administration. These studies began in 1962 when James Weeks developed a technique such that animals could intravenously inject themselves with drugs. Weeks' procedure involved surgically implanting a chronic indwelling venous catheter in rats (Weeks 1962). The catheter was protected by a harness the rats wore so that they could not pull out the catheter, and the distal end of the catheter was connected to an infusion pump. The rats could inject themselves by pressing a lever, and the lever press in turn activated electronic equipment that operated the infusion pump. Using this technique, Weeks reported that rats would inject themselves with morphine. These findings have been confirmed and extended in many ways.

Generality of Findings

The fact that animals will self-inject the same drugs that humans abuse and will not self-inject the drugs that humans do not abuse has been well established (Griffiths et al. 1980; Johanson and Balster 1978). Drugs from several pharmacological classes serve as reinforcers, such as psychomotor stimulants (including nicotine), opioids, dissociative anesthetics, and general depressants (including ethanol, barbiturates, benzodiazepines, gaseous anesthetics, and some solvents). Drugs also serve as reinforcers when taken via a number of different routes. For example, drugs serve as reinforcers when injected intravenously (Young and Herling 1986), intragastrically (Altshuler et al. 1975; Yanagita and Takahashi 1973), intramuscularly (Goldberg et al. 1976; Katz 1979), and intracerebrally (Goeders and Smith 1983), and when taken orally (Meisch and Carroll, in press) and by inhalation (Wood et al. 1977; Yanagita et al. 1970). Also, wide species generality is found (Griffiths et al. 1980). For example, d-amphetamine functions as a positive reinforcer and is self-injected by baboons (Griffiths et al. 1976), rhesus monkeys (Balster and Schuster 1973), squirrel monkeys (Goldberg 1973), dogs (Risner 1975). and rats (Pickens and Harris 1968). However, this wide species generality should not obscure the fact that within species there are significant differences among animals in their levels of drug-reinforced behavior.

Similarities in the Drug-Seeking Behavior of Humans and Other Animals

Unlike the home cage ethanol studies, a large and consistent body of data has emerged from studies of drug-reinforced behavior, and

there are important similarities between the findings of human and animal studies. These similarities have been reviewed by Griffiths et al. (1980) and include comparable functional relationships between independent controlling variables and measures of drug self-administration. For example, with both humans and other animals, variables such as type of drug, drug dose, reinforcement schedule, and size of schedule requirement exert comparable control.

Establishment of Orally Delivered Drugs as Reinforcers

Procedures have been devised to establish orally delivered drugs as reinforcers (Meisch and Carroll, in press). This line cf research is an outgrowth of the conceptual approach that characterized studies of intravenous drug self-administration. However, the first drug to be studied using this approach was ethanol (Meisch and Thompson 1971). To establish orally delivered drugs as reinforcers, two problems must be overcome: the aversive taste of most drug solutions and the delay that occurs between drinking and the onset of the interoceptive effects that follow absorption (Mello and Mendelson 1971). To overcome these difficulties, several related techniques have been developed. Basically these involve using food-deprived animals and then inducing water drinking by feeding the animals during the experimental session. Once a stable pattern of water drinking is established, a dilute solution of ethanol (or some other drug) is substituted for the water. Across sessions, the concentration of ethanol is slowly increased. When an intermediate concentration such as 8 percent (weight/volume (w/v)) is reached, food is no longer given during the experimental session but is given after the session is over. Under these conditions, water drinking drops to low levels, but ethanol drinking persists (Meisch and Thompson 1971; Meisch and Thompson 1974). These same findings also occur when rhesus monkeys serve as subjects (Meisch et al. 1975) and when drugs other than ethanol are tested (Meisch and Carroll, in press).

EFFECTS OF GENOTYPE ON BEHAVIOR REINFORCED BY ORALLY DELIVERED DRUGS

In the last several years, these techniques have been used to try to establish ethanol as a reinforcer for two selected lines of rats and for several inbred strains of rats and mice (Elmer et al. 1986; Elmer et al., in press a; Elmer et al., in press b; Ritz et al. 1986; Suzuki et al., submitted for publication). More recently, these techniques have been used in an attempt to establish etonitazene, a potent opioid, as a reinforcer for inbred rats (Suzuki et al., unpublished data). A major purpose was to determine whether there are genetic influences on drug-reinforced behavior.

Selectively Bred Lines: The Alcohol-Accepting and the Alcohol-Nonaccepting Rats

Three sets of studies were conducted. One concerned the establishment of ethanol as a reinforcer for alcohol-accepting (AA) and alcohol-nonaccepting (ANA) rats. These rats were selectively bred from an original foundation stock based on high and low ethanol drinking in a two bottle choice paradigm (Eriksson 1968). A variant of previous procedures was used. These rats were maintained at 75 percent of their free-feeding weight and were induced to drink water in the operant chamber by giving them food in their home cage 60 minutes prior to the start of the session. Their water bottles were removed when they were given food but were placed back on their cages after the session. Once a stable pattern of water-reinforced responding was present, they were given a sequence of increasing ethanol concentrations: 0.5, 1, 2, 4, and 5.7 percent. After behavior was stable at 5.7 percent, the time of feeding was shifted to after the session.

Figure 1 shows that during the induced drinking phase both the AA and ANA lines consumed progressively larger amounts of ethanol (g/kg) as the concentration was increased. At 5.7 percent the AA rats ingested 1.5 g/kg and had blood ethanol levels of 176 mg%. The ANA rats consumed 0.9 g/kg and had blood ethanol levels of 116 mg%. When access to food was shifted to after the session, however, responding of the AA rats was maintained by 5.7 percent ethanol, while the responding of the ANA rats dropped to low levels that were not different from subsequent water control values. Thus, ethanol came to function as a reinforcer for the AA but not for the ANA rats. The differential maintenance of responding in the AA rats relative to the ANA rats was confirmed by subsequent manipulations where, over blocks of sessions, the rats were given water, then 5.7 percent ethanol (a second time), and then a final block of water sessions. Figure 2 shows that in the AA but not in the ANA rats, ethanol consistently maintained high rates of responding that substantially exceeded water control levels (Ritz et al. 1986). In a related experiment, the ethanol concentration was varied between 8 and 32 percent (w/v), and responding by the AA rats was well maintained at all concentrations (Ritz et al., unpublished data).

Selectively Bred Lines: The Ethanol-Preferring and Ethanol-Nonpreferring Rats

At Indiana University, rats have been selectively bred for ethanol preference (P line) and for ethanol nonpreference (NP line). In one experiment, the intragastric self-administration of ethanol was studied (Waller et al. 1984). Rats from the P line intragastrically self-infused ethanol up to 9.4 g/kg of body weight per day. When water was substituted for the ethanol solution, responding extinguished but returned to previous levels when ethanol once again replaced water. Thus, for the rats in the P line, ethanol appeared to serve as a reinforcer. In contrast, rats in the NP line self-administered only 0.7 g/kg per day. As the

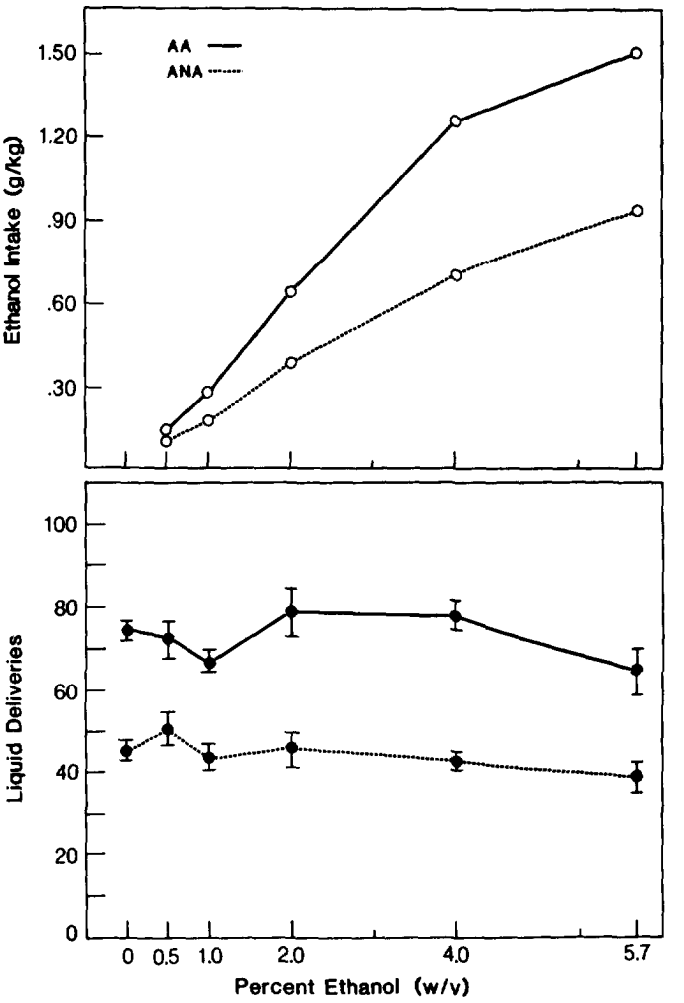

FIGURE 1. *Ethanol intake (g/kg) and liquid deliveries as a function of ethanol concentration for AA (n=8) and ANA (n=8) rats under food-induced conditions on a fixed-ratio (FR) 1 reinforcement schedule*

NOTE: Each data point represents a group mean for 5 consecutive test days. The mean blood ethanol level at 5.7 percent for the AA rats was 176±20 mg% (mean+SEM). and for the ANA rats it was 116±24 mg%.

SOURCE: Ritz et al. 1986, Copyright 1966, Pergamon Journals, Ltd.

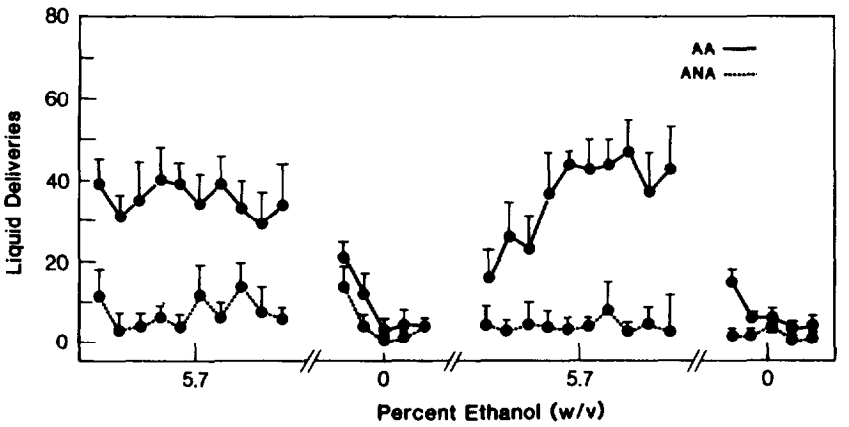

FIGURE 2. *Liquid deliveries on consecutive test days obtained by AA (n=8) and ANA (n=8) rats as a function of liquid present : 5.7 percent ethanol or 0 percent ethanol (water vehicle)*

NOTE: Repeated measures ANOVA: Line. $F(1,14)=15.42$. $p<0.002$: concentration, $F(3,42)=18.40$. $p<0.0001$; ANA, $F(3,21)=1.08$. n.s.; AA, $F(3,21)=18.14$, $p<0.0001$. AA Dunnett's t (df=12): 5.7 percent vs. retest=1.71, n.s.; 0 percent vs. retest=0.16, n.s.; 5.7 percent vs. 0 percent=4.15. $p<0.01$. one-tailed.

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investigators noted, these findings indicate that the reinforcing effects of ethanol are postabsorptive and not due to ethanol's taste or smell.

Studies With Inbred Strains of Rats and Mice

The establishment and maintenance of ethanol-reinforced behavior has been studied in two inbred rat lines, the Lewis and Fischer 344 rats (Suzuki et al., submitted for publication). These lines were studied because they have had no common ancestors for at least 75 years, thereby maximizing their possible genetic divergence. Ethanol was established as a reinforcer using a food-induced drinking procedure. The rats were maintained at 80 percent of their free-feeding weight. They were then given their daily food ration in the operant conditioning chamber where they could obtain small volumes of water by pressing a lever. A stable pattern of eating followed by water drinking soon developed. Subsequently a series of increasing ethanol concentrations was

substituted for water. After responding stabilized at 5.7 percent, feeding was shifted to the home cage after completion of the experimental session.

For both the Lewis and Fischer 344 strains, ethanol maintained higher response rates and was consumed in larger volumes than the water vehicle. In addition, in both strains blood ethanol levels increased with increases in ethanol concentration. However, Lewis rats drank substantially more ethanol than Fischer rats. The typical inverted U-shaped dose-response function between ethanol concentration and number of drug deliveries was observed for the Lewis rats, whereas for the Fischer rats responding did not consistently exceed that for water. For the Lewis strain, as the fixed-ratio (FR) size was increased, the number of responses increased almost in direct proportion to the FR size, so that at the lower FR values the rats were obtaining similar numbers of deliveries at different FR sizes. In contrast, for the Fischer strain, response rate was an inverted U-shaped function of FR size, and the number of deliveries and blood ethanol levels decreased with increases in FR size. At FR 16, responding of the Lewis rats was high, while that of the Fischer rats decreased to low values. Overall, Lewis rats showed significantly higher values of response rates, ethanol deliveries, and blood ethanol levels. Ethanol-induced behavioral activation was also observed in Lewis but not in Fischer rats. These results support the conclusion that ethanol serves as a strong positive reinforcer for Lewis rats and as a weak positive reinforcer for Fischer rats.

In a third set of experiments, two inbred mouse strains, the C57BL/6J and the BALB/cJ mice have been studied. As in previous studies, ethanol drinking was initially induced by maintaining the mice at a reduced body weight and feeding them one meal a day. After eating food pellets, the mice reliably drank water. When a stable pattern of water drinking was established, a series of increasing ethanol concentrations (1, 2, 4, and 8 percent w/v) replaced the water. Mice from both strains drank substantial amounts of ethanol. At 8 percent ethanol, C57BL/6J mice had blood levels of 269 mg/dl, and the BALB/cJ mice had blood levels of 183 mg/dl. However, when access to food was switched to after the session, large differences emerged between the two strains. The C57BL/6J mice persisted in drinking substantial amounts of ethanol (2.45 g/kg/30-min session), whereas the BALB/cJ mice drank very little (0.57 g/kg/30-min session). To document that ethanol was serving as a reinforcer, water was substituted for ethanol, and responding by the C57BL/6J mice greatly decreased. When 8 percent ethanol again replaced water, responding increased to previous levels. Lever presses by the BALB/cJ mice were much lower in number and were only slightly higher than water values. Thus, ethanol had come to serve as a reinforcer for the C57BL/6J mice but probably not for the BALB/cJ mice (Elmer et al., in press a).

These findings were systematically replicated in a second experiment where ethanol concentration was varied from 1 to 32 percent. At 8 and 16 percent w/v, responding by the C57BL/6J mice reliably

exceeded water control values, whereas responding by the BALB/cJ mice never rose above water values. The pattern of responding was similar to that seen when ethanol serves as a reinforcer for other species; the highest rate of responding occurred at the beginning of the session and was negatively accelerated (Elmer et al., in press b). In a third experiment with C57BL/6J and BALB/cJ mice, ethanol deliveries occurred under an intermittent schedule of reinforcement, specifically an FR schedule. As the FR value was increased from 1 to 2 to 4, the rate of responding of the C57BL/6J mice increased and reliably exceeded water values. In contrast, responding by the BALB/cJ mice was only marginally maintained (Elmer et al., in preparation). Thus, ethanol functioned as an effective reinforcer for the C57BL/6J mice and as a marginal or ineffective reinforcer for the BALB/cJ mice.

In our studies, differences among strains in the reinforcing efficacy of ethanol parallel differences found in earlier preference studies of ethanol drinking. This suggests that these two types of ethanol-drinking behavior share at least some common underlying mechanisms. However, these mechanisms may be related to preabsorptive rather than postabsorptive factors.

We have shown that genotype has large effects on both the establishment and maintenance of ethanol-reinforced behavior. These findings have been obtained with inbred strains of rats and mice as well as with selected lines of rats. Our findings of operant responding reinforced with orally delivered ethanol complement results from the study of operant responding reinforced with intragastrically delivered ethanol (Waller et al. 1984). Taken together, these studies demonstrate the importance of genotype as a determinant of ethanol-reinforced behavior.

Etonitazene Intake by Lewis and Fischer 344 Rats

To determine whether genotype also influences the establishment and maintenance of drug- (other than ethanol) reinforced behavior, we employed similar procedures to induce drinking of etonitazene solutions. In brief, food-deprived rats were given their daily ration of food in the operant conditioning chamber. After eating the food, the rats drank water. Once a stable pattern of water drinking was established, a series of increasing etonitazene concentrations was substituted for water. The drug concentration was gradually increased to 5 µg/ml. At this concentration, the time and location of feeding were changed. Food was given after the session and in the home cage. Thus, drinking was no longer induced by feeding. The Lewis rats continued to drink the etonitazene solution, whereas the Fischer rats did not. When the drug solution was presented under FR schedules of reinforcement, responding by Lewis rats increased with increases in the size of the schedule. In contrast, Fischer rats displayed very low response rates. When water was substituted for etonitazene, responding by the Lewis rats declined, while responding by Fischer rats remained at low levels. Thus, etonitazene came to serve as a reinforcer for Lewis but not for Fischer rats (Suzuki et al., unpublished

data). These findings differ from the earlier ethanol study, where ethanol served as a reinforcer for both strains to different degrees. The results with etonitazene are of interest in that, apart from studies with ethanol, these are the first findings of strain differences in drug-reinforced operant behavior.

CONCLUSIONS

Genetic factors are probably important determinants of reinforcing effects of all abused drugs. The effects of genotype can be large in magnitude. However, in quantitative terms it is not known precisely how important genetic variables are. Also, the mechanisms of these effects are not known. It is unlikely, however, that strain and selected line differences are due solely to acceptance or rejection of novel tasting substances, since genetic factors are also important determinants of drug action when drugs are simply administered to an organism (e.g., intragastrically).

Drug-reinforced behavior is complex in that it is a learned operant behavior that is determined by many variables including the animal's experimental history, the dose of the drug, deprivational states, and schedule of reinforcement. This means that there are many possible points at which strains may differ. For example, two strains may show identical behavior at a low drug dose but differences at high doses. Also, strains may have equivalent drug intakes under an FR 1 schedule but different intakes at higher ratio values. A third example is that strains may show equivalent performance under an intermittent schedule of drug reinforcement but differ in the amount of responding emitted when the behavior is extinguished. Such differences may relate to other behaviors such as the probability of resuming drug self-administration when the drug is again made available.

The complexity of drug-reinforced behavior has several implications for the analysis of genetic determinants. First, comparisons among strains should be made using several independent variables and a range of values of each independent variable e.g., a range of drug doses). Second, the complexity of the behavior increases the number of possible mechanisms that may account for strain differences. Third, the complexity of the behavior makes the use of involved genetic methods such as selective breeding studies more difficult. Despite these problems, genetic studies with animals are very important and should be actively pursued, since they permit investigation of genetically controlled mechanisms that may act in humans.

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ACKNOWLEDGMENTS

This work was supported in part by a grant from the University of Minnesota's Office of Alcohol and Other Drug Abuse Programming, by grant DA-00944 to R.A. Meisch from the National Institute on Drug Abuse, and by New Investigator Research Awards AA-06104 and AA-06924 to F.R. George from the National Institute on Alcohol Abuse and Alcoholism.

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Family Pedigree Studies of Biological Vulnerability to Drug Dependence

James R. Stabenau

INTRODUCTION

Epidemiologic studies have characterized the frequency of behavioral disorders such as alcoholism and drug abuse/dependence in the general population (Weissman et al. 1980; Robins et al. 1984). Family pedigree studies have employed similar case finding methods in surveys of biologically linked members in several generations for probands with a given disorder (Winokur et al. 1970; Cotton 1979; Stabenau and Hesselbrock 1980; Rounsaville et al. 1982c; Cloninger and Reich 1983; Mirin et al. 1984b). When rates of a disorder in biological relatives of probands with the disorder are significantly higher than in the general population, such data provide the first order of confirmation for a genetic vulnerability hypothesis for the disorder (Cloninger and Reich 1983). When rates for two disorders are compared in extended families of probands who differ for those two disorders, the dependence or independence of those two disorders may be statistically established (Cloninger and Reich 1983; Hill et al. 1977; Merikangas et al. 1985a).

Thus, family pedigree studies represent the first stage in the scientific assessment of genetic/biological vulnerability. Well-controlled pedigree studies provide sufficient information to suggest that specific syndromes of clinical characteristics are transmitted through families (Merikangas et al. 1985a; Cloninger and Reich 1983; Winokur et al. 1970; Stabenau 1984). They also provide the statistical basis for determining whether or not different behavioral disorders are transmitted independently (Cloninger et al. 1981a). For most behaviorally determined disorders, however, family pedigree studies are not as specific as cross-fostering adoption studies in identifying discrete genetic risk factors as separate from cultural rearing influences.

The major strengths of the family pedigree model are the capacities to explore hypotheses and the ease of accomplishment at low cost compared to twin and adoption studies. In the study of substance abuse, where use of most drugs is illegal, case finding is

significantly easier among a series of related individuals than among groups of adoptees or twins. The major limitation with the family study method is that for any biological risk factor, the genetic risk and family rearing experience are not readily separable as to independent effect. To achieve this, the adoption cross-fostering model, where influences of biological and rearing parents are separately controlled, is required (Goodwin et al. 1973; Cadoret and Gath 1978; Cloninger et al. 1981b). However, when familial and cultural environmental factors are measured for index probands plus their biological relatives and for control probands plus their biological relatives, such variables can be entered into statistical models along with estimates of genetic risk (Rice et al. 1983).

The purpose of this paper is to review the results of application of family pedigree methods in assessing biological vulnerability for substance abuse including alcohol, heroin and other opiates, cocaine and other stimulants, and hypnotic and sedative drugs. This review includes the issues of clinical and genetic heterogeneity and potential personality and biochemical "correlates" of substance-seeking behavior.

Research in substance abuse/dependence has been principally directed at the phenomenology of drug abuse with predominantly epidemiologic studies (Dembo et al. 1985). This approach, involving "what, where, and when research," has utilized theoretically framed models of social and environmental factors. Four explanatory frameworks dominating the field are: (a) problem behavior proneness (Jessor and Jessor 1977); (b) social learning theory (Burgess and Akers 1966); (c) self-derogation theory (Kaplan 1980); and (d) socialization theory (Kandel 1975). Of these four, problem behavior proneness and the degree to which individuals learn social norms might have a biological basis.

The concept of risk must not only assess the environmental and cultural variables that place individuals at risk for drug use but also the possible biological factors that may be under genetic control. Such factors may constitute personality/behavior variables that could lead to drug-seeking behavior as a means of satisfying an inner neurophysiologic, neurochemical "need" (Inwang et al. 1975). Recent efforts have been directed at identifying the biological factors that may explain differences in drug-seeking behavior, phases of initiation as well as cessation of chronic use, and degrees of tolerance and dependence (Kauffman et al. 1984: Nahas 1981). Research must intearate the power of survey methodology and statistical explanation with the understanding of the subject's perception and definition of the initiation and sustenance of drug use, if prevention is to become a possibility (McBride and Clayton 1985). Study of brain mechanisms and drug behavior is important, since psychoactive drugs act primarily on the brain at both the molecular level, by altering neurotransmitter turnover among other things, and at the neuronal level, by altering the function of key brain structures (Nahas 1981).

GENETIC HETEROGENEITY OF ALCOHOLISM

Genetic heterogeneity and risk hypotheses for alcohol abuse and dependence have been tested (Cloninger and Reich 1983; Lewis et al. 1983; Stabenau 1984; Stabenau and Hesselbrock 1984; Hesselbrock et al. 1984; Cadoret et al. 1985; Stabenau 1986a). Analysis of family pedigree data for DSM-III alcohol-dependent subjects in a "typology" sample of 321 male and female inpatients has demonstrated a high frequency (43 percent) of alcoholism associated with DSM-III Anti-Social Personality diagnosis (ASP) and a high frequency (89 percent) of subjects reporting a parent or sibling of a parent who was alcoholic by Family History Research Diagnostic Criteria (FHRDC) (Stabenau and Hesselbrock 1984). Using FHRDC methods for psychopathology diagnosis of first-degree family members and spouses, evidence of considerable assortative mating for alcoholism and ASP was also noted in this sample (Stabenau and Hesselbrock 1980; Stabenau and Hesselbrock 1984).

A separate analysis of the first 210 volunteer DSM-III alcohol-dependent patients (156 male and 54 female, with a mean age of 39 years) from the same "typology" sample has also been reported (Stabenau 1984). The results suggested: (1) types of family history of alcoholism (FHA) were not related to the natural course of alcohol dependence in male or female subjects; (2) ASP was significantly associated with an earlier onset of the first stages of alcohol abuse; (3) compared with the probands having no family alcoholism and those with alcoholism on one side of the family, probands with alcoholism on both sides of their families experienced significantly more impaired control over their drinking behavior, more physical symptoms, and more pathologic symptoms associated with chronic alcohol use; (4) women began the early stages of alcohol abuse at a later age than men but reached the later stages of alcoholism about the same time as men; (5) family history, ASP, and gender did not differentiate this sample in terms of age at first treatment for alcoholism; and (6) the sex of the proband, the presence of ASP, and the type of family pedigree for alcoholism were not interactive but contributed separate independent additive effects. Thus, this study suggested that factors under separate genetic control may be independently operative in the pathogenesis of DSM-III alcohol dependence.

GENETIC HETEROGENEITY OF SUBSTANCE ABUSE/DEPENDENCE AND RISK MODELS

A separate "high-risk" study consisted of 116 offspring with a hospitalized DSM-III alcohol-dependent biological parent (i.e., parents were probands in the typology study) and 103 dental clinic control subjects recruited for their participation in a "Health Survey." This prospective study cohort (n=219) consists of 98 males with a mean age of 24.2 years and 121 females with a mean age of 25.5 years. Methods similar to the typology study (Hesselbrock et al. 1983) were employed, including the National

Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS), estimates ofquantity and frequency of alcohol use, reasons to drink or not to drink alcohol, the MMPI, and neurocognitive testing (Stabenau 1986a). DSM-III criteria were applied to establish current and lifetime diagnosis of ASP and alcohol and/or drug abuse/dependence. The distribution of lifetime alcohol or drug abuse/dependence diagnoses was not significantly different for the two subsamples. Fifty-five percent of alcohol abuse/dependence subjects and 48 percent of drug abuse/dependence subjects were offspring of alcoholics, while 45 percent of alcohol abuse/dependence subjects and 52 percent of drug abuse/dependence subjects were dental control subjects (X^2=1.4, df=2, and x^2 = 5.1, df=2, NS.) Family History Research Diagnostic Criteria (FHRDC) were used in the diagnosis of parental alcohol abuse and/or dependence from data provided by the proband. Fourteen male and six female proband subjects had lifetime DSM-III ASP diagnoses. For 40 percent of the subjects, neither parent had FHRDC diagnosis of alcoholism, while 31 percent had an alcoholic father, 15 percent had an alcoholic mother, and for 14 percent both father and mother were alcoholics. Table 1 shows the lifetime rates of DSM-III alcohol or drug abuse/dependence analyzed by genetic group (i.e., with (+) or without (-) ASP diagnosis or family history of alcoholism (FHA)). Alcohol and drug dependence rates were highest for ASP subjects with *or* without a family history of alcoholism. Prevalence rates of dependence or abuse for either alcoholism or drugs were consistently higher for males than for females. The lifetime and current rates for alcohol abuse/dependence were 37.4 percent and 18.2 percent for males and 19.1 percent and 9.2 percent for females. Similarly, for drug abuse/dependence lifetime and current rates were 23.2 percent and 7.1 percent for males and 15.8 percent and 4.2 percent for females. ASP and FHA, when combined,

TABLE 1. *Lifetime prevalence of DSM-III alcohol and drug abuse or dependence by genetic group*

	ASP+ FH+		ASP+ FH-		ASP- FH+		ASP- FH-		Total	
	n	%	n	%	n	%	n	%	n	%
Alcohol Abuse or Dependence*	5	83.3	9	64.3	34	21.2	12	16.2	60	27.4
					X^2=25.1, df=6, p<.001					
Drug Abuse or Dependence*	4	66.7	7	50.0	20	16.0	11	14.9	42	19.2
					X^2=13.9, df=6, p<.05					
Total Subjects in Group	6		14		125		74		219	

*Some subjects have both diagnoses.

provided the greatest risk for lifetime alcohol and/or drug abuse/dependence, with 66 percent of ASP+/FH+ and 35 percent of ASP+/FH- subjects receiving DSM-III diagnoses of alcohol and drug abuse/dependence. The frequency of subjects with no alcohol or drug dependence or abuse diagnosis was highest for those classified as ASP- with either FH+ (63 percent) or FH- (82 percent).

Initial data have suggested that more individuals either remain abusers of, or dependent on, alcohol and/or drugs or stop abusing both. When they remit, they remit from both substances significantly more often than do other subgroups of subjects. Nine of the twenty-nine subjects (31 percent) who currently abused or were dependent on alcohol were also currently abusing or dependent on drugs, while 11 of 31 subjects (35 percent) who remitted from alcohol abuse or dependence had also remitted from previous drug abuse or dependence (x^2=62.4, df=4, p<.001) (Stabenau 1986a).

When ASP diagnosis, parental alcoholism, and gender were used as risk terms, eight "phenotypes" were formed to describe liability. A logistic regression model utilizing the three factors plus age of the subject demonstrated that the improvement x^2 was greatest for ASP, then gender, and lastly for FH in describing the risk for the development of a lifetime diagnosis of phenotypic alcohol dependence and abuse. Age did not contribute to the description of risk (Stabenau 1986a). The observed rates of liability for lifetime diagnosis of DSM-III alcohol abuse and dependence in this sample replicated the risk observed by Lewis and colleagues (1983) for male and female medical and surgical patients (mean age 39 years) for a lifetime diagnosis of definite alcoholism established with Feighner criteria. Table 2 shows the mean observed rate of lifetime diagnosis of alcoholism from the two studies.

MODELS OF RISK FOR SUBSTANCE ABUSE AND DEPENDENCE

A genetic vulnerability hypothesis for alcoholism or alcohol dependence has been supported by family pedigree (Winokur et al. 1970; Cotton 1979; Stabenau and Hesselbrock 1980), twin (Kaij 1960; Hrubec and Omenn 1981). and adoption studies (Goodwin et al. 1973; Cadoret and Gath 1978; Cloninger et al. 1981b). Alcohol dependence is heterogenous and appears to have three different subforms: primary alcoholism without family history of alcoholism; primary alcoholism with a family history of alcoholism; and secondary alcoholism associated with antisocial personality disorder. The latter two subforms have strong genetic vulnerability components (Cloninger and Reich 1983; Lewis et al. 1983; Stabenau 1984; Cadoret et al. 1985; Merikangas et al. 1985a; Stabenau 1986a). Base rates of risk for lifetime alcoholism are higher for males as compared to females when family history of alcoholism and ASP diagnosis are not present. Rates for both males and females are twice as high as base rates when family history of alcoholism is positive and especially when definite diagnosis of ASP is present (table 2). However, diagnosis of depression and family history of ASP have not been found to be correlates of risk for alcoholism (Lewis et al. 1983; Cadoret et al. 1980).

TABLE 2. *Mean lifetime risk of phenotypic alcoholism observed in two studies* based upon gender, family history of alcoholism in a first-degree relative, and antisocial personality diagnosis of the proband*

"Alcoholism" Phenotype					
Gender	FHA	ASP	Number of Subjects	Number "Alcoholic"	Percent "Alcoholic"
M	+	+	19	17	89.5
M	-	+	28	15	53.6
F	+	+	26	7	26.9
F	-	+	26	8	30.8
M	+	-	73	28	38.4
M	-	-	107	21	19.6
F	+	-	140	22	15.7
F	-	-	209	13	6.2

*Lewis et al. 1983; Feighner Diagnostic Criteria for ASP and definite alcoholism diagnosis; 131 males, 281 females. Stabenau 1986a; DSH-III Diagnostic Criteria for ASP and "alcoholism" as alcohol abuse or dependence diagnosis; 98 males, 121 females.

Genetic studies of substances other than alcohol have included family pedigree studies of dependent subjects and their biological relatives (Lewis et al. 1983; Stabenau and Hesselbrock 1984; Mirin et al. 1984b; Rounsaville et al. 1982c; Lewis et al. 1985a; Hill et al. 1977) (table 3), several twin studies of patterns of substance use (Pederson 1981; Cederlof et al. 1977; Kaprio et al. 1978), and adoption studies with a primary focus on alcohol dependence or sociopathy and a secondary description of use of drugs (Goodwin et al. 1973; Crowe 1974). It is difficult to compare studies where substance misuse is described by different diagnostic classifications. Three operational systems which utilize substance dependence behaviors and psychosocial consequences of dependence are the Feighner criteria (Feighner et al. 1972), the Research Diagnostic Category (RDC) criteria (Spitzer et al. 1978), and the DSM-III criteria (American Psychiatric Association 1980). Opioid dependence has been reported as heterogenous, but all three diagnostic groups included substantial numbers of subjects with DSM-III ASP diagnoses (Rounsaville et al. 1982b). In a study comparing opiate abusers to abusers of sedative-hypnotics and stimulants, most opiate abusers had ASP diagnoses (Mirin et al. 1984b). Other studies of substance-abusing/dependent subjects have demonstrated rates of ASP diagnosis substantially higher (Lewis et al. 1983; Stabenau and Hesselbrock 1984; Rounsaville et al. 1982a;

TABLE 3. *Rates of psychopathology in probands using DSM-III, RDC, and Feighner criteria in samples at differing risk for substance abuse/dependence*

Study Characteristics	Sample Type:	Community Survey[a]	Community Survey[b]	Birth Cohort[c]	Medical & Surgical Inpatients[d]	Alcohol Dependence[e]	Alcohol Dependence[f]	Substance Abuse (Opiate)[g]
Sr. Author		Robins	Weissman	Lewis	Lewis	Stabenau	Cadoret	Mirin
Year		1984	1980	1985	1983	1984	1984	1984
Dx Method		DSM-III	RDC	Feighner	Feighner	DSM-III	DSM-III	DSM-III
N of M&F		M=7,816 F=5,727	M=219 F=291	M=104	M=97 F=234	M=168 F=59	M&F=85	M&F=91
Age (Yrs.)		18 to 65	26 to 76+	33	42	39	35	30
Proband Diagnosis								
Alcoholism		M=24.3 F=4.4	M=10.1 F=4.1	M=15.4	M=26.0 F=6.0			M&F=45.1
Substance Abuse/ Dependence		M=7.0 F=4.4		M=1.0	M=7.0 F=6.0	M=42.0 F=36.0	M&F=17.7	
Major Depression		M=3.1 F=7.2		M=20.2	M=24.0 F=44.0	M=34.0 F=60.0		M&F=17.6
Bipolar Disorder								M&F=3.3
Any Affective Disorder								
ASP		M=4.6 F=0.8		M=2.9		M=48.0 F=15.0		M&F "mostly ASP"

TABLE 3. (Continued)

Study Characteristics	Sample Type:	Substance Abuse (Stimulant)[g]	Substance Abuse (Depressant)[g]	Opiate Addiction[h]	Narcotic Dependence[i]	Affective Disorder Study[j]	Birth Cohort ASP[c]	Medical & Surgical ASP[d]	Alcohol Dependence ASP[f]	Affective Disorder ASP[j]
Sr. Author		Mirin	Mirin	Rounsaville	Croughan	Lewis	Lewis	Lewis	Cadoret	Lewis
Year		1984	1984	1982	1982	1985	1985	1983	1984	1985
Dx Method		DSM-III	DSM-III	RDC	Feighner	RDC	Feighner	Feighner	DSM-III	RDC
N of M&F		M&F=36	M&F=33	M=403 F=130	M=100 F=100	M=104	M=119	M=34 F=47	M&F=94	M=23
Age (Yrs.)		30	30	27	25	37	33	32		33
Proband Diagnosis										
Alcoholism		M&F=41.6	M&F=36.4	M=37.0 F=26.9	M=26.0 F=14.0	M=31.7	M=42.9	M=65.0 F=28.0		M=56.5
Substance Abuse/ Dependence						M=19.2	M=18.5	M=32.0 F=13.0	M&F=54.3	M=47.8
Major Depression		M&F=30.6	M&F=18.2	M=48.9 F=69.2	M=39.5 F=44.0		M=25.2			
Bipolar Disorder		M&F=22.2	M&F=6.1	M=3.7 F=10.8						
Any Affective Disorder				M=70.7 F=85.4						
ASP				M=29.5 F=16.9	M=73.0 F=61.5		M=34.4	M=26.0 F=17.0	M&F=42.3	M=10.6

TABLE 3. (Continued)

REFERENCES FOR TABLE 3

[a]Community Survey; Robins et al. 1984; DSM-III; M=7,816; F=5,727.

[b]Community Survey; Weissman et al. 1980; RDC; M=219; F=291.

[c]Birth Cohort; Lewis et al. 1985b; Feighner; M=223.

[d]Medical and Surgical Inpatients; Lewis et al. 1983; Feighner; M=131; F=281.

[e]Alcohol Dependence; Stabenau and Hesselbrock 1984; DSM-III; M&F=227; $M1^0$=555; $F1^0$=555.

[f]Alcohol Dependence; Cadoret et al. 1984; DSM-III M&F=179.

[g]Substance Abuse; Mirin et al. 1984b; DSM-III; M&F-160; $M1^0$=338; $F1^0$298,

[h]Opiate Addiction; Rounsavllle et al. 1982c; RDC; M=403; F=130.

[i]Narcotic Dependence; Croughan et al. 1982; Feighner; M=91; F=88.

[J]Affective Disorder Study; Lewis et al. 1985a; RDC; M=216.

Rounsaville et al. 1982b; Rounsaville et al. 1982c; Croughan et al. 1982; Cadoret et al. 1984; Lewis 1984) than in community survey populations (Robins et al. 1984). In those populations with a substantially elevated frequency of ASP, rates of alcohol and other drug abuse were both higher (Lewis et al. 1985a; Lewis et al. 1985b) than several community survev rates (Robins et al. 1984). High frequency of affective disorder is seen in most substance-abusing/dependent populations (Mirin et al. 1984a: Rounsaville et al. 1982b; Rounsaville et al. 1982c; Croughan et al. 1982; Lewis et al. 1985b) but is predominantly secondary to drug dependence (Mirin et al. 1984a; Croughan et al. 1982). However, stimulant abusers had significantly more first-degree biological relatives with affective disorder than did opiate or sedative-hypnotic abusers (Mirin et al. 1984b). One study demonstrated independence in the familial transmission of alcoholism and opiate abuse, but biological relatives were not interviewed for diagnosis (Hill et al. 1977). Comparative pedigree studies should provide structured interviews (Robins et al. 1981) with all available relatives utilizing dependence criteria (American Psychiatric Association 1985).

PREFERENCE FOR ALCOHOL AND ALCOHOL-SEEKING BEHAVIOR AS A MODEL FOR DRUG-SEEKING BEHAVIOR

To become dependent upon alcohol, there must be a choice to drink alcohol, rather than not to drink alcohol. The multivariate approach to alcohol dependence has suggested at least four reinforcement contingencies for alcohol use or avoidance of alcohol use and subsequent dependence (Caddy 1977). Positive biological reinforcers for alcohol use include such items as "enjoyed the taste" or "to help me sleep," and positive psychosocial reinforcers for alcohol use include items such as "just to be sociable" or "to relieve boredom." Negative biological reinforcers and negative psychosocial reinforcers that might reduce alcohol use include items from “I don't like the effect it produces" to "my

parents disapprove." Subjects rated these items for themselves as reasons for drinking or not drinking alcohol (Stabenau 1986b).

The reasons to drink or not to drink alcohol were compared for subjects in the "high-risk" study (n=219). For the non-alcohol-dependent/abusing subjects (n=159), there was a high positive correlation between consumption of alcohol in the 6 months prior to the study and reasons to drink and a negative correlation with reasons not to drink. In this sample, males (37 percent) were more frequently abusers of or dependent on alcohol and drugs than were females (19 percent). A correlation between gender and reasons to drink or not drink alcohol demonstrated that there was a significantly greater biological and psychosocial "preference" for alcohol drinking among nondependent, nonabusing males as compared to females.

Alcohol-seeking behavior was compared for DSM-III alcohol-dependent individuals from the "typology" sample (Stabenau 1984). Self-reported estimates of ounces of alcohol (as absolute) consumed in the previous month, corrected for body weight at admission to the study, were compared. The conclusions were: Male and female alcohol consumption corrected for body weight was not related to age; male and female alcoholics showed no differences when compared within subtypes of alcoholism; and, regardless of sex, ASP alcoholics drank significantly more alcohol than non-ASP alcoholics (Stabenau et al. 1986).

One method for evaluating drug-seeking behavior would be to evaluate personality variables that have been associated with risk for substance abuse and concomitantly to evaluate potential biochemical correlates of neurotransmitter activity in a sample of hospitalized individuals and their biological first-degree relatives. Personality variables may include high sensation-seeking behaviors as measured by the Sensation Seeking Scale (Galizio et al. 1985); elevations on the Psychopathic deviant (Pd), Mania (Ma), and Depression (D) scales of the MMPI (Loper et al. 1973); and high scores on impulsivity and monotony avoidance behaviors as measured by the Karolinska Personality Scale (Rydelius 1983). There has been little effort to test the relationship between such personality measures and clinical diagnosis of specific drug dependence syndromes. Family pedigree studies would enable researchers to compare family members based on differences in psychopathology and/or personality phenotypes and different substance dependence syndromes.

Potential markers of neurotransmitter activity include platelet monoamine oxidase (MAO) activity and platelet serotonin (5-HT) uptake. Low platelet MAO activity has been shown to be associated with a number of disorders including depression (Murphy and Weiss 1972) and alcoholism (Wiberg et al. 1977). In addition, low MAO was reported in the biological relatives of alcoholics (Sullivan et al. 1979). Brain 5-HT has been shown to be lower in selectively bred strains of rats (Murphy et al. 1982), and 5-HT uptake-inhibiting drugs can reduce alcohol seeking in such

alcohol-preferring strains (Amit et al. 1984). In humans, platelet 5-HT uptake has been reported as significantly lower for both alcoholics (Kent et al. 1985) and depressed patients (Meltzer et al. 1981). At present, it is difficult to determine whether low 5-HT uptake and low platelet MAO represent a primary "trait" or a "state" secondary to the effects of alcohol use and/or depressed affect. The study of such correlates should advance understanding about whether MAO and/or 5-HT might serve as "markers" in prevention of alcohol- and/or drug-seeking behavior. Identification of a significant relationship among first-degree relatives of alcohol- and/or drug-dependent individuals for sensation-seeking and monotony avoidance behaviors, platelet MAO and platelet 5-HT uptake, and heightened alcohol- and/or drug-seeking behavior would enhance screening for individuals at high risk for substance misuse.

These data could have substantial impact for the prevention and treatment of alcohol and/or drug dependence. For example, using log linear regression models, any genetic or biochemical factors found to correlate with lifetime risk for alcohol or drug dependence could be employed for establishing preventive programs in the early school years. Also, by elaborating upon the predictors or correlates for differential risk, more specific treatment programs for dependence upon various psychoactive substances could be developed.

CLINICAL AND GENETIC HETEROGENEITY OF SUBSTANCE ABUSE/DEPENDENCE

While a model of genetic heterogeneity for alcoholism has been evolving, it is equally important to assess the degree of clinical psychopathologic and genetic heterogeneity in individuals who are drug abusers or drug dependent, in order to provide treatment that is specific to any subform of drug dependence that may be etiologically related to different psychopathologic states and different genetic vulnerability traits (Stabenau 1986c).

Table 3 lists the rates of psychopathology in probands in samples at differing risk for substance abuse/dependence according to DSM-III, RDC, or Feighner diagnostic criteria. When the studies using similar diagnostic criteria were compared for psychopathology diagnosis (table 3), the following observations could be made: The frequency of ASP among alcoholic and opiate addicts is higher than for the general population, and the rates of alcoholism and drug dependence are higher among ASP subjects as compared to non-ASP subjects.

The rates of alcohol abuse, drug abuse, depression, and antisocial personality among first-degree family members of probands with such diagnoses frequently exceed those found in the general population. Independent genetic transmission has been proposed for alcoholism (Cloninger and Reich 1983), ASP (Cloninger and Reich 1983), depression (Cloninger and Reich 1983; Merikangas et al. 1985b), and opiate dependence (Hill et al. 1977). A higher rate of stimulant substance abuse was found among subjects who were

depressed and had significantly greater family history of depression as compared to depressant and sedative abusers (Mirin et al. 1984b). Opiate-dependent subjects and alcohol-dependent subjects each had respectively more first-degree biological relatives with opiate abuse and alcohol abuse (Hill et al. 1977). While ASP and depression each had been considered as risk correlates of substance abuse (Rounsaville et al. 1982b; Mirin et al. 1984b), the contribution of genetic vulnerability through family history of psychopathology has only infrequently been assessed through controlled study of psychopathology variables in probands and first-degree family members when evaluating substance abuse.

CONCLUSIONS

Family pedigree study of classes of substance abuse provides a valuable method for assessing biological vulnerability or risk factors for substance abuse and/or dependence. If biological markers are identified in family pedigree studies, subsequent twin and adoption studies of putative biological correlates of abuse/dependence could provide a basis for distinguishing the genetic factors from the cultural factors in their expression.

Alcohol abuse/dependence etiologic models have demonstrated a genetic heterogeneity to the lifetime vulnerability of alcohol misuse. Several personality and biochemical variables have suggested ways of researching the biological mechanisms of heightened alcohol-seeking behavior. These methods may have similar applicability in the attempt to understand the biology of drug-seeking behavior.

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ACKNOWLEDGEMENTS

This research was supported in part by grant AA03510-06 from NIAAA.

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The Twin Method in the Study of Vulnerability to Drug Abuse

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INTRODUCTION

The twin study is a powerful research methodology for estimating the relative contributions of genetic and environmental factors in the development of a disorder. Apart from alcohol use, cigarette smoking, and coffee drinking, however, the twin method has rarely been employed in the study of drug abuse. The purpose of this paper will be to (1) describe the rationale and assumptions of the method, (2) review results of previous studies in the area, (3) discuss limitations (and underlying assumptions) of the approach, and (4) present preliminary results from an ongoing twin/family study of alcoholism and drug dependence.

RATIONALE OF METHOD

In separating the effects of genes and environment, the twin method capitalizes on differences in number of genes shared by monozygotic (identical), and dizygotic (fraternal) twins. Monozygotic (MZ) twins develop from a single fertilized egg that separates early in development to create two genetically identical organisms. Because they are genetically identical, any difference in the expression of a disorder by members of an MZ pair can only be attributable to nongenetic (environmental) factors. In contrast, dizygotic (DZ) twins develop from two separately fertilized ova and are genetically no more alike than ordinary siblings. Because they share, on the average, only half of their genes, any difference in the expression of a disorder by DZ twins may be due to genetic and/or environmental factors.

Intrapair twin similarity for discontinuous measures (such as being categorized as alcoholic or drug dependent) is expressed quantitatively by concordance, which is the proportion of cases where both members of a twin pair are affected by a disorder (Plomin et al. 1977). Concordance rates may range from 0 (where none of the cotwins are affected) to 1 (where all of the cotwins are affected). In estimating genetic and environmental influences, concordance rates of MZ and same-sex DZ twins are compared. If MZ twins show

higher concordance rates than DZ twins, genetic factors are implicated. However, if MZ and DZ twins show similar concordance rates, the role of genetic factors appears minimal. In estimating genetic influences, absolute concordance rates are less important than relative MZ/DZ differences, since absolute concordance rates are determined by a number of factors including criteria used in diagnosing a disorder.

For continuous measures (e.g., number of symptoms or magnitude of effect), genetic influences are typically estimated by calculation of heritability (h^2). Heritability is a population statistic that describes the proportion of the observed variance that is due to genetic factors (Plomin et al. 1977). Heritability values may range from 0 (no genetic component) to 1 (all of the variance is attributable to genetic effects). An estimate of heritability can also be calculated from concordance rates for discontinuous measures.

PREVIOUS STUDIES

Twin Studies of Substance Use

In the area of psychoactive substance use, fewer than 20 twin studies have been reported. The majority of these studies have focused on the quantitative aspects of substance use (Clifford et al. 1984; Kaprio et al. 1981), rather than the clinical syndrome of substance dependence. Findings with substance use may not generalize to substance dependence, however, as factors that contribute to initiation and pattern of substance use may be different from those involved in development of substance dependence.

The majority of substance use studies have focused on the heritability of alcohol drinking (i.e., quantity and frequency of consumption). Results of these studies have been inconsistent. For example, in two studies conducted with large twin samples, a Finnish group reported significant genetic influences in frequency and amount of alcohol drinking (Partanen et al. 1966), while a Norwegian group found no genetic influences in similar measures (Jonsson and Nilsson 1968).

Apart from alcohol, twin studies of other drug use have focused primarily on cigarette smoking and coffee drinking. In the larger studies, significant genetic effects for smoking status (i.e., ever smoked) and quantity of coffee drinking (number of cups per day) have been found, with over one-half of the variance being attributed to genetic factors (Kaprio et al. 1981; Pedersen 1981).

Apart from cigarette smoking and coffee drinking, however, twin studies of other drug use have been rare. Of the reported studies, most concerned the use of prescription drugs such as tranquilizers and sleeping pills. Again, the results from these studies have been contradictory, with some studies reporting higher concordance rates for drug use in MZ than DZ twins, and others finding no significant differences (Pedersen 1981).

Substance Dependence

The above studies focused on continuous measures of quantity and frequency of substance use. From a clinical perspective, however, it is more important to focus on categories of substance use (that is, whether the proband met clinical criteria for being diagnosed as alcoholic or drug dependent). Quantity and frequency of substance use are clinically distinguishable from substance dependence; a high level of substance use is a necessary but not sufficient condition for the development of dependence. Most definitions of dependence, for example, require evidence of tolerance, physiological dependence, and/or harmful consequences (American Psychiatric Association 1980; Feighner et al. 1972).

To date, only three twin studies of substance dependence have been reported, and all concerned alcoholism rather than other types of drug dependence. The first study was conducted in Sweden by Kaij (1960). The probands were all males ascertained from County Temperance Board registrations. In Sweden, an individual can receive a Temperance Board registration for a variety of alcohol-related problems, ranging from a single conviction for drunkenness to heavy continuous abuse with social maladjustment and medical complications. Zygosity was determined by similarities in appearance and, in doubtful cases, by blood-group analyses (n=58 MZ and n=138 DZ pairs). Kaij found significant MZ/DZ concordance rate differences for all levels of alcoholism, from least to most severe. However, the MZ/DZ differences were greatest for the most severe type of alcoholism, with concordance rates of .71 in MZ and .32 in DZ twins.

The second study, conducted in the United States by Hrubec and Omenn (1981), ascertained alcoholic twins by examining Veterans' Administration (VA) hospital records (n=15,924 pairs). The probands were all males who had served in the U.S. Armed Forces. Information on alcohol drinking problems was obtained from military service records, VA records, and from questionnaires. Zygosity was determined primarily by response to questionnaire items concerning the similarity of the twins as children. These investigators reported higher MZ than DZ concordance rates for VA hospitalizations with index diagnoses of alcoholism, alcoholic psychosis, and liver cirrhosis. For alcoholism, concordance rates of .26 and .12 were obtained, respectively, for MZ and DZ twins.

The third study was conducted by Gurling and colleagues (1981) in Great Britain. These investigators examined concordance for the alcohol dependence syndrome (rather than alcoholism per se) in both males (n=28 pairs) and females (n=28 pairs). The twins were ascertained through a psychiatric twin register, and presumably included probands with high rates of psychiatric disorders. Information about drinking problems was obtained from official records and personal interviews. Zygosity was determined by a physical resemblance questionnaire and blood-group analyses. In contrast to the results of the first two studies, Gurling and colleagues found no evidence for genetic factors in alcoholism for either male or

female twins. In fact, there was essentially no difference in concordance rates for the disorder, with rates of .33 versus .30 in MZ and DZ males and .08 versus .13 in MZ and DZ females.

Thus, the results of previous twin studies of alcoholism have not been consistent. Although two studies found higher concordance rates in MZ than DZ twins, the third study reported no significant MZ/DZ differences. Also, in the two studies supporting a genetic influence, there were differences in the absolute concordance rates obtained (i.e., .71 versus .26 for MZ twins and .32 versus .12 for DZ twins). There are a number of possible causes of these discrepant findings, including differences in criteria used to diagnose alcoholism, sampling errors due to recruitment bias, and incorrect estimates of concordance rates due to inadequate sample size (Svikis and Pickens, this volume).

ASSUMPTIONS OF TWIN METHOD

Interpretation of twin studies is only as good as the validity of the assumptions on which the method is based. The first assumption is that twins are representative of the general population. If twins are not representative of singletons, then the results of twin studies may not be generalizable to the population at large. Although a number of factors distinguish twins from singletons (e.g., twins have higher infant mortality rates), several studies have shown that twin data generalize quite well to the larger population; therefore, this assumption appears valid (Fuller and Thompson 1978).

A second assumption is that MZ and DZ twins share equally similar rearing environments. This assumption states that environmental variance is constant across MZ and DZ twins, with the rearing environment of MZ twin pairs being no more similar than that of DZ twin pairs. A number of studies, however, have questioned the validity of this assumption. Monozygotic twins have been found to share more similar intrauterine and extrauterine environments than dizygotic twins (Vandenberg 1976). In an effort to test the validity of the assumption, investigators have examined the relationship between degree of environmental similarity and degree of behavioral similarity across twin pairs. For a number of behavioral traits, no significant relationship between these two measures has been found (Loehlin and Nichols 1976). This suggests that, although MZ twins may share more similar rearing environments than DZ twins, this increased environmental similarity does not significantly contribute to concordance rate differences in MZ and DZ twins.

The third assumption is parental panmictic mating. When estimating the heritability of a particular disorder, the twin method assumes that the parents of MZ and DZ twins have mated randomly. In alcoholism research, however, studies of spouse choice suggest that parents of alcoholic individuals mate assortatively (Hall et al. 1983). That is, similarities in members of a spouse pair are greater than expected if mating were random. Assortative mating by

parents of twins differentially affects the additive genetic variance shared by MZ and DZ twins. While MZ twins are unaffected, assortative mating results in an increase in shared genetic variance for DZ twins. That is, DZ twins will appear more similar than would be expected if parental mating were random. Thus, additional research is needed to test the validity of this assumption in twin studies of alcohol and drug dependence.

PRESENT STUDY

With these methodological issues in mind, we will present some preliminary data from an ongoing twin/family study of substance abuse. These findings should be viewed as preliminary, as they are subject to change as the size of our twin sample increases. Unlike previous studies, the present subjects were twin pairs in which at least one member of each pair had been admitted for treatment of alcoholism or drug abuse. To minimize recruitment bias, the twins were ascertained by screening all admissions to 16 alcoholism and drug abuse treatment programs throughout the state of Minnesota, including public and private detoxification, outpatient, and residential treatment programs for both adolescents and adults.

Participation in the study was a two-phase process. In the first phase, both twins completed a brief questionnaire. In the second phase, both participated in a personal interview and provided a blood sample for definitive zygosity determination. To insure an adequate sample size, when completed the present study is expected to include data from at least 100 pairs of MZ and 100 pairs of same-sex DZ twins. Also, to minimize volunteer bias, efforts will be made to collect data from at least 75 percent of the twins ascertained during the study. To insure participation, subjects are paid $25 for questionnaire completion and $75 for the personal interview.

The questionnaire collects data on demographics, lifetime pattern of alcohol and other drug use, lifetime psychopathology indicators (including psychiatric symptomatology and sociopathic behavior), twin zygosity indicators, and alcohol/other drug use history in first-degree relatives. In the personal interview, formal psychiatric diagnoses, current and most extensive alcohol use, family alcoholism and psychiatric disorders, medical history, and personality assessment from each twin are obtained. Assessment was also made of how well the twins knew one another, and each twin was asked to report on the alcohol and drug use of the cotwin. Finally, we obtained a blood sample for definitive zygosity determination (based on similarity of serum proteins and RBC antigens) and permission to examine school records for academic performance and behavioral problems. In addition, corroborative information about each twin's alcohol/drug use and family history is being obtained from a significant other (usually the spouse).

Zygosity was determined by comparing twin pairs on responses to questionnaire items about early behavioral and physical similarity (i.e., "As children, were you and your twin as alike as two peas in

a pod?" and "As children, did people, even relatives, have difficulty telling you apart?"). While this approach has been previously shown to be 90 to 96 percent accurate in distinguishing "normal" MZ and DZ twins (Cederlof et al. 1961; Cohen et al. 1973), its accuracy has never been tested with a sample of alcoholic twins. Therefore, when blood-group data had been collected for 43 pairs of twins, we compared the blood-group results to the results of questionnaire data for zygosity determination. The proband questionnaire data were found to be 91 percent accurate in determining zygosity. That is, in 91 percent of cases, substance-abuse twins were correctly classified as MZ or DZ on the basis of their answers to the questionnaire items.

To date, data have been collected from both members of 139 pairs of twins in which at least one member of each pair (proband) met DSM-III criteria for Alcohol Abuse/Dependence. The twins were categorized as MZ or DZ on the basis of questionnaire and/or blood-group data. Based on this classification, 64 pairs were identical, and 75 pairs were fraternal. The demographic characteristics of the two groups are described in table 1. The data for the MZ and DZ twins were similar. The mean age for both was in the middle to late thirties, approximately two-thirds of each sample was male, and the majority were Caucasian. There were no statistically significant differences between MZ and DZ twins for age, sex, or race.

TABLE 1. *Demographic characteristics of the sample*

	MZ Twins	DZ Twins
Number of Pairs	64	75
Mean Age (Years)	35.2	38.7
Percent Male	63%	71%
Race		
Caucasian	92%	99%
American Indian	5%	1%
Black	3%	0%

To examine the role of genetic and environmental factors in the etiology of alcoholism, proband-wise concordance rates for DSM-III diagnoses of Alcohol Abuse and/or Dependence were calculated. Twins received a diagnosis of Alcohol Abuse if they reported both a pattern of pathological use (e.g., morning drinking) and problems resulting from alcohol use (e.g., losing a job due to drinking). Twins received a diagnosis of Alcohol Dependence if they reported either a pattern of pathological use or problems associated with alcohol use and evidence of tolerance or withdrawal from alcohol.

Table 2 shows alcoholism concordance rates for MZ and DZ twins. For lifetime prevalence of Alcohol Abuse/Dependence, the MZ concordance rate was .55, and the DZ concordance rate was .41. The MZ/DZ difference was not statistically significant (.10<p<.20).

TABLE 2. *Concordance for DSM-III Alcohol Abuse/Dependence*

All Twins (n=139 pairs):	
Monozygotic Twins (n=64 pairs)	.55
Dizygotic Twins (n=75 pairs)	.41
	MZ/DZ Ratio=1.3
Males Only (n=93 pairs):	
Monozygotic Twins (n=40 pairs)	.70
Dizygotic Twins (n=53 pairs)	.43
	MZ/DZ Ratio=1.6*
Females Only (n=46 pairs):	
Monozygotic Twins (n=24 pairs)	.29
Dizygotic Twins (n=22 pairs)	.36
	MZ/DZ Ratio=0.8

*p<.02.

For males, the alcoholism concordance rates were .70 in MZ and .43 in DZ twins (table 2 The MZ/DZ difference was statistically significant at p<.02 (x^2=6.5). In females, however, concordance rates were .29 and .36, respectively, in MZ and DZ twins, a difference that was not statistically significant. These results suggest that genetic factors may be important in male but not female alcoholism.

The present findings for males agreed with the results of twin studies by Kaij and by Hrubec and Omenn. All three studies found significant MZ/DZ differences for male alcoholism. All three studies disagreed with the results of Gurling et al., who failed to find significant MZ/DZ differences for male alcoholism. The present findings agreed with those of Gurling et al., however, who failed to find significant MZ/DZ differences in female alcoholism. (Kaij's and Hrubec and Omenn's studies included only male alcoholics.) In adoption studies, Goodwin et al. (1974) have also found evidence for genetic factors in male but not female alcoholism.

In addition to alcoholism, we also examined concordance rates for problematic use of other drugs (excluding alcohol and tobacco).

Problematic drug use was defined as psychoactive drug use resulting in family, social, occupational, legal, health, or emotional problems for the twin. The sample consisted of 66 same-sex twin pairs in which at least one member (proband) reported family, social, medical, or occupational problems related to use of other drugs. Of the 66 twins, 62 also met DSM-III criteria for Alcohol Abuse/Dependence and were included in the previous analysis. Using the same zygosity indicators described previously, we found 37 to be monozygotic and 29 to be dizygotic twins. The mean ages of the MZ and DZ twins were 31.2 and 32.4 years, respectively. The MZ sample was 59 percent male, while the DZ sample was 55 percent male. There were no statistically significant MZ/DZ differences for age or sex. Because of the small number of subjects that would have been involved in an analysis by type or class of drug, we did not analyze the data separately, but for all drugs combined (table 3).

TABLE 3. *Concordance rates for problematic drug use*

All Twins (n=66 pairs):	
Monozygotic Twins (n=37 pairs)	.43
Dizygotic Twins (n=29 pairs)	.28
MZ/DZ Ratio=1.5	
Males Only (n=38 pairs):	
Monozygotic Twins (n=22 pairs)	.55
Dizygotic Twins (n=47 pairs)	.31
MZ/DZ Ratio=1.8	
Females Only (n=28 pairs):	
Monozygotic Twins (n=15 pairs)	.27
Dizygotic Twins (n=13 pairs)	.23
MZ/DZ Ratio=1.2	

Concordance rates for problematic drug use were .43 in MZ and .28 in DZ twins, yielding an MZ/DZ ratio of 1.5. The MZ/DZ difference was not statistically significant ($.10<p<.20$). When examined by sex of subject, concordance rates were .55 in MZ and .31 in DZ males (MZ/DZ ratio=1.8), and .27 in MZ and .23 in DZ females (MZ/DZ ratio=1.2). Neither difference was statistically significant (for males, $.10<p<.20$; for females, $p>.80$). Thus, while similar MZ/DZ ratios were obtained for both alcoholism and problematic drug use, because of the larger number of subjects involved, only the differences for alcoholism in males were statistically significant.

CONCLUSIONS

Twin studies offer a powerful research methodology for estimating the relative contributions of genetic and environmental factors in the development of a trait or disorder. In the area of substance abuse, several twin studies of alcoholism have been reported, but the method has rarely been used to study other types of drug dependence. Such studies are needed, as their results would be important in improving our understanding of the basic nature of such disorders. However, twin studies are expensive to conduct, and twin subjects who are drug dependent are difficult to locate. In addition, research is needed to determine the validity of the assumptions that underlie use of the twin method in studies of alcohol and drug dependence.

If the results of such studies suggest a genetic component to drug dependence, then it would be important to know whether the influence is drug specific (i.e., limited to a single drug), applies to classes of drugs (e.g., sedatives, stimulants), or applies to psychoactive drugs in general. Specific attention should focus on the relationship between genetic factors in alcoholism and other forms of drug dependence.

Use of twin data may also help to identify environmental factors important in drug dependence. Because any differences between members of an MZ pair must be due to environmental factors, a comparison of MZ twins who are discordant for drug dependence may suggest environmental factors that either predispose to or protect individuals from developing the disorder. Such findings may be of considerable clinical significance when applied in programs for preventing drug dependence.

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Etiologic Factors in Substance Abuse: An Adoption Study Perspective

C. Robert Cloninger

INTRODUCTION

In this article, I will first review studies of the classification and inheritance of alcohol abuse. Then I will describe the adoption study method, review recent findings about the prediction of susceptibility to alcoholism from childhood antecedents, and relate these findings to studies of the prediction of substance abuse in general. Next, the neurobiological basis of susceptibility to substance abuse will be considered in relation to three neural systems that have been suggested to mediate susceptibility to personality disorders (Cloninger 1987b), anxiety states (Cloninger 1986), and alcoholism (Cloninger 1987a). These neural systems are involved in modulation of the activation, maintenance, and inhibition of behavioral responses to novel, appetitive, and aversive stimuli, including stimulants, opiates, and antianxiety drugs. It is proposed here that drug-seeking behavior is a special case of exploratory appetitive behavior and involves different neurogenetic processes than does susceptibility to behavioral tolerance and dependence. It is supposed that drug seeking and susceptibility to tolerance and dependence may be modulated by three putative neural systems whose functions can be behaviorally measured by quantitative ratings of personality and stimulus-response learning patterns.

TYPE 1 AND TYPE 2 ALCOHOLISM

Two types of alcoholism were first identified in a large-scale adoption study initiated in Sweden by Michael Bohman and his coworkers. The subjects included all 862 men and 913 women of known paternity who were born to single women in Stockholm, Sweden, from 1930 to 1949 and were adopted by nonrelatives at an early age. Most of the subjects were separated from their biological relatives in the first few months of life, and all had their final placement in the adoptive homes before they were 3 years of age. Information about alcohol abuse, psychopathology, and medical treatment was available for the entire lifetimes of the adoptees and their parents from hospitals, clinics, and several registers that are systematically maintained in Sweden. Identification of alcohol

abuse, using these sources, identifies about 70 percent of alcoholics; those so identified are representative of alcoholics in general, with no appreciable bias for either type 1 or type 2 alcoholics (Öjesjo 1980).

The adoption study was initiated to evaluate the relationship between the clinical features of alcohol abusers on the one hand, and the pattern of interaction of genetic and environmental factors on the other. Alcohol abuse in the adoptive parents was not associated with an increased risk of abuse in the children they reared, so there was no evidence that alcoholism is familial because children imitate their rearing parents (Cloninger et al. 1981; Bohman et al. 1981). In contrast, biological fathers with any registered alcohol abuse had a twofold excess of sons with alcohol abuse (22.8 percent of 268) compared to the sons of parents with no alcohol abuse (14.7 percent of 571). Likewise, biological mothers with any registered alcohol abuse had a similar excess of sons with alcohol abuse (28.1 percent of 32) compared to sons of parents with no alcohol abuse. However, alcohol abuse was significantly increased in the adopted-away daughters only if the biological mother was an alcohol abuser (9.8 percent of 51). not if the biological father was an alcohol abuser (3.5 percent of 285), compared to the daughters of biological parents with no registered alcohol abuse (2.8 percent of 577).

These sex differences suggested that some types of alcohol abuse may be heritable in both men and women, whereas other forms are heritable primarily in men. In addition, alcohol abuse in the families of female alcoholics was found to have adult onset of mild abuse without associated criminal behavior (Bohman et al. 1981). In contrast, families with alcohol abuse in the biological father but not the biological mother were found to have teenage onset of both criminality and alcohol abuse more often than families with alcohol abuse in the biological mother (Cloninger et al. 1981). Accordingly, the families with early onset of recurrent alcohol abuse and criminality in the biological fathers, but not mothers, were designated as showing type 2 or "male-limited" alcoholism. The families with alcohol abuse in the biological mother, or with alcohol abuse and minimal criminality in the biological father, were designated as representing type 1 alcoholism. The actual classification was based on a discriminant analysis that took into account all available information about alcohol abuse and criminality in the biological parents (Cloninger et al. 1981).

Given this subdivision of the biological parent backgrounds of the adoptees, we evaluated the interaction between the biological predisposition and the postnatal environment. Both genetic predisposition and postnatal provocation were found to be necessary for adopted-away sons to express susceptibility to loss of control (type 1) alcoholism (table 1). If the biological parents were type 1 alcoholics and if the adoptee was likely to be exposed to a pattern of heavy recreational drinking, as expected in the homes of adoptive fathers with unskilled occupations, there was more than a twofold increased risk of severe alcoholism. If either a genetic

predisposition or a provocative postnatal milieu was present (but not both), then the risk of alcohol abuse was lower than in the general population. Consequently type 1 alcoholism has been described as "milieu limited."

TABLE 1. *Cross-fostering analysis of severe* type *1 alcohol abuse in men in the StockhoIm adoption study*

Is Genetic Background Type 1?	Is Environmental Backgound Severe?	Male Adoptees Obsereved	
		Total No.	% With Severe Abuse
No	No	376	4.3
No	Yes	72	4.2
Yes	No	328	6.7
Yes	Yes	86	11.6*

*Risk is significantly increased compared to all others (x^2=5.6, p<.02).

In contrast, in adopted-away sons of fathers with spontaneous alcohol seeking (type 2), there was an increased risk of alcoholism regardless of environmental background (table 2). In these families, the risk of alcohol abuse was increased ninefold in the adopted-away sons of type 2 alcoholic fathers compared to the sons of all other fathers.

TABLE 2. *Cross-fostering analysis of type 2 alcohol abuse in men in the Stockholm adoption study*

Is Genetic Background Type 2?	Is Environmental Backgound Type 2?	Male Adoptees Observed	
		Total No.	% With Type 2 Abuse
No	No	567	1.9
No	Yes	196	4.1
Yes	No	71	16.9*
Yes	Yes	28	17.9*

*Risk is significantly increased in those with type 2 genetic background compared to others (p<.01).

Other aspects of the inheritance of alcoholism in adoptees have been reviewed in more detail elsewhere (Cloninger et al. 1985; Cloninger 1987a). These two groups of alcoholics also differ in neuropsychological, neurophysiological, and neurochemlcal responses to alcohol, as reviewed elsewhere (Cloninger 1987a).

INHERITANCE OF CLINICAL SUBGROUPS OF ALCOHOLISM

Many studies of the inheritance of substance abuse have treated alcoholism and drug abuse as if they were discrete disease entities. However, factor- and cluster-analytic studies indicate that social problems, medical problems, family problems, and core symptoms of dependence or loss of control are only weakly correlated with one another (Cloninger and Reich 1983). In the past, Jellinek emphasized the clinical importance of distinguishing alcoholics who had persistent alcohol-seeking behavior ("inability to abstain entirely") from others who could abstain from alcohol for long periods but were unable to terminate drinking binges once they had started ("loss of control") (Jellinek 1960a; Jellinek 1960b). Jellinek assumed that these clinical differences were caused by different sociocultural backgrounds, but it has recently been shown that genetic factors are important antecedents of such clinical differences.

Two syndromes of alcohol abuse that aggregate in different families have been distinguished in terms of alcohol-related symptoms and in terms of antecedent personality traits (Cloninger 1987a). The characteristics that distinguish these two types of alcoholism are summarized in table 3. In a large family study of hospitalized alcoholics, the number of type 1 and type 2 symptoms were negatively correlated ($r=-.23$, $p<.01$) in the male relatives of alcoholics. Women were usually type 1 alcoholics: type 1 symptoms were five times more common than type 2 symptoms in women. In contrast, men were more heterogeneous: type 1 and type 2 symptoms were equally common in men (Gilligan et al. 1987). Furthermore, type 1 symptoms were frequent in the male relatives of alcoholic women, whereas type 2 symptoms were frequent in the male relatives of alcoholic men. This suggested that the familial aggregation of type 1 and type 2 alcoholism reflects differences In variables, such as personality traits, whose expression is influenced by the sex of the individual, but are inherited in the same way regardless of the sex of the parent or child.

Type 1 alcoholics have the triad of personality traits that are characteristic of individuals with passive-dependent or "anxious" personality: they are high in reward dependence (that is, eager to help others, emotionally dependent, warmly sympathetic, sentimental, sensitive to social cues, and persistent); high In harm avoidance (that is, cautious, apprehensive, pessimistic, inhibited, shy, and easily susceptible to fatigue); and low in novelty seeking (that is, rigid, reflective, loyal, orderly, and attentive to details). In contrast, type 2 alcoholics have the triad of traits that are characteristic of individuals with antisocial personality, which is the reverse of the configuration seen in passive-dependent

personality: high in novelty seeking (that is, impulsive, exploratory, excitable, disorderly, and distractible); low in harm avoidance (that is, confident, relaxed, optimistic, uninhibited, carefree, and energetic); and low in reward dependence (that is, socially detached, emotionally cool, practical, tough-minded, and independently self-willed) (Cloninger 1987a).

TABLE 3. *Distinguishing characteristics of two types of alcoholism*

Characteristic Features	Type of Alcoholism	
	Type 1	Type 2
Alcohol-Related Problems		
Usual age of onset (years)	after 25	before 25
Spontaneous alcohol seeking (inability to abstain)	infrequent	frequent
Fighting and arrests when drinking	infrequent	frequent
Psychological dependence (loss of control)	frequent	infrequent
Guilt and fear about alcohol dependence	frequent	infrequent
Personality Traits		
Novelty seeking	low	high
Harm avoidance	high	low
Reward dependence	high	low

Individual differences in each of these three personality dimensions (novelty seeking, harm avoidance, and reward dependence) are largely independent of one another (Cloninger 1986; Cloninger 1987b). However, different combinations of these traits lead to unique integrated patterns of response to novel, appetitive, and aversive stimuli. The characteristic behaviors that arise from these functional interactions are summarized in figures 1 to 3, showing the three possible two-way combinations of three personality dimensions (Cloninger 1986; Cloninger 1987b). Thus, alcoholics have the full range of personality traits seen in the general population, but differ quantitatively in the frequency and combinations of those traits. Alcoholics also have variable patterns of

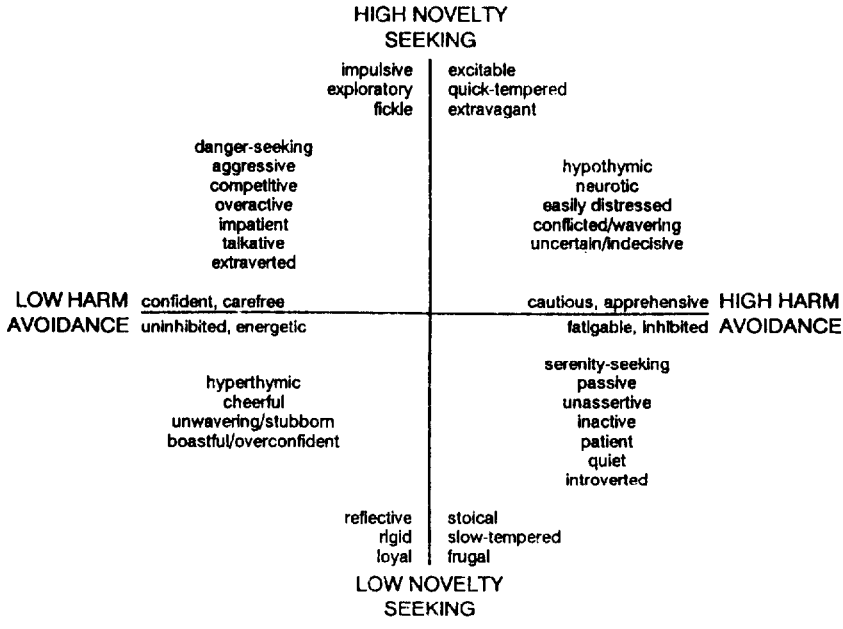

FIGURE 1. *Interaction of two personaity dimensions: Novelty seeking and harm avoidance*

predisposition to seek out alcohol and to become tolerant of and dependent on it. Consequently, it has been proposed that the varying combinations of these personality traits reflect differences in brain systems that determine individual tendencies to seek behavioral reinforcement from alcohol and other drugs, or to become tolerant and dependent following exposure to various drugs (Cloninger 1987a).

Individuals with type 1 alcoholism, which is associated with guilt, fear, and loss of control of drinking, usually begin to have problems in late adulthood after an extended period of exposure to heavy drinking that is personally or socially encouraged, such as drinking to relieve tension during "happy hours" after work. In contrast, individuals with type 2 abuse, which is associated with impulsive-aggressive behavior and other forms of risk taking, usually begin to seek out alcohol and other drugs during adolescence and early adulthood, regardless of external circumstances. Consequently, the patterns of inheritance or gene-environment interaction seen in these two types of alcoholism are strikingly different (Cloninger et al. 1981; Cloninger et al. 1985).

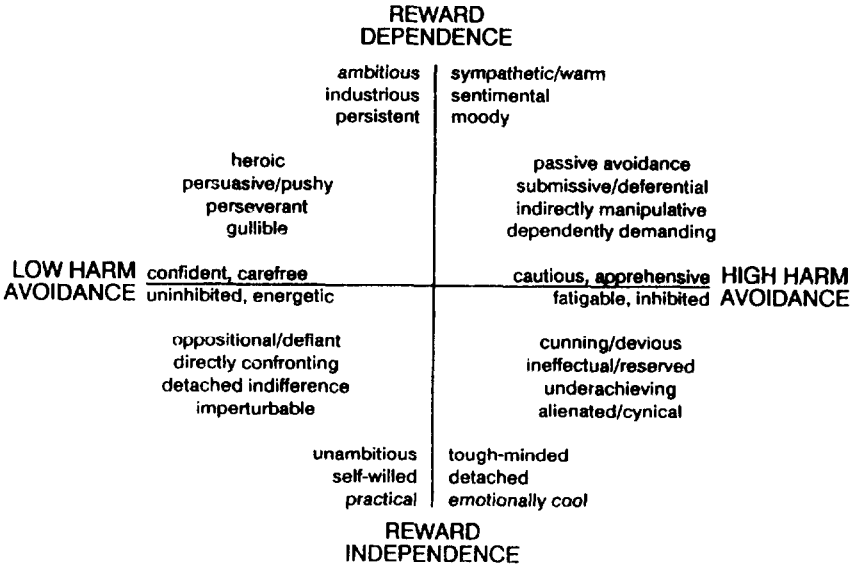

FIGURE 2. *Interaction of two personality dimensions: Reward dependence and harm avoidance*

CLINICAL AND NEUROGENETIC ANTECEDENTS OF SUSCEPTIBILITY

Several prospective longitudinal and familial high-risk studies have been carried out to evaluate the possibility that childhood and adolescent personality traits are predictive of susceptibility to later alcoholism. Most studies have found that the premorbid traits characteristic of antisocial personality, including being impulsive, aggressive, overactive, distractible, impatient, and excitable, are predictive of alcohol and drug abuse in young adults (Aronson and Gilbert 1963; Robins 1966; Jones 1968; McCord 1972; Loper et al. 1973; Kammeier et al. 1973; Hoffman et al. 1974; MacAndrew 1979; MacAndrew 1981; Vaillant 1983; Knop et al. 1985; Hagnell et al. 1986). Furthermore, several prospective longitudinal studies, retrospective or cross-sectional studies, and family studies have found that antisocial or impulsive traits are characteristic of most early-onset alcoholics and/or polydrug abusers, but of only a minority of alcoholics with later onset (Cloninger et al., in press). Later onset of alcoholism or abuse of antianxiety drugs is associated with passive-dependent or oral personality traits, such as crying easily, feeling guilty or worried, and being rigid, pessimistic, inactive, and passive. In an important large-scale prospective study, both antisocial and passive-dependent personality configurations were found to increase the risk of later

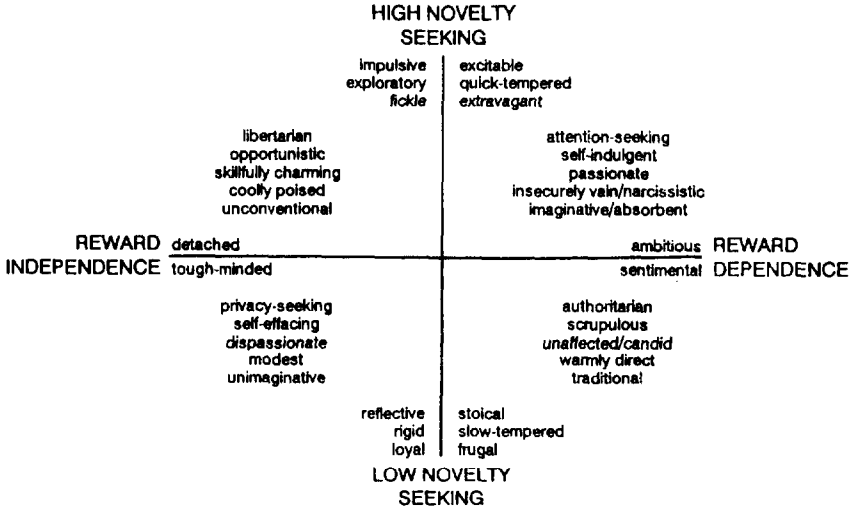

FIGURE 3. *Interaction of two personality dimensions: Novelty seeking and reward dependence*

alcoholism in the Berkeley and Oakland longitudinal studies of child development (Block 1971). Boys with passive-dependent traits were called "anomic extroverts" because they tended to cry easily and to worry excessively even though they were usually friendly and warmly sociable; they had a tendency to drink and smoke heavily in middle adulthood, but had few or no behavioral problems during adolescence. Boys with antisocial traits were called "unsettled undercontrollers" because they had been impulsive, aggressive, and disorganized since childhood; they had a history of risk taking, including substance abuse, since adolescence. More recently, Cloninger et al. (in press) showed that childhood ratings of high novelty seeking, low harm avoidance, and low reward dependence were each strongly predictive of alcohol abuse in early adulthood. Extreme deviations in the opposite direction (high harm avoidance, high reward dependence, and low novelty seeking) were also associated with increased risk of alcohol abuse, but this passive-dependent configuration had a less prominent effect before 28 years of age (which was the time of last information) than had the antisocial personality configuration, as expected, since type 1 alcohol abuse usually begins in later adulthood.

Among 75 studies that report on associations within individuals among alcoholism, drug dependence, and antisocial personality, 76 to 80 percent found positive associations between each possible pair of these diagnoses (Grande et al, 1984). Individuals with early onset of antisocial behavior are particularly likely to abuse

both alcohol and other prescribed or illicit drugs (Lewis 1984). Not all studies have found a strong association between antisocial personality and substance abuse. However, the non-antisocial substance abusers tend to be individuals with adult onset of problems with anxiety or depression, which is self-medicated with alcohol and other antianxiety drugs.

In the Stockholm adoption study, it has been possible to identify individuals at high risk for alcoholism based on their personal history of anxiety or criminality, as well as the history of alcoholism and criminality in their biological parents. Cognitive anxiety or frequent anticipatory worrying is associated with the personality trait of high harm avoidance, particularly when reward dependence is high and novelty seeking is low (Cloninger 1986); this pattern is similar to that associated with loss of control or type 1 alcoholism. In contrast, individuals with high somatic anxiety have the personality traits of high novelty seeking and low harm avoidance, which are associated with spontaneous alcohol-seeking behavior or type 2 alcoholism. The relationship between personality and alcoholism was supported by the finding of increased risk of alcoholism in individuals with either somatic anxiety or cognitive anxiety (Cloninger et al. 1986). However, the importance of distinguishing the two subtypes of substance abusers was shown by the inverse relationship between cognitive anxiety and criminality: adoptees with cognitive anxiety had fewer criminal biological parents than in the general population, whereas adoptees with somatic anxiety had more criminal biological parents than in the general population (Cloninger et al. 1986).

This evidence of clinical and genetic heterogeneity among alcohol abusers suggests that such heterogeneity may be even more obvious in relation to drug abuse in general. Individuals with passive-dependent or anxious personality traits (high reward dependence, high harm avoidance, and low novelty seeking) seldom take risks or seek out alcohol or other drugs at an early age. Furthermore, they prefer antianxiety drugs and are often overstimulated by even mild stimulants like caffeine. These individuals are susceptible to cognitive anxiety and find antianxiety drugs strongly positively reinforcing because of the reduction of anxiety. In contrast, individuals with antisocial personality traits (high novelty seeking, low harm avoidance, and low reward dependence) engage at an early age in much exploratory appetitive behavior and impulsive risk taking, including abuse of a wide variety of drugs, including alcohol, stimulants, and opiates.

A NEUROBIOLOGICAL LEARNING MODEL OF SUBSTANCE ABUSE

The clinical and genetic heterogeneity observed among substance abusers suggests the importance of personality variables in understanding substance abuse. Elsewhere I have described in detail the initial development of a tridimensional model of personality and its relationship to three neural systems involved in the regulation of behavioral inhibition, behavioral activation, and behavioral maintenance (Cloninger 1986; Cloninger 1987a;

Cloninger 1987b). The stimulus-response characteristics of these putative brain systems are summarized in table 4. Each system is complex, involving multiple brain structures and neurotransmitters, but each of the three brain monoamines (serotonin, dopamine, norepinephrine) appears to have a major neuromodulatory role in only one system. Neuropsychopharmacological information relevant to drug abuse is summarized here for each of the three proposed systems.

Behavioral Activation System

Novelty seeking refers to a heritable tendency toward frequent exploratory activity and intense exhilaration in response to novel or appetitive stimuli. It is hypothesized to reflect variation in the brain's "incentive," or behavioral activation, system. Dopaminergic cell bodies in the midbrain receive inputs from several sources and then project impulses to the forebrain, thereby possibly acting as a final common pathway for behavioral activation in response to novel or appetitive stimuli (Routtenberg 1978; Wise 1980; Wise 1984; Wise and Bozarth 1982; Stellar and Stellar 1985). Spontaneous exploratory behavior by mammals in a novel environment is dependent on integrity of mesolimbic dopaminergic projections, particularly from the ventral tegmental area to the nucleus accumbens (Kelley and Stinus 1984; Iversen 1977). Low doses of ethanol have an excitatory effect on ventral tegmental area neurons, suggesting that this action of ethanol may provide a pharmacological "reward" that would facilitate alcohol-seeking behavior (Gessa et al. 1985). Dopamine agonists, like amphetamines and cocaine, as well as alcohol, opiates, and opioid neuropeptides, facilitate dopaminergic transmission and behavioral activation, whereas dopamine blockers, like haloperidol, reduce exploratory behavior and responsiveness to positive reinforcement (Kelley and Stinus 1984; Iversen 1977; Pickens et al. 1978; Wise 1984). Self-stimulation with electrodes at sites of dopaminergic neurons is rapid and accompanied by marked locomotor activation and positive reinforcement of eliciting behavior in mammals and by reports of subjective experience of pleasure and satisfaction in humans (Heath 1964; Stellar and Stellar 1985). Cocaine administration directly into the frontal cortex and the nucleus accumbens also has positive reinforcement effects (Goeders and Smith 1983). Administration of opiates and opioid neuropeptides intravenously or into the ventral tegmental area leads to positive reinforcement of behavior; such positive reinforcement by opiates is similar to that seen with dopamine agonists like cocaine or amphetamine rewarding effects, and can be blocked or reduced by dopamine antagonists such as pimozide or cis-flupenthixol (Ettenberg et al. 1982; Bozarth and Wise 1983; Stellar and Stellar 1985). Thus, drug-seeking behavior for ethanol, cocaine, amphetamine, and opiates all depend on integrity of mesolimbic dopaminergic projections to the forebrain, suggesting that dopamine has an essential neuromodulatory role for activation of behavior in response to novel or appetitive stimuli.

TABLE 4. *Three major brain systems influencing stimulus-response characteristics*

Brain System (Related Personality Dimension)	Principal Monoamine Neuromodulator	Relevant Stimuli	Behavioral Response
Behavioral Activation (Novelty Seeking)	Dopamine	Novelty	Exploratory pursuit
		Potential rewards or their conditioned signals	Appetitive approach
		Potential relief of monotony or punishment or their conditioned signals	
Behavioral Inhibition (Harm Avoidance)	Serotonin	Conditioned signals for punishment, novelty, or frustrative nonreward	Passive avoidance Extinction
Behavioral Maintenance (Reward Dependence)	Norepinephrine	Conditioned signals for reward or relief of punishment	Resistance to extinction

Drug-seeking behavior for dopaminergic drugs may be considered a special kind of exploratory appetitive behavior. Administration of dopaminergic drugs when a mammal is in a particular side of a chamber leads to preference for the place that has been rewarded (Stellar and Stellar 1985). Alcohol-preferring rats, which have low basal dopamine concentrations in the cortex and nucleus accumbens, show greater locomotor activation and greater increases in dopamine turnover after low doses of alcohol than do alcohol-nonpreferring rats (Murphy et al. 1983; Waller et al. 1986; Li 1987). Rodent strains that show high exploratory activity and low fearfulness behavior, such as C57BL mice, show greater alcohol-seeking behavior than other animals. Rodent strains that show little spontaneous exploratory or alcohol-seeking behavior, such as BALB/c and DBA/2 mice, have a biphasic response to alcohol with greater suppression of dopamine release with lower doses of ethanol and smaller increases at higher doses than C57BL/6 mice (Nichols 1972; Tabakoff and Ritzmann 1979; Kiianmaa and Tabakoff 1983). Long-term ethanol intake produces behavioral tolerance to the high-dose depressant effects of ethanol, but not to these low-dose activating effects.

Schuckit and coworkers have used inhibition of prolactin release by dopamine to study the effects of alcohol on dopamine release in human subjects who are at high or low risk for alcoholism (Schuckit et al. 1983). Prolactin increased by 30 minutes and returned to baseline by 90 minutes for the controls, but continued to decline until 150 minutes for the men with a family history of alcoholism. This is consistent with the hypothesis that much drug-seeking behavior is caused by dopaminergic behavioral activation. Low basal firing rates of dopaminergic neurons are thought to be associated with greater postsynaptic sensitivity to dopamine when it is released, lower turnover of dopamine as measured by cerebrospinal fluid concentrations, and greater novelty seeking. More detailed reviews of the behavioral activation system are presented elsewhere (Cloninger 1986; Cloninger 1987a; Cloninger 1987b).

Behavioral Inhibition System

Harm avoidance is a heritable tendency to respond intensely to aversive stimuli and their conditioned signals, thereby facilitating learning to inhibit behavior in order to avoid punishment, frustrative omission of expected rewards, and uncertainty about the safety of novel stimuli. Harm avoidance may reflect variation in the brain's "punishment" or behavioral inhibition system, which includes the septohippocampal system, serotonergic projections from the raphe nuclei in the brain stem, and cholinergic projections to the frontal neocortex from the basal nucleus of Meynert near the amygdala and perhaps from the midbrain reticular formation near the ventral tegmental area. Ascending serotonergic neurons from the raphe nuclei project to the limbic system, including the septum and hippocampus, as well as to the prefrontal cortex. The septohippocampal system is thought to function as a comparator, checking predicted against actual events, and then interrupting behavior when the unexpected is encountered (Warburton 1977; Gray 1982).

Ascending serotonergic projections from the dorsal raphe nuclei to the substantia nigra inhibit nigro-striatal dopaminergic neurons and are essential for conditioned inhibition of activity by signals of punishment and frustrative nonreward (Thiebot et al. 1984). In response to novel stimuli, ascending cholinergic projections excite the frontal cortex and stimulate release of stress hormones, such as cortisol (Warburton 1977). In turn, frontostriatal projections reduce exploratory activity by inhibiting dopaminergic neurons in the caudate nucleus (Iversen 1977).

Ethanol, barbiturates, benzodiazepines, and other antianxiety drugs block the expression of behavioral inhibition acquired by operant conditioning in which a particular behavioral response is learned to predict punishment, omission of rewards, or dangerous novel stimuli. The clinical antianxiety effects of these drugs in human subjects are strongly correlated with their effects on passive avoidance learning in rodents (Sepinwall and Cook 1980; Stein 1981). These antianxiety effects are thought to be a consequence of inhibition by gamma-aminobutyric acid of serotonergic neurons originating in the dorsal raphe nuclei (Stein 1981). In any case, the reduction of anxiety is positively reinforcing. Presumably as a result of positive reinforcement by antianxiety effects of such sedative drugs, serotonergic projections have been strongly implicated in the development of behavioral tolerance to the sedative effects of alcohol. In rodents, the development of tolerance is accelerated (and, conversely, loss of tolerance is slowed) by procedures that increase serotonergic activity or postsynaptic sensitivity, whereas the development of tolerance is slowed (and loss is accelerated) by procedures that reduce serotonin effects (Khanna et al. 1980; Kalant 1985; Le et al. 1981; Melchior and Tabakoff 1981; Melchior and Tabakoff 1984).

In human subjects, serotonergic activity, as measured by cerebrospinal fluid concentrations of serotonin metabolites, is strongly correlated with harm avoidance (Cloninger 1986; Linnoila et al. 1983; Banki and Arato 1983; Asberg et al. 1984; Brown et al. 1982). Increased serotonergic activity also inhibits dopaminergic activity, so that dopamine and serotonin turnover are strongly correlated in human subjects and other mammals (Agren et al. 1986). Consequently, high harm avoidance is expected to inhibit appetitive exploration for dopaminergic drugs, like cocaine, amphetamines, opiates, and ethanol, and to accelerate the development of behavioral tolerance and psychological dependence on antianxiety drugs, like barbiturates, benzodiazepines, and ethanol. This expectation is consistent with findings in clinical and family studies that low harm avoidance is associated with type 2 drug-seeking syndromes and high harm avoidance is associated with type 1 loss-of-control syndromes.

Behavioral Maintenance

Reward dependence is hypothesized to involve variation in behavioral maintenance or resistance to extinction of previously rewarded behavior (Cloninger 1986; Cloninger 1987a). This resistance to

extinction is hypothesized to result from facilitation of paired-associate learning by a brain system that is activated primarily at the onset of reward or the offset of punishment, thereby facilitating the formation of conditioned signals of reward or relief from punishment. Norepinephrine seems to satisfy the characteristics required of the major neuromodulator for this system and may play a critical role in the learning of new paired associations (Frith et al. 1985). The major ascending noradrenergic pathways arise from the locus coeruleus in the pons and project to the hypothalamus and limbic structures, then branch throughout the entire cerebral cortex. Norepinephrine seems to modulate the general level or "tone" of neuronal activity by inhibiting spontaneous firing rates of affected neurons and simultaneously increasing their response to other afferents; in this way, the signal-to-noise ratio is increased, permitting important stimuli to stand out from irrelevant stimuli.

In human subjects, short-term reduction of norepinephrine release by acute infusion of the alpha-2 presynaptic agonist clonidine selectively impairs paired-associate learning, particularly the acquisition of novel associations (Frith et al. 1985). Similar cognitive deficits arise from long-term destructive lesions of the locus coeruleus, as in Korsakoff's amnestic syndrome in which norepinephrine and arginine vasopressin levels in the cerebrospinal fluid are decreased. Vasopressin is known to enhance memory when injected immediately after learning trials, but this enhancement is dependent on integrity of the noradrenergic projections in the dorsal bundle (i.e., dorsal longitudinal fasciculus) (DeWeid and Bohus 1979; Kovacs et al. 1979).

Similarly, vasopressin injections maintain tolerance to alcohol beyond the time it is usually lost, but this maintenance effect is dependent on the integrity of the dorsal noradrenergic bundle (Hoffman et al. 1983). In addition, acquisition of behavioral tolerance to the sedative effects of ethanol is not possible after destruction of noradrenergic projections in mice, or after destruction of both serotonergic and noradrenergic projections in the rat (Khanna et al. 1980; Kalant 1985; Melchior and Tabakoff 1981; Melchior and Tabakoff 1984). Furthermore, in rhesus monkeys, individuals with low basal noradrenergic activity at rest show more severe depressive-like responses to separation and have greater increases in norepinephrine release after receiving low doses of ethanol (Kraemer et al. 1984; Kraemer et al. 1985). Furthermore, abstinent alcoholics with low basal levels of norepinephrine metabolites in their cerebrospinal fluid have greater psychological craving and dependence on alcohol than do other alcoholics (Borg et al. 1983a; Borg et al. 1983b). These observations, together with evidence that noradrenergic activity is conditionally inhibited at the onset of punishment or offset of rewards and that low basal firing rates are associated with greater postsynaptic sensitivity to norepinephrine, support the hypothesis that individuals with low basal firing rates of the locus coeruleus will have a greater tendency to respond to signals of reward, such as social approval, and to persist in reward-seeking behavior even when frustrated. In

contrast, individuals with higher basal noradrenergic activity (hence lower postsynaptic sensitivity to norepinephrine) will tend to be less sensitive to social cues and to be more practical, quickly stopping activities when they are no longer tangibly gratifying (Cloninger 1986; Cloninger 1987a).

Altogether, these findings support the suggestion from clinical and genetic studies that high reward dependence reflects individual differences in a brain system modulated by norepinephrine. Furthermore, the findings provide preliminary support for the hypothesis that reward dependence reflects neuroadaptive processes that are critical in the acquisition of behavioral tolerance to the sedative effects of drugs and in susceptibility to loss of control of antianxiety drugs.

OVERVIEW AND CONCLUSIONS

A major obstacle in studying the inheritance of drug abuse is that exposure to drugs varies widely in terms of both the type and the amount of drugs that are used by family members, especially between generations. Studies of the inheritance of drug abuse would be most informative if they could focus on susceptibility factors that are (1) stably expressed regardless of exposure to drugs, (2) predictive of later drug abuse or complications from drug exposure, and (3) at least moderately heritable. The availability of such stable and heritable risk factors would permit studies of relevant heritable traits across generations that differ in exposure to different types of drugs.

Recent advances in research on the inheritance of susceptibility factors to alcoholism provide a model that could be even more powerful when applied to drugs in general than when limited to a single drug, like alcohol. The three personality dimensions of novelty seeking, harm avoidance, and reward dependence seem to reflect variations in underlying brain systems that modulate behavioral responses to novel, appetitive, and aversive stimuli in general, including various classes of drugs. Specific combinations of deviations in stimulus-response characteristics are associated with different patterns of response to drugs, including differences in preferences for stimulant or antianxiety drugs. Individuals who are high in novelty seeking and low in harm avoidance, as in antisocial or histrionic personalities, prefer dopaminergic agonists, like cocaine and amphetamines, and have early onset of type 2 drug abuse syndromes with inability to abstain and frequent antisocial behavior. In contrast, individuals with high harm avoidance and high reward dependence, as in passive-dependent or passive-aggressive personalities, prefer antianxiety drugs because the relief of anxiety leads to strong conditioned signals of reward that are highly resistant to extinction. Individuals who are high in both novelty seeking and reward dependence, as in histrionic and passive-aggressive personalities, have a predisposition to both spontaneous drug seeking and to development of behavioral tolerance and psychological dependence on drugs. Most important, these adaptive personality traits have consistently been found to be

moderately stable from childhood to adulthood (Sigvardsson 1987) and to have heritabilities from 40 to 60 percent (Cloninger 1986; Cloninger 1987a). Furthermore, ratings of childhood personality traits are predictive of later drug use (Cloninger et al., in press).

Taking these personality traits as indices of intervening susceptibility factors in drug abuse, the variable exposure to various types of drugs in family members becomes an advantage, rather than an obstacle. In other words, the variation in exposure to drugs becomes an informative natural experiment in which individuals with similar quantitative personality configurations develop different clinical outcomes in response to different environmental stimuli (that is, the provocative stimuli of exposure to drugs in different types or amounts). Unfortunately, many past clinical family studies have treated drug abuse as if it were a discrete phenotype that was inherited. It is more plausible to assume that susceptibility to drug abuse is heritable, but that drug abuse itself is not heritable. Furthermore, use of the model described here facilitates integration of experimental work on neuroadaptive mechanisms in nonhuman animals with clinical studies of human subjects who vary in susceptibility to drug abuse. This has the important benefit of facilitating investigations that can test hypotheses about the pathophysiology of signs and symptoms of drug abuse. Neglect of the clinical and etiological heterogeneity among drug abusers, combined with variable exposure patterns, has led to limited progress in understanding drug abuse. The opportunity is now available to characterize the inheritance of drug abuse in human subjects in terms of underlying neuroadaptive mechanisms.

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ACKNOWLEDGMENTS

This work was supported in part by Research Scientist Award MH-00048 and Clinical Research Center grant MH-31302 from the National Institute of Mental Health; Alcohol Research Center grant AA-003539 from the National Institute on Alcoholism and Alcohol Abuse; and a grant from the MacArthur Foundation Network on Risk and Protective Factors in Major Mental Disorders.

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The High-Risk Paradigm in Alcohol and Drug Abuse Research

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INTRODUCTION

The high-risk paradigm is based on the assumption that the likelihood of developing a medical illness, behavioral disorder, or psychiatric disturbance is not equally distributed in the population. A negative outcome may be influenced by organismic predisposition, and as such, vulnerability can be viewed as lying along a spectrum ranging from low to high. For example, the offspring of a schizophrenic mother has a probability of about 1 percent for developing this condition (Mednick and Schulsinger 1968). If there is also a history of perinatal insult, however, the likelihood of the child becoming schizophrenic increases to about 10 percent (Mednick and Baert 1980). Thus, the probability of an adverse outcome (risk) is related to the number and type of characteristics (vulnerability) present in the individual.

Vulnerability can also be viewed as localized in one or more levels of biological organization. With respect to alcoholism, certain individuals show a genetically determined vulnerability (Goodwin 1983; Cloninger et al. 1981), which may be expressed through various biological pathways and reflected in neurochemical (Gottfries 1980), neurophysiologic (Begleiter et al. 1984; Pollack et al. 1983), neurologic (Lee-Feldstein and Harburg 1982; Hegedus et al. 1984), endocrine (Schuckit et al. 1983; Monnelly et al. 1983), and behavioral (Alterman and Tarter 1983; Tarter et al. 1985a) deviations. The delineation of the vulnerability need not, however, be reduced to biological mechanisms. For example, it is more parsimonious to describe the risk for hepatitis from the standpoint of a homosexual lifestyle rather than from a perspective of the biological determinants of homosexuality. Nonetheless, recent genetic research into the etiology of psychiatric disorders and, in particular, alcoholism has revealed substantial evidence pointing to their heritable basis. It is, therefore, heuristic at this time to consider the biological and perhaps behavioral manifestations of gene expression underlying the vulnerability to alcoholism, insofar as it may serve as a model for clarifying the etiology of drug abuse.

In clarifying the risk for developing a substance abuse disorder, where social policy and law enforcement regulates availability, cost, and distribution of the putative addictive agent, it is safe to conclude that factors besides biology influence the likelihood of an unfavorable outcome. To cite one extreme example, the rate of alcoholism is close to nonexistent in fundamentalist Moslem nations where presumably the genotype is, nonetheless, present in a segment of the population. It would thus appear that to understand fully the risk parameters of alcohol and other drug abuse, biological and psychosocial factors must both be considered as determinants of outcome.

The present paper addresses the rationale underlying use of the high-risk paradigm and examines some of the factors that contribute to the results obtained. Following this discussion, the strengths and weaknesses of this paradigm are briefly presented. No attempt will be made here to review the plethora of findings from studies that have employed the high-risk paradigm for elucidating the antecedents to drug and alcohol abuse. A comprehensive review of this subject can be found elsewhere (Tarter et al. 1985a). Rather, the purpose of this discussion is to highlight the conceptual and methodological issues that are involved in using the high-risk paradigm.

RATIONALE FOR EMPLOYING THE HIGH-RISK PARADIGM

The assumption underlying use of the high-risk paradigm is that individuals deemed to be at elevated risk are discriminable from those at low risk according to some characteristic. With respect to alcoholism, risk classification has most frequently been made according to the presence or absence of alcoholism in another family member, usually a first-degree relative (i.e., parent or sibling). Inasmuch as alcoholism tends to run in families, it is expected that the particular feature under study, if indeed comprising the vulnerability, is more frequently or more strongly present in individuals with a family history of alcoholism. This paradigm is based on the empirical demonstration of both a familial aggregation and transgenerational high prevalence of alcoholism (Cotton 1979; Goodwin et al. 1973).

Another approach for classifying subjects according to high and low risk for development of alcohol abuse is guided by theory. Using hypotheses regarding predisposition to alcohol use and abuse, such studies have defined risk on the basis of sensation seeking (Zuckerman 1972), left-handedness (Lee-Feldstein et al. 1982), and type A personality (Folsom et al. 1985)--characteristics which have been empirically linked to the risk for augmented alcohol and substance abuse. Investigations in which several such risk factors were analyzed together have revealed that it is the total number of factors (more than the specific characteristic of the vulunerability) which best predicts outcome. For example, in a high-risk study of substance abuse, Bry and colleagues (1982) reported that the total number of vulnerability characteristics

was more important than the specific type of risk factors in predicting cigarette, alcohol, and cannabis use.

Other vulnerability characteristics for substance abuse have also been identified, including poor school performance, perceived use of drugs by adults, psychological disorders (e.g., depression and conduct disturbance), low self-esteem, perception of parental drug use, low religious involvement, conflict with parents, excitement-seeking behavior, lack of a sense of purpose, a reduced sense of social responsibility, and childhood hyperactivity. These latter characteristics, comprising the dispositional characteristics of the individual, have been implicated to comprise vulnerability to alcoholism and, in some studies, drug abuse as well. However, each variable by itself has not been found to be a powerful predictor of outcome. Rather, as noted above, it is the aggregation of such factors which appears to best predict outcome.

In summary, the classification of subjects into high- and low-risk groups can be conducted according to either empirical or theoretical criteria. To date, theory-driven research has not been systematically conducted. Tarter et al. (1985a), for instance, suggest that a temperament perspective of alcoholism vulnerability may have heuristic value in elucidating both the characteristics and mechanisms underlying alcohol and/or drug abuse vulnerability. Such an approach affords the opportunity to conduct multidisciplinary research into the genetic predisposition, its biological manifestations, and the psychosocial factors which predispose to either a favorable or an unfavorable outcome. To date, one study employing this comprehensive research strategy has been reported. The results, however, underscore the value of such an approach (Werner 1986).

Contexts of Expression of the Vulnerability

Differences between high- and low-risk subjects have been observed both while they were sober and during an acute alcohol challenge. For example, while Schuckit (1985a) found no differences between high- and low-risk subjects at baseline, after a challenge dose of 0.75 ml/kg of alcohol, the high-risk subjects exhibited less body sway. Although these results are intriguing, it needs to be emphasized that the results obtained regarding static ataxia are still preliminary and are not entirely consistent across investigations. Differences across studies with respect to the subject sample and method of measurement of ataxia undoubtedly have contributed to this lack of consistency. Nevertheless, the point of this discussion is that the vulnerability may be expressed under different organismic conditions. Indeed, it may even be specific to how the drug is metabolized (Schuckit and Rayses 1979). The evidence in this regard, however, is far from conclusive.

Other investigations have revealed that alcohol attenuates the experience of stress for high-risk individuals. Sher and Levenson (1982) reported that high-risk young adult subjects, classified by their high score on the Minnesota Multiphasic Personality

Inventory (MMPI) and MacAndrew Scale and a low score on the Cooperative Preschool Inventory Socialization Scale, obtained a stress-dampening effect from alcohol. That is, subjects who are behaviorally raucous and disinhibited, socially behaving in a nonnormative fashion, experience a reduction in experienced distress following alcohol consumption. This effect was not observed in the low-risk subjects. Heavy drinkers, unlike moderate drinkers, have also been found to experience an analgesic effect from alcohol (Cutter et al. 1976). Moreover, several studies indicated that persons at elevated risk may experience either a more positively reinforcing or less punishing consequence following their first and subsequent experience with drugs and alcohol (Haertzen et al. 1983). Thus, the emerging evidence indicates that the state of the organism as well as the reaction to the substance may be critical for identifying the presence of a vulnerability characteristic. Further complicating the picture is the observation that cognitive variables may differentially affect the reaction to alcohol in vulnerable individuals (Newlin 1985).

Composition of the High-Risk Sample

Not all individuals deemed to be at high risk are likely to become alcoholic. Moreover, there is evidence indicating that there may be more than one type of genetic predisposition to alcoholism (Cloninger et al. 1981). An important issue, therefore, concerns the criteria for selection of individuals who comprise the high-risk sample. This is especially salient, since the age of onset, familial characteristics, and premorbid characteristics may help to distinguish among the various subtypes of individuals who eventuate to an alcoholism outcome.

Another important consideration concerns whether or not current drinkers and drug users should be included in the sample of high-risk individuals. Whereas this is not an issue for the study of very young children, it is of consequence where the sample comprises adolescents or older subjects, since the effects of the experience with alcohol or other substances may themselves be determinants of the characteristics that are otherwise presumed to be associated with the vulnerability. In a recent study, it was found that when current young adult heavy drinkers were excluded from a high-risk sample, the score on a socialization scale no longer discriminated high- from low-risk individuals (Sher 1985). This finding suggests that the presence of certain vulnerability characteristics may be detectable in only those persons at greatest risk; namely, individuals who have already commenced heavy substance use. Thus, depending on the age of the sample, a trade-off must be contemplated where the inclusion of current drinkers could potentially confound the results obtained.

Specific vs. Generalized Vulnerability Characteristics

Studies of alcoholism vulnerability have not attempted to systematically ascertain whether the characteristics found in high-risk

subjects are also present in persons at risk for other psychopathological disorders including drug abuse. For example, low MAO levels may not be a specific characteristic associated with risk for alcoholism, since this finding has also been reported in other psychopathological conditions such as depression and schizophrenia (Bucksbaum et al. 1976).

Also, controlling for the presence of antisocial disorder reveals no differences in childhood hyperactivity between high- and low-risk subjects (Tarter et al. 1985b). Childhood hyperactivity has been implicated in family, high-risk, and longitudinal research to comprise one aspect of the vulnerability to alcoholism in men (Tarter et al. 1985b); however, this behavioral disposition does not appear to be specific to just an alcoholism outcome.

A particularly salient issue concerns whether the same vulnerability underlies alcohol and other drugs of abuse. Although there is a paucity of research on this issue, the available findings do indicate that alcohol and substance abusers share a number of similarities (Lang 1983). It has even been argued that there are commonalities among all disorders of excess, including gambling, sexual conduct, and drug and alcohol abuse (Orford 1985). Peele and Brodsky (1975) proposed that substance abuse is but one particular type of manifestation of an underlying vulnerability to developing a compulsive disorder.

Further evidence pointing to a certain degree of commonality among alcohol and drug abusers stems from the very high co-occurrent use of such substances (Carmody et al. 1985; Newcomb et al. 1986). It is also interesting to note that alcoholics prefer amphetamines as the second drug of choice (Cadoret et al. 1984), suggesting that the consumption of alcohol may not relate to only one specific pharmacologic effect. It is possible, although as yet empirically untested, that different drugs may be used by the same person under various circumstances in the same way that a jukebox is played to satisfy one of several different types of musical needs. Moreover, it is a well-documented clinical phenomenon that the cessation of use of one substance often results in the abuse of another. In particular, alcohol and the benzodiazepines have been linked in this regard (Vaillant 1983). Vaillant and Milofsky (1982) also report that other pathways to recovery from alcoholism are substituting smoking and candy for alcohol. These data indicate that there may be a common proclivity for substance abuse.

In summary, the available evidence indicates that alcohol and drug abusers may share a number of common characteristics, perhaps pointing to a common basis for the vulnerability. It is conceivable that there is a genetic predisposition to substance abuse, but that the particular agent abused is determined by sociocultural and economic factors as well as the availability of the substance. Also, it is quite possible that socialization factors may lead vulnerable persons to develop other types of psychopathology as well. For example, individuals with anorexia nervosa and borderline personality have higher rates of alcoholism in the

family. These individuals also show psychological characteristics similar to those of alcohol abusers (Tarter et al. 1985a). Guze (1975) has argued that hyperactivity in childhood places females at risk for Briquet's Syndrome and males at risk for antisocial personality disorder. Thus, there may be a common vulnerability, or at least a number of shared characteristics, among a variety of psychopathological disorders.

It should be pointed out, however, that appropriate studies have not, as yet, been conducted either to confirm or refute this supposition. Specifically, paradigms have not incorporated high-risk control groups that can allow for the differentiation of vulnerability characteristics associated with different types of substance abuse from those associated with other forms of psychopathology.

Vulnerability and the Environment

As used in this discussion, vulnerability denotes a characteristic that predisposes an individual to a negative outcome. Presumably, the greater the vulnerability, the lower the required impact of environmental factors to induce an unfavorable outcome. At present, however, the interaction between the type and magnitude of organismic vulnerability and environmental stressors in the development of substance abuse has not been carefully researched.

Studies are needed to clarify the organismic and environmental factors that could conjointly protect the person from an adverse outcome. Field and population studies have implicated a number of environmental variables which appear to influence both the onset and maintenance of alcohol and drug abuse. For example, peer influence, socioeconomic status, cost and availability of the substance, and demographic status all contribute to the likelihood of a child's developing a pattern of habitual drug or alcohol use. Research is needed, however, to delineate how these latter factors interact in the vulnerable person to ultimately influence the outcome.

Summary

The above brief review illustrates that there may be numerous vulnerability characteristics that exist across multiple levels of biological organization which portend future alcohol or drug abuse. These vulnerability features may be manifest either dispositionally (i.e., in the drug-free state) or specifically during drug or alcoholic intoxication. From a methodological and sampling standpoint, the identification of vulnerable individuals can be made according to empirical criteria, such as the frequently documented association of substance abuse within families, or according to some theoretical supposition regarding the physiological or psychological propensities for substance abuse. The heterogeneity of the population of alcohol and drug abusers and the fact that the vulnerability characteristics may be evident only during specific stages of an individual's life illustrate

some of the difficulties involved in elucidating the predisposition to substance abuse. Furthermore, there is the important theoretical issue concerning whether alcoholism vulnerability is distinct from the predisposition to other types of drug abuse, other forms of addictive behavior, and/or other forms of psychopathology. Finally, the micro- and macroenvironments, by providing the opportunity for an unfavorable outcome, emphasize the need for learning more about how and by what pathways the vulnerability ultimately leads to psychopathology in adulthood.

A DIATHESIS-STRESS MODEL OF ALCOHOL AND DRUG ABUSE ETIOLOGY

The above discussion illustrates that numerous variables comprising organismic vulnerability combine with a variety of environmental factors to impact on individuals in a complex fashion. A simple cause-and-effect model of alcohol or substance abuse etiology is clearly inadequate, since either a positive or negative outcome ultimately is determined by a wide range of factors and their idiosyncratic interplay within the individual. Since it is not unreasonable to conjecture that there are potentially many different pathways to either a good adjustment or, alternatively, an unfavorable outcome, an indeterminate model of substance abuse etiology can be proposed. This model asserts that there is no single necessary or sufficient causal variable underlying the development of alcohol or substance abuse. Rather, the route to a negative outcome varies within the population and is less than certain for any given individual.

Figure 1 graphically illustrates how this model relates organismic vulnerability to outcome risk. The figure depicts some of the key environmental factors which can attenuate or exacerbate the vulnerability to produce a particular degree of risk for the individual. In this model, it is important to note that the vulnerable person does not merely react passively to the environment but plays an active role in shaping his or her environment. To cite one example, it is noteworthy that a young child with a difficult temperament (Thomas and Chess 1977) is more inclined to elicit negative reactions from primary caregivers. In similar fashion, parental reaction in turn influences the child's developing behavioral repertoire and emotional adjustment. Thus, the psychological characteristics comprising the vulnerability to substance abuse should be viewed as the dispositions of an active organism that reacts to, as well as creates, environments that can potentially increase or decrease the risk for an adverse outcome in adulthood. Since temperament traits are largely influenced by genetic factors and may comprise the behavioral correlates of alcohol and drug abuse vulnerability (Tarter et al. 1985a). this example is most salient to the present discussion. If temperament contributes to vulnerability, then it would be important to examine how these traits are modified by environmental influences during infancy to produce specific personality styles that predispose to substance abuse.

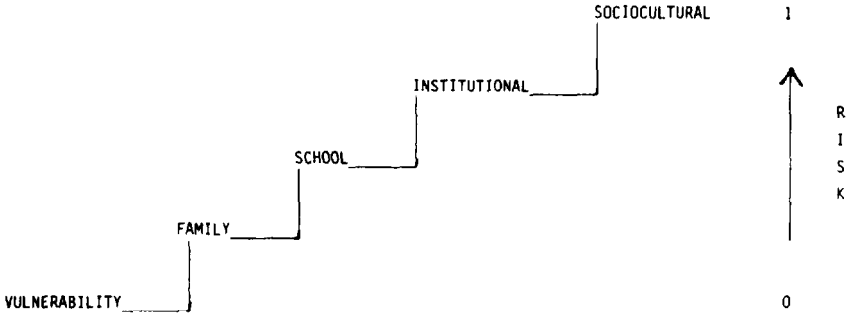

FIGURE 1. *Diathesis-stress model*

As shown in figure 1, the family is the first and probably the most important influence on the psychosocial development of the child. Numerous factors related to child-rearing style and family organization have been implicated to importantly influence the child's adjustment. These factors, operating on the vulnerable child, can thus exacerbate the vulnerability so as to ultimately augment the risk of an unfavorable outcome. For example, it is not uncommon for children of alcoholic parents to be physically abused. In one study (Tarter et al. 1984). it was shown that physically abused children obtain lower scores on tests of intellectual capacity, educational achievement, and neuropsychological capacity. It is thus not clear, however, whether the poor cognitive performance reported in children of alcoholics is due to an inherited limitation or to their disrupted homelife and other environmental factors. Additionally, parental modelling of alcohol excess and aggression, poor development of competency in school (thereby increasing the likelihood of social deviancy), low intellectual capacity (resulting in poor and maladaptive problem-solving skills), and family disorganization (resulting in the absence of an opportunity to develop appropriate social and personal values) contribute to the risk for an adverse outcome. Apart from one genetic study (Cloninger et al. 1981) and one short-term outcome study that has yet to follow the subjects into the period of maximum risk (Werner 1986), no attempts have been made to elucidate how family characteristics interact with the vulnerable child to attenuate or exacerbate the risk of an unfavorable outcome. The study by Tarter et al. (1984), however, illustrates that there are potentially numerous family influences that could substantially influence outcome.

Apart from the immediate milieu of the family, the social reference group of the child, consisting of both informal friendship patterns and formal institutional affiliations, also exercises a major influence on the development of behavioral patterns, attitudes, and values. These institutional and peer influences are embedded within the larger socioeconomic and cultural framework that contains both the symbols and sanctions regarding the appropriate and inappropriate use of drugs and alcohol. Peer influence in adolescence is an especially important factor in facilitating deviant behavior, especially nonnormative use of drugs and alcohol. Peer influences can also have a protective effect through strong negative sanction (e.g., church involvement) as well as group identification (e.g., Al-Ateen).

The period from midadolescence to young adulthood is probably the period of maximum risk for developing problems with the habitual use of licit and illicit pharmacological substances. The controlling influence of the family is diminished substantially by midadolescence, and the child is under increasingly greater influence by peers. Greater autonomy combined with some discretionary fiscal resources afford the opportunity to select the lifestyle and environment that either facilitate or diminish the likelihood of substance abuse. Depending on the work environment and social affiliations, ambivalence and implied acceptance of substance use can substantially augment the risk for an unfavorable outcome in vulnerable individuals.

Finally, it should be noted that macroenvironment controls, which regulate the sale and distribution of alcohol and drugs, can also exert an effect on outcome. For example, while Prohibition was not a popular policy for eliminating alcohol consumption, it did reduce the incidence of liver cirrhosis. Thus, it appeared to attenuate some of the problems associated with chronic and excessive use of alcohol.

In conclusion, biological or behavioral vulnerability alone does not necessarily culminate in an unfavorable outcome. Rather, numerous environmental variables interact with the vulnerable person to determine the magnitude of risk. However, it is reasonable to conjecture that the greater the vulnerability, the less the environmental stress required to produce an unfavorable outcome. As yet, studies of high-risk samples, attempting to elucidate the sequential events that occur during psychosocial development to maximize the risk for alcoholism or drug abuse in adulthood, have not been conducted. Moreover. studies are needed to clarify why certain vulnerable individuals are able to avoid a negative out: come in adulthood, which is of great importance from the standpoint of prevention intervention.

ADVANTAGES AND DISADVANTAGES OF THE HIGH-RISK PARADIGM

Results obtained using the high-risk paradigm do not predict or provide an estimate of the risk for an adverse outcome. They

merely differentiate individuals, with varying degrees of specificity, according to some putative dimension. Risk, as noted previously in this discussion, must be viewed in the context of numerous subject characteristics interacting with various environmental parameters and determined only upon longitudinal follow-up. Definitive conclusions about alcohol and drug abuse etiology are not, therefore, obtainable by the use of the high-risk paradigm alone. The high-risk research strategy, however, has several noteworthy advantages and disadvantages which were reviewed by Schuckit (1985b).

The advantages include:

- Subjects can be recruited from the nonclinical population; thus, problem behaviors or other features of the vulnerability can be studied in persons who have not been affected by treatment interventions.

- Used in conjunction with a prospective longitudinal study, the high-risk paradigm can potentially reveal the predictors of outcome and determine how vulnerability and environmental variables interact to ultimately influence the outcome.

- The high-risk paradigm enables unequivocal demonstration of whether certain characteristics of alcoholism or drug abuse may in fact presage the condition. (For example, low MAO levels, antisocial tendencies, a field-dependent perceptual style, and learning and memory problems are among the reported characteristics associated with alcoholism; however, whether these characteristics, implicated to comprise alcoholism vulnerability, fully or partially antedate drinking onset, or are the consequence of alcohol abuse, remains unsettled.)

The disadvantages include:

- Without conjointly conducting a high-risk and longitudinal study, it is not possible to ascertain whether any variable discriminating high- from low-risk subjects is actually related to outcome.

- The high-risk approach yields correlative, not causal, associations between vulnerability characteristics and outcome.

- It is difficult to document or control for serendipitous environmental events in tracking the pathway to a negative outcome.

- It is difficult to control for the effects of psychiatric illness in second-degree relatives, the effects of assortative mating, verifying the pedigree, and a host of other relevant factors that could substantially influence the results obtained.

SOCIAL AND CLINICAL APPLICATIONS OF THE HIGH-RISK PARADIGM

Prevention interventions can be targeted specifically to the population at known heightened risk rather than to the whole population. Prevention, which currently consists of general didactic interventions, could be directed specifically at identified features of the vulnerability. Once the vulnerability characteristics are revealed, the effectiveness of treatment interventions for already affected persons may be markedly improved. For instance, high activity level during childhood may predispose to alcoholism. Studies suggest that stimulant medication may be therapeutic for both high activity level and some forms of alcoholism (Wood et al. 1976).

SUGGESTED DIRECTIONS FOR FUTURE RESEARCH

A major, if not central, issue concerns delineating both the general as well as the specific aspects of childhood vulnerability that predispose to an adverse outcome. In carrying out such research, a multidisciplinary theory-driven strategy is essential that not only distinguishes children at high risk for alcohol and substance abuse from normals, but also from groups of other children at risk for other psychopathological disorders. In this regard, research should be broadly based to include subjects at high risk, but who eventually make a successful adjustment. Thus, by combining the risk paradigm with prospective longitudinal research, the pathways to both positive and negative outcomes can be determined.

Attention should be given to special groups. For example, neonates afford the opportunity to learn about genetic factors that are relatively unaffected by environmental influences. Low-risk groups can yield valuable information about the factors which could protect the person from an adverse outcome. To this end, cross-cultural studies should be very informative in clarifying both the dimensions of vulnerability and the dynamic interplay of factors which determine ultimate risk status.

Finally, a reevaluation of alcohol and drug abuse research at the national policy level is recommended. To determine whether there are distinct features that differentiate children at risk for alcoholism from those at risk for substance abuse as well as from children at risk for other psychopathology requires a stable source of multi-institute funding. Perhaps a national center could be targeted for such research that derives support from the various agencies having a stake in these problems--specifically, the institutes within the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and the National Institute of Child Health and Human Development. In this fashion, comprehensive and coordinated research into the early identification and prediction of outcome in children at high risk for alcohol and substance abuse can be conducted most efficiently.

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Personality Factors in Drug Addiction

James N. Butcher

INTRODUCTION

The question as to whether there is an addictive personality has been addressed many times in the past. Ancient writings give clear awareness of the idea of an alcoholic personality, with the implication that the condition was hereditary. For example, Plutarch (Langhorne and Langhorne 1853) observed that "Drunkards beget drunkards." Writings during the 19th century commonly emphasized the hereditary nature of alcoholism and the importance of personality factors and personal deterioration in drunkenness (Gustafson and Gustafson 1888).

In spite of the fact that elements of character have long been considered instrumental in the development of addictive problems, evidence for an "addictive personalty" pattern has heretofore eluded researchers. The idea that a unitary set of personality factors precedes and results in the development of addictive disorders has not been widely accepted in alcohol and drug treatment research and theory (Syme 1957; Sutherland et al. 1950; Jellinek 1960). The failure to isolate a personality pattern that is consistently associated with eventual development of drug or alcohol problems has caused some researchers to minimize any causal role for personality factors in substance abuse.

The fact that a causal link between a unitary "addictive personality" and the development of drug and alcohol problems has not been consistently identified, however, does not eliminate personality factors from the causal chain. There is a great deal of evidence to indicate that personality factors play an important part in understanding patterns of addiction. A number of recent researchers have noted relationships between personality factors, especially personality disorders, and alcohol and drug addiction (Khantzian and Treece 1985; Hesselbrock et al. 1985; Kosten et al. 1985; Cook and Winoker 1985). In a recent review of the literature on personality disorders and alcoholism/drug abuse, Grande (1984) reported that from 75 to 80 percent of the studies surveyed showed a positive association among the three conditions. He

concluded that a common etiological matrix predisposes one to behaviors that are diagnostic of the three conditions. The personality factors that appear central to the three conditions were: Impulsivity, failing to inhibit behavior that previously led to negative consequences, and placing value on immediate drug effects (e.g., intoxication) over long-term consequences (e.g., liver damage).

A number of recent studies have pointed to genetic factors in personality. For example, Bouchard (1984) found that twins reared apart had substantial similarities in personality. In particular, personality characteristics such as introversion-extraversion, impulsiveness, dominance, and flexibility showed high heritabilities.

PROBLEMS IN ASSESSING PERSONALITY CHARACTERISTICS

Part of the reason for the generally poor showing of personality factors in substance abuse is that rigorous longitudinal personality research is extremely difficult to conduct. Research examining the premorbid personality of alcohol or drug abusers has been marked with numerous methodological problems. For example, it is difficult to obtain an accurate premorbid picture of personality characteristics using only measures administered at a single point in time during the adult years. Retrospective research designs do not allow us to know what the individual personality was like prior to the abuse. Additionally, measuring personality during an episode of alcohol- or drug-abusing behavior is fraught with problems, since the instruments are likely to reflect situational problems in addition to other personality factors.

In contrast, prospective studies in which personality factors are measured early in the individual's life and followed up after the addictive disorder has developed have been rare and problematic. Also, they have been hindered by the scarcity of standardized measures applicable to both adolescent and adult subjects. Also, longitudinal studies measuring preaddiction personality characteristics are problematic in that, even if it were possible to conduct prospective studies, there are few reliable and valid personality measures that would provide usable information across time.

Several studies have employed objective personality measures (e.g., the Minnesota Multiphasic Personality Inventory (MMPI)) and found personality characteristics associated with later addiction (Hoffmann et al. 1974; Kammeier et al. 1973; Loper et al. 1973).

PERSONALTY AND ALCOHOL AND DRUG ABUSE

The salience of personality factors in alcohol- and drug-abusing populations is well documented. A recent review of the MMPI research in alcohol- and drug-abusing populations (Graham and Strenger, in press) shows that the extensive use of the MMPI in predicting alcohol and drug abuse problems results from its

considerable power to differentiate these individuals in clinical settings. Several MMPI indices have been found to be successful at detecting alcohol and drug abuse problems.

A large number of studies using the MMPI have found a strong association between personality factors and addiction. These studies reported personality correlates of addiction as measured through MMPI clinical scales, profile patterns, and special scales developed to assess patterns of addiction. An overview of MMPI findings in addictive behavior documents the relationship between measured personality characteristics and addiction.

Early work on MMPI Scale 4 (Psychopathic Deviance) documents the relative elevation of this scale among groups of alcoholics (Hewitt 1943; Graham, unpublished manuscript; Button 1956; Hoyt and Sedlacek 1958; MacAndrew and Geertsma 1963; MacAndrew 1978).

Several MMPI code types have been related to patterns of addictive behavior (Gilberstadt and Duker 1965; Marks and Seeman 1963; Schroeder and Pierce 1979).

Several studies have documented that MMPI profile characteristics, found through multivariate clustering methods, are associated with addictive disorders (Goldstein and Linden 1969; Whitelock et al. 1971; Nerviano and Gross 1983).

Special scales for assessing addiction patterns have been developed. The most promising of these is the MacAndrew Scale (MacAndrew 1965; MacAndrew 1967; MacAndrew 1979; MacAndrew 1981; Sher and McCrady 1984; Schwartz and Graham 1979).

In summary, research on alcohol- and drug-abusing populations with the MMPI has shown several MMPI-measured personality characteristics to be associated with the manifestation of substance abuse. It is probable that some aspects of this characteristic personality pattern are reactive to the disorder. However, the available evidence suggests that certain personality characteristics probably precede the development of the disorder.

The MMPI is being restandardized at this time by James Butcher (University of Minnesota), Grant Dahlstrom (University of North Carolina), and Jack Graham (Kent State University) in order to provide more relevant contemporary norms with a revised and expanded item pool that reflects more substantially the clinical problems currently being encountered.

With regard to assessment of problems of addiction, a number of new items dealing with alcohol and drug abuse (including prescription medications were included alona with a number of items dealing with treatment potential and comclipliance. In the Adult Version of the MMPI, the 154 new experimental items were added to assess several areas of psychopathology not well represented in the original version of the test. In addition, a number of items were included that showed promise for measuring treatment amenability

and change. These additional items were selected through a broad sampling of views of MMPI experts in order to determine needed coverage in other content domains.

Several studies are presently under way to evaluate the effectiveness of the revised version of the MMPI with alcohol- and drug-abusing populations. McKenna and Butcher (in preparation) have conducted an extensive study of approximately 1,300 alcoholics and drug abusers at the Hazelden Center in Centre City, MN. The performance of this population on the revised version of the MMPI was compared to that of a sample of abusers from the same center 10 years before (McKenna and Pickens, unpublished manuscript). The study demonstrated the continuity of the MMPI for assessing alcohol and drug abuse personality factors. In the future, the experimental items on the revised version of the MMPI will be used to determine if alcohol and drug abuse problems can be more accurately detected with a revised addiction scale.

Adler and Butcher (in preparation) have begun an extensive study of personality factors in alcohol- and drug-abusing adolescents. This study is aimed at exploring personality factors noted in early involvement with drugs and alcohol. Information related to the actuarial description of MMPI alcohol and drug problem types is being collected. The revised MMPI item content, relevant to assessment of adolescent problem behavior, will be used to develop an adolescent addiction proneness scale.

SUMMARY

In spite of the fact that past research has not found a unitary concept of an "alcoholic personality," personality factors have been found to be important in the development of alcohol abuse disorders. Personality characteristics measured by the MMPI, particularly the Pd scale and the MAC scale, have been shown to be related to the development of alcohol abuse disorders. Research is currently under way to explore the ability of the revised version of the MMPI to detect and describe problems of alcohol abuse.

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Individual Differences in Drug Response

James R. Wilson

INTRODUCTION

In mainstream psychology, it is not yet quite proper to hypothesize that genetics may contribute something to behavior. It does not seem to be illegal to do so, merely indecent. This remnant of radical behaviorism is still with us and still influential. However, the constraints on thought of considering only environmental causation are being loosened, and some of us can admit, even in public, that we are behavioral geneticists by trade.

The term behavior(a1) genetics (BG) may go too far the other way. Do we now claim that all behavior is to be traced to genetics and only genetics? I think the answer is "no." Of the hundred or so behavioral geneticists I know, all seem to believe in the existence of the environment. In fact, genetically informative experimental designs are often environmentally informative as well, at least in the sense that the proportion of variance attributable to environmental factors is routinely estimated from BG designs.

In alcoholism research, there is persuasive evidence from Kaij (1960; Kaij 1972), Goodwin et al. (1973; Goodwin et al. 1974; Goodwin et al. 1977). Schuckit (1980; Schuckit 1981; Schuckit 1984; Schuckit 1985), Schuckit and Rayses (1979). Schuckit et al. (1985), Cloninger et al. (1979; Cloninger et al. 1981), and others that genetic variation contributes to the expressed variation in alcohol abuse and/or alcoholism. The mechanisms that mediate vulnerability to alcoholism may include differential sensitivity or differential development of acute tolerance to alcohol, with the supposition that those relatively insensitive to alcohol would be at greater risk for increasing the amount they imbibe, thereby increasing their risk for alcohol abuse.

The present paper will report on some of the large individual differences in sensitivity to ethyl alcohol from an ongoing BG study. Though genetic and environmental parameter estimation will have to await completion of data collection (in about 1 more year), this paper will describe the research design used in the study. It is

important to note that similar strategies may be employed in the study of individual differences in response to a variety of drugs.

METHODS

To further our understanding of the genetic architecture that might be involved in the development of substance abuse, the present study is recruiting "normal drinkers" in subject pairs from the following groups: 50 pairs monozygotic (MZ) twins (within-pair differences are environmental); 50 pairs dizygotic (OZ) twins (differences are both genetic and environmental); 50 pairs nontwin siblings (to test "special twin environment"); 50 pairs unrelated, reared in the same family (adoptees) (common family environment; no genetic variance in common); 30 retest subjects (to estimate repeatability of tests); and 20 placebo controls (to estimate practice/fatigue effects). Thus, upon completion of the study, 450 individuals will have been tested. At present, individual 12-hour alcohol tests have been administered to over 300 persons, and computer files exist with over 1,000 individual measurements for 290 of these people.

Estimation of various genetic and environmental parameters underlying responses to alcohol is facilitated by this experimental design. For example, an MZ twin pair shares all genes plus common family environment. Thus, the degree to which members of a pair are alike reflects these components; the degree to which they are unlike must be attributed to aspects of the environment which have been different for members of the pair. The adoptee pairs, on the other hand, have no genetic variance in common but, having been reared in the same home, may resemble each other due to common environmental influence. For pair resemblances in each group, intraclass correlations ($\underline{t}$) are computed for measures that have a continuous or quasi-contiiiuous distribution. Using Falconer's (1981) method as an example, heritability (broad sense) for a trait may be estimated by doubling the difference between the MZ and DZ $\underline{t}$s. This follows from:

$$\underline{t}_{MZ} = [V_A + V_D + V_{E(c)}]/V_P$$

$$\underline{t}_{MZ} = [1/2\ V_A + 1/4\ V_D + V_{E(c)}]/V_P$$

$$2(\underline{t}_{MZ} - \underline{t}_{DZ}) = [V_A + 6/4\ V_D]/V_P \cong V_G/V_P = h^2$$

In practice, the genetic and environmental parameter estimates are obtained by using information from all groups simultaneously and using iterative, maximum-likelihood statistical packages such as LISREL or MINUIT on a high-speed computer.

In addition to screening prospective participants for the genetic relationships listed above, volunteer subjects must also meet the following criteria: (a) report that they drink alcohol at least once per month; (b) report no alcohol or drug abuse problems; and

(c) report no medical contraindications to dosing with alcohol. The subjects are asked to report to the testing laboratory at 8 a.m., with the expectation of remaining until 8 p.m. A summary of the testing day is shown in table I. Three test sessions were completed prior to alcohol dosing (0.8 gm/kg), and three post-alcohol test sessions were completed while blood alcohol level (BAL) was held near 100 mg/dl for 3 hours via supplemental alcohol doses.

TABLE 1. *Summary of the testing day*

Time	Activity
0800	Interview; Raven and Vocabulary tests; light breakfast
0900	Test Session 1 (Pre-1)
1000	Test Session 2 (Pre-2)
1030	Cortical evoked response (CER baseline)
1045	Test Session 3 (Pre-3)
1115	Alcohol dose (0.8 gm ethanol/kg body weight)
1140	Test Session 4 (Post-1)
1220	Cortical evoked response (CER sensitivity)
1240	Supplemental alcohol (to hold 100 mg/dl BAL)
1250	Test Session 5 (Post-2)
1340	Supplemental alcohol
1350	Test Session 6 (Post-3)
1420	Lunch in the laboratory
1450	Subject rests; tester scores and enters data
1630	Cortical evoked response (half-peak BAL)
1640	Test Session 7 (half-peak BAL)
1710	Subject rests
2000	Subject leaves, if BAL < 20 mg/dl

For most subjects, this schedule is quite accurate. However, given individual differences in metabolic clearance rates for alcohol, there is variability in time for the half-peak BAL tests and for being allowed to leave the laboratory.

The measurements taken during each test session included: Body temperature, systolic blood pressure, diastolic blood pressure, pulse rate, the Body Sway (Eyes Open) Test, the Body Sway (Eyes Closed) Test, the Hand Steadiness Test, the Sequence Memory Test (Simon game), the Pursuit Rotor Test (hand-eye coordination), the Visual Acuity Test (Snellen), the Perceptual Speed (Written) Test, the Cancellation Speed Test (clerical speed), the Sentence Completion Test (logic), the Card Rotations Test (spatial ability), the Reaction Speed (Written) Test, the Block Rotations Test (spatial ability), reaction and movement time (1 light, 10 trials), reaction and movement time (4 lights, 10 trials), reaction and movement time (8 lights, 10 trials), the Rail-Walking Test, the Dowel-Balancing Test, Space Armada game score, and the Profile of

Mood States Test. Test descriptions and procedures are discussed more fully in Wilson and Plomin (1985).

RESULTS AND DISCUSSION

For the present study, the administered alcohol dose was meant to bring BAL to 100 mg/dl, on average. The mean BAL curve is shown in figure 1. As can be seen, the obtained average is nearer 95 mg/dl. Also, there are wide individual differences in peak BAL (from 70 to 130 mg/dl), apparently as a result of differences in rate of absorption, rate of clearance, and volume of distribution.

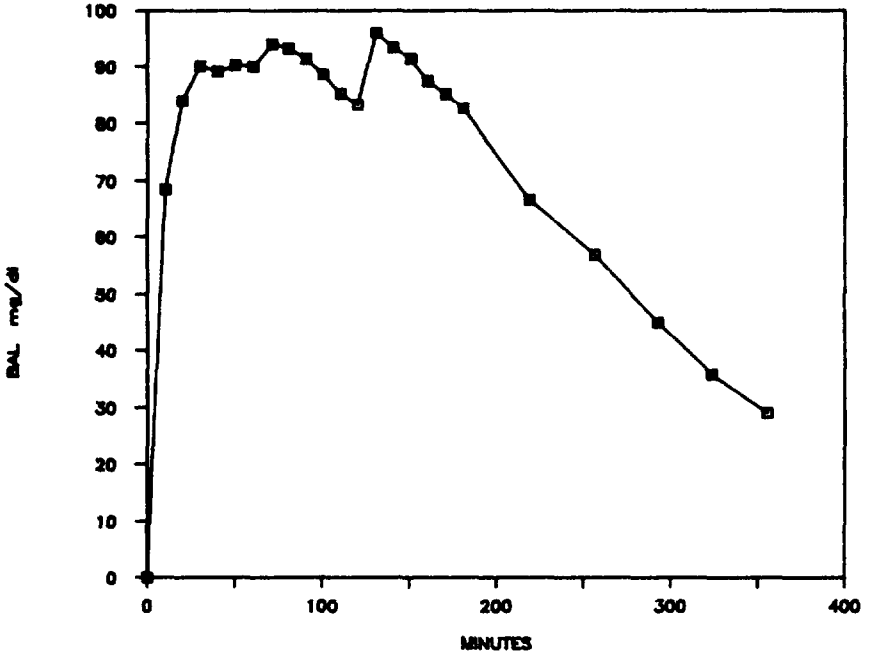

FIGURE 1. *Mean blood alcohol level (BAL)*

NOTE: The initial dose, given in the 15 minutes prior to Time 0, was 0.8 gm ethanol/kg body weight. Small "topping up" doses were given at 60 minutes and 120 minutes in an attempt to maintain the BAL of each individual near the initial peak BAL for 3 hours, for tests of acute behavioral tolerance to ethanol (ABTE).

However, the "topping up" doses are meant to keep an individual as near his/her initial peak BAL as possible, so that the initial effects of alcohol can be compared to the effects after 3 hours at about 100 mg/dl BAL in order to measure acute behavioral tolerance to ethanol (ABTE) (Wilson et al. 1984).

An individual BAL curve is shown in figure 2. The 0.8 gm/kg dose of alcohol was administered during the 15 minutes prior to Time 0 on the graph. For most people, this amounts to 4 to 6 bar drinks taken during a 15-minute period. BAL estimates, derived from breath samples with an Intoxilyzer, are taken every 10 minutes for 3 hours and every 30 minutes thereafter. Test Session 4 (Post-1) begins 10 minutes after the end of dosing and, for most people, spans the later parts of the absorption phase, up to and including the initial peak BAL. "Topping up" doses are administered at 60 minutes and again at 120 minutes to try to maintain a relatively constant BAL for a period of 3 hours. The Post-2 and Post-3 tests follow 10 minutes after each "topping up" dose. From these curves, several parameters are derived, including: Time-to-peak BAL (measure of absorption time), peak BAL (measure of volume of distribution), Beta60 (linear rate of clearance), and relative volume of distribution (Widmark r). Linear extrapolation of the Beta60 (Wilson and Erwin 1983) line to the Y-axis yields what Widmark called the "instantaneous dosage" estimate (C_0). I am

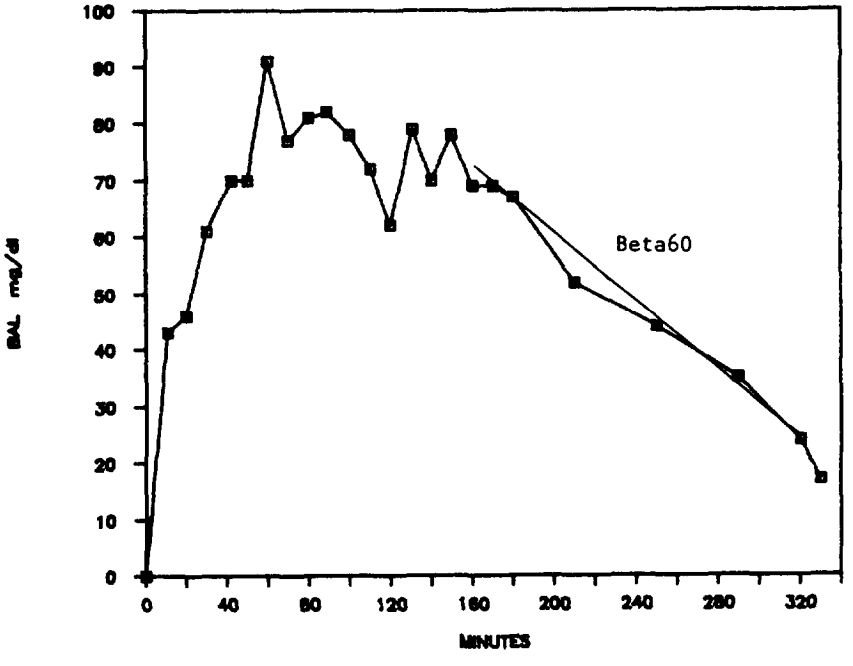

FIGURE 2. *An individual blood alcohol level (BAL)* plot

NOTE: From the BAL data from each individual, the linear clearance rate (Beta60), the "instantaneous dosage" (C_0), and the relative volume of distributlon (Widmark r) were estimated.

currently attempting to refine this estimate, using the area under the curve rather than the somewhat exaggerated area Widmark used (Wilson, in press). A better instantaneous dosage estimate will yield better estimates for the apparent volume of distribution and the Widmark r.

A plot of mean body sway (eyes closed) across the seven test sessions is shown in figure 3. Test session is shown on the abscissa, and mean score or measurement is shown on the ordinate. The placebo control group mean (n=21) is plotted with pluses, and the alcohol group (n=269) is plotted with squares. Consonant with the literature, there is an average decrement in performance, as indicated by the increase in sway after dosing. The mean change-score at Test Session 4 (Post-1) is a typical indicator of sensitivity. If performance improves from Test Session 4 (Post-1) to Test Session 6 (Post-3), the test shows acute behavioral tolerance effects (ABTE). An immediate criticism, though, is that practice effects might lead to the improvement. Therefore, for an estimate of ABTE, we need to compare the slope of improvement in the experimental group with the slope of improvement in the control group.

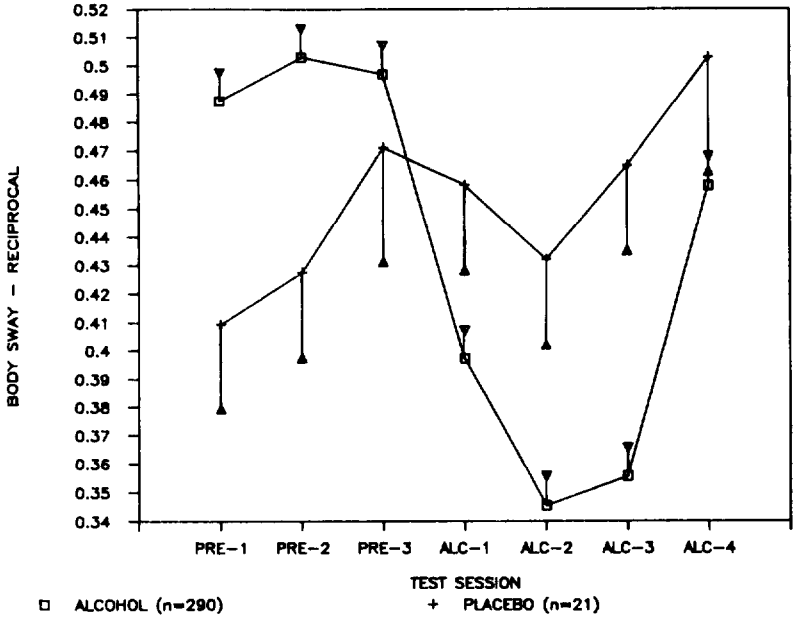

FIGURE 3. *Body Sway (Eyes Closed) Test*

NOTE: Means and standard errors were computed from the reciprocal of inches of sway for each individual, so more sway is Indicated by a lower score.

In practice, the relative sensitivity score for each person on each test is determined by computing the standardized residual from linear regression of each person's Post-1 score on his/her baseline score (where the baseline score is an average of the Pre-2 and Pre-3 scores) after correction for control group scores at Post-1 and baseline. Then a computer can sort subjects on the basis of sensitivity score, arranging subjects from most to least sensitive on each function. This method of computing sensitivity scores is based on a recommendation by Cohen and Cohen (1975), and the methodology used is explained more fully in Nagoshi et al. (1986). The method has several advantages over the difference scores (pretest score minus posttest score) or ratio scores (posttest/pretest), which have often been employed as a means of taking into account the large preexisting individual differences in abilities.

Figure 4 shows mean reaction time over the seven test sessions. Mean sensitivity to alcohol on this function can be seen from the increase in reaction time after dosing. What might be ABTE can also be seen from the decrease in reaction time between the Post-1 and Post-3 tests while BAL has been held near 100 mg/dl. The slope in this interval appears to be different from that for the

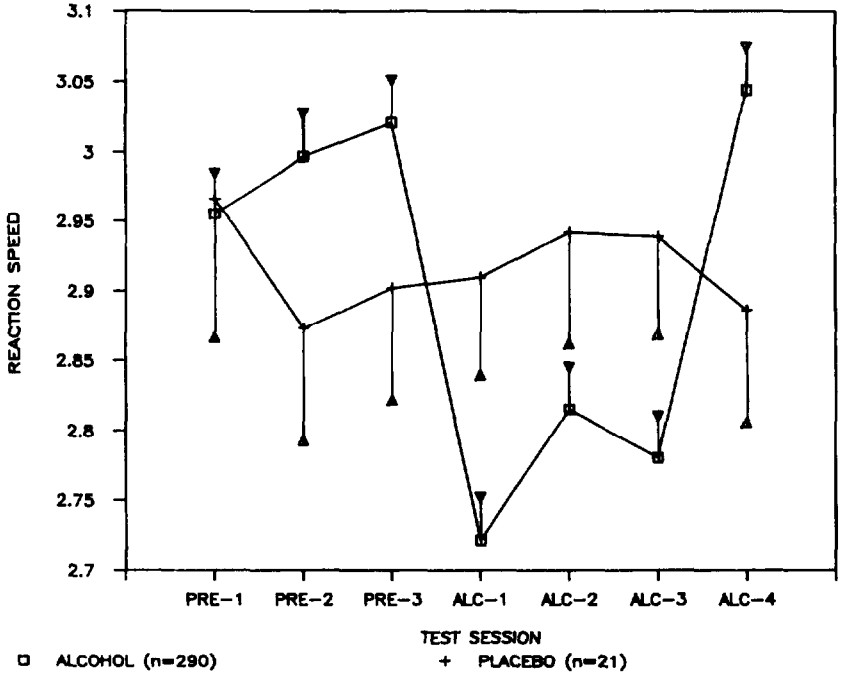

FIGURE 4. *Reaction Speed Test (single stimulus light)*

control group, so practice effects are not a likely alternative explanation. In actuality, a relative ABTE score for each individual on each test is obtained by computing the standardized residual from linear regression of the Post-3 scores on the Post-1 scores after correction for the control group scores at Post-3 and Post-1. This procedure is also explained more fully in Nagoshi et al. (1986). Analogously, total tolerance ("delayed sensitivity") is obtained as the standardized residual from regression of Post-3 scores on baseline and control group Post-3 and baseline scores.

Figure 5 shows mean pursuit rotor scores across the seven test sessions. This test shows a strong practice effect, as can be seen from the increasing scores for the control group. Despite this practice effect, the sensitivity effect can be easily visualized from the drop in the mean score for the alcohol group at Post-1 testing. It is also clear that the minor improvement seen at Post-3 testing is probably due to practice, not ABTE. Parenthetically, it may be noted that on this test (and most others), the function beinq measured has recovered almost completely by

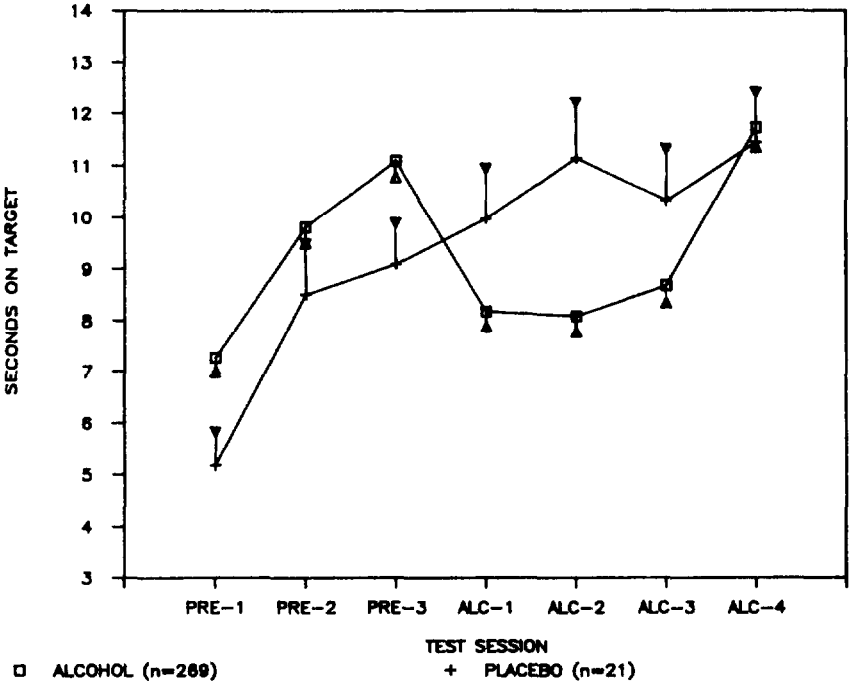

FIGURE 5. *Pursuit Rotor Test*

NOTE: A consistent affect of practice can be seem from the increase In scores Over test sessions. The small increment in mean scores for the alcohol-treated group between Alc-1 and Alc-3 is not significant.

Post-4 testing, although BAL at this time for most people is still typically about 50 mg/dl. This is another indicator of acute tolerance to ethanol, after possible practice effects are taken into account.

The intent of the preceding figures was not to belabor the well-established fact that ethanol generally depresses function, but rather to outline the methodology of obtaining standardized sensitivity and tolerance scores for individuals. These are the individual differences that will figure prominently in the planned maximum-likelihood analyses to obtain genetic and environmental parameter estimates of responses to alcohol. As indicated earlier, the study is not complete; therefore, these estimates cannot be given now. However, some of the obtained individual differences will be highlighted below.

For example, table 2 (from the Hawaii Alcohol Study (Wilson et al. 1984)) describes the percentage of individuals showing an improvement rather than a decrement during the sensitivity testing period. These numbers are simply the percentages of subjects who improved (from their baseline performance) during testing after alcohol dosing. No correction for practice has been made. While some of these tests show practice effects, others do not. In this latter group, it is apparent that gains from practice are possible even while at 100 mg/dl BAL, and the expectation of a performance decrement does not hold for all individuals.

TABLE 2. *The percentage of Subject who show improvement in test score during alcohol-sensitivity testing*

Test	Percent
Dowel-Balancing	30
Rail-Walking	19
Body Sway (Eyes Open)	41
Body Sway (Eyes Closed)	26
Reaction Time	34
Sentence Completion	21
Card Rotations	30
Cancellation	19
Colorado Perceptual Speed	4
Hand Steadiness	20
Tapping Speed	33
Iconic Memory	34
Pursuit Rotor	17
Apple Invader	28

SOURCE: Wilson et al. 1984. Copyright 1984, the American Medical Society on Alcoholism and Other Drug Dependencies, the Research Society on Alcoholism.

Table 3 shows the proportion, by test, of the alcohol-treated group which equalled or exceeded the average of the placebo control group at Test Session 6 (Post-3). If a BAL of about 100 mg/dl for 3 hours had no effect, we would expect the proportions to be about 50 percent. As they stand, they indicate the percentages, by test, of people at 100 mg/dl who performed the test as well as an average sober person who also had five practice trials during the preceding several hours. These results exemplify the difficulty of discriminating those with a BAL of 100 mg/dl from those with a BAL of zero via roadside sobriety tests.

TABLE 3. *Proportion of the alcohol-treated* group *which equalled or exceeded the placebo control group mean at Test Session 6*

Measure	Percent
Systolic blood pressure	61 (lower)
Diastolic blood pressure	58 (lower)
Pulse rate	39 (lower)
Visual Acuity Test	47
Rail-Walking Test	27
Dowel-Balancing Test	18
Pursuit Rotor Test	31
Hand Steadiness Test	40
Space Armada	29
Body Sway (Eyes Open) Test	41
Body Sway (Eyes Closed) Test	29
Perceptual Speed Test	29
Cancellation Speed Test	43
Sentence Completion Test	53
Card Rotations Test	43
Block Rotations Test	34
Reaction Speed (Written)	49

Figures 6 and 7 have two purposes. First, they illustrate, using frequency histograms, the visual appearance of two of the obtained score distributions which had statistically different means. Second, they describe two individuals within the histograms who responded very differently at different stages of alcohol metabolism.

In figure 6, for all three panels, the rail-walking score is on the abscissa, and the frequency or proportion of people obtaining that score is on the ordinate. The lowest panel is a histogram of score frequency at baseline (prealcohol). The middle panel is a frequency plot of scores immediately after alcohol (sensitivity testing). Both an increase in dispersion and a relatively small shift in mean can be noted. The top panel is a frequency plot

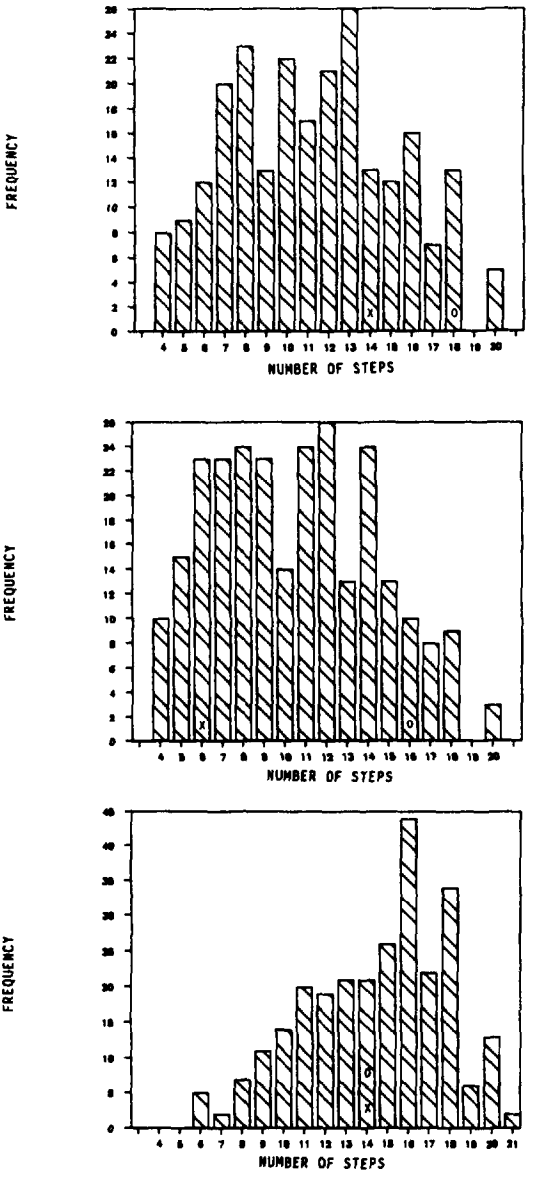

FIGURE 6. *Frequency histograms of rail-walking scores from the alcohol-treated group*

NOTE: The bottom panel includes baseline (prealcohol) scores, the center panel includes scores obtained 10 to 30 minutes after alcohol doslng (sensitivity testing), and the top panel includes scores taken after BAL was maintained near 100 mg/dl for 3 hours. (See text for explanation of X end 0 symbols.)

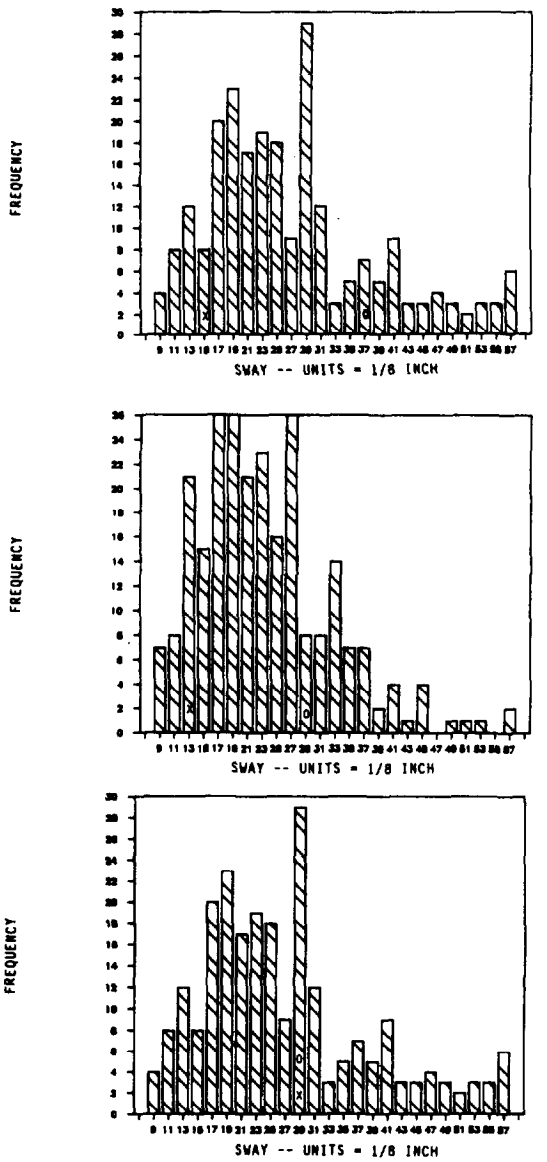

FIGURE 7. *Frequency histograms for Body Sway (Eyes Closed) Test*

NOTE: The panels are arrayed as in figure 6. (See text for explanation of X and O symbols.)

after 3 hours at a BAL of about 100 mg/dl (for tolerance estimates). Note the individuals marked X and O who were chosen as being near the mean at baseline. During sensitivity testing (middle panel), X proves to be very sensitive, while O is not. During ABTE testing, X has recovered function, and O is actually above his/her baseline score.

In figure 7, a similar comparison of score distributions before and after alcohol is shown for body sway. Again, note the increase in dispersion after dosing and the differential shift within the distributions of individuals X and O. Body sway shows little tolerance effect and thus may be a useful roadside test. Of course, some apparatus for measurement accuracy may be needed, and comparison O BAL sway scores are not usually available.

SUMMARY AND CONCLUSIONS

In conclusion, there seem to be large, pervasive individual differences before and after dosing with ethyl alcohol. As estimates for sensitivity and tolerance to alcohol imply a change from a previous measurement, regression procedures were used to obtain sensitivity and acute tolerance scores for each subject on each test. It seems likely that this regression procedure would be equally applicable for estimation of sensitivity and tolerance to any other drug.

With the quantitative behavioral genetic design being employed, it will be possible to partition the sensitivity and tolerance variances into genetic and environmental components. These estimates of the relative contributions of genes and environment should prove useful in risk estimates of alcohol abuse for individuals and perhaps will facilitate attempts to ameliorate the effects of alcohol abuse.

It is encouraging that NIDA is focusing some of its attention toward the study of biological vulnerability to drug abuse. The careful use of quantitative behavioral genetic designs in studies of drug use and drug response will, when such designs are feasible, yield a more complete picture of the genetic and environmental bases for drug abuse than would studies which do not include a genetic component. Admittedly, cohort differences in drug availability may make parent/offspring designs unfeasible (i.e., the drug may not have been available a generation ago). However, parent/offspring designs which involve a correlated character (e.g.,) sensation seeking) or a biochemical measurement may prove useful.For example, the "high" stimulated by some drugs may reflect adrenal medullary activation, and this could be assessed by measurement of blood epinephrine and norepinephrine. Also, behavioral genetic designs which involve twins, siblings, and adoptees should be directly applicable to studies of drug use and effects, as the subjects are either the same age or can be chosen within certain age limits. These designs would largely avoid undesired cohort effects, such as the unavailability of certain

drugs a generation ago, yet would yield estimates of genetic and environmental influences on drug use or drug response.

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ACKNOWLEDGMENTS

The support of NIAAA grant AA-03527 and Biomedical Research Support grant RR-07013-20 is gratefully acknowledged. In addition, it is a pleasure to acknowledge the fine collaboration on this project of Professor V. Gene Erwin, School of Pharmacy, University of Colorado; Professor Robert Plomin, who is at the Center for Advanced Study in the Behavioral Sciences in Palo Alto, CA, this year, and then will be taking up his new position at Pennsylvania State University; and Dr. Craig Nagoshi, who is a NIDA postdoctoral fellow working on the project.

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The Role of Psychopathology in the Familial Transmission of Drug Abuse

Bruce J. Rounsaville

INTRODUCTION

Since there is some evidence that alcoholism and/or drug abuse are transmitted in families (e.g., Goodwin 1976), the next question is, What is being transmitted? To identify the mechanism of transmission, two models have been formulated. In the first, the familial pattern of inheritance may be the result of drug-related factors (i.e., related to mechanism of action or metabolism of the substance). In this case, the familial-transmitted factor may be broad (e.g., especially high level of positive reinforcement from psychoactive substance use) or narrow (e.g., special sensitivity to specific classes of drugs such as sedatives or stimulants).

The alternative hypothesis is that familial clustering is the result of factors not directly related to drug use. For example, drugs may be more accessible to individuals with drug-abusing parents, thereby making it more likely that they will also use drugs. Another possible class of familial-transmitted factors that may predispose to substance abuse is psychopathology. In this case, symptoms of another psychiatric disorder (e.g., depression) predispose an individual to drug abuse. For example, drug abuse may arise from a need to use drugs to reduce anxiety and/or depression.

Identification of the familial transmission mechanism of drug abuse, however, does not resolve the issue of the relative contribution of genetic and environmental factors in the etiology of the disorder; both biological and/or behavioral factors may contribute to the mechanisms described above. For example, if drug abuse arises from self-medication of depression, then it would be important to determine the etiology of the depressive symptoms.

The purpose of this chapter is to describe evidence that might suggest that psychopathology is being transmitted in the families of substance abusers and that it is an underlying cause of some forms of substance abuse. Other chapters will cover evidence for more direct familial predispositions to substance abuse per se.

In considering the different models for familial transmission of substance use disorders, it should be noted that (a) the models are not mutually exclusive, so there can be multiple familial-transmitted pathways to substance abuse (e. g., depression plus or minus variants in opioid receptors), and (b) the population of substance abusers is likely to be heterogenous, so, for example, some may have become substance abusers because of familial predisposition to antisocial personality, others in relationship to a familial predisposition to depression, and still others with no familial predisposing factors whatsoever (Rounsaville et al. 1982a).

To support the hypothesis that psychiatric disorders are transmitted in the families of substance abusers, and this transmission is related to the substance abuse, there should be evidence of several kinds: (a) increased rates of psychiatric disorders in substance abusers; (b) increased rates of substance abuse in individuals with other psychiatric disorders; (c) increased rates of psychiatric disorders in the families of substance abusers and a more than expected co-occurrence of the two types of disorders within the families; and (d) increased rates of substance abuse in the families of those with the hypothetically related psychiatric disorders, showing a more than expected co-occurrence of the two types of disorders in the same family members.

COEXISTENT PSYCHIATRIC DISORDERS IN SUBSTANCE ABUSERS

At present, the best information on associated psychopathology in nonalcoholic substance abusers has been obtained with opioid addicts. Since my research has also focused primarily on opioid addicts, the present paper will, to a large extent, focus on this disorder. It should be noted, however, that problems and strategies encountered in the study of opioid addicts will be applicable to the study of other types of drug abuse as well.

In research evaluating psychopathology in abusers of different classes of psychoactive substances, it is sometimes assumed that the associated psychopathology will be different for various drug classes. Moreover, many studies evaluate familial transmission of a predisposition to specific forms of substance abuse (e.g., cocaine abuse). This implies that transmission may be distinct for the different classes of drugs, making it harder to evaluate whether a more general transmission of substance abuse is taking place. In fact, polysubstance abuse is the rule rather than the exception, a finding that broadens the scope of research questions but also reduces the definitiveness of findings.

To determine the specific psychiatric disorders that are most prevalent in the families of opioid abusers, two studies evaluating psychiatric disorders in treated opioid addicts, using structured and specified diagnostic criteria, were recently completed. In the New Haven study of 533 treated opioid addicts (Rounsaville et al. 1982b), the three disorders covered by Research Diagnostic Criteria with rates far in excess of those

found in the community were Major Depression (53.9 percent), Antisocial Personality (26.5 percent), and Alcoholism (34.5 percent). These findings are mirrored by a Cambridge, MA, study of 133 opioid addicts, using DSM-III criteria (Khantzian and Treece, in press), which found rates of 56 percent for Depression and 35 percent for Antisocial Personality.

Because these rates were derived from treatment-seeking groups, they may be artifactually high (i.e., having two disorders may predispose to treatment seeking). To evaluate this possibility, the New Haven study also evaluated a community sample of non-treatment-seeking opioid addicts and found that only Major Depression showed a rate difference (Rounsaville and Kleber 1985). While treatment-seeking addicts were more likely to be depressed than community addicts, even the latter group showed higher rates of Major Depression than expected from a community survey (Weissman et al. 1978).

Because treatment-seeking groups are special in many ways, the importance of community data is high. Unfortunately, community surveys have not provided useful data about the coexistence of opioid addiction and psychopathology. The most definitive community findings on rates of substance use have been obtained from National Institute on Drug Abuse (NIDA)-sponsored household (Miller et al. 1983) and high school (Johnston et al. 1983) national surveys which have focused exclusively on quantity and frequency of drug use. These studies are of little help in the study of either substance abuse or coexisting psychopathology, because they do not determine whether the patterns of drug use would allow diagnosis of a substance use disorder, nor do they evaluate associated psychopathology.

The major study which has evaluated both substance use disorders and psychopathology in general community surveys is the Epidemiology Catchment Area (ECA) Study (Myers et al. 1984; Robins et al. 1984). While this is a landmark study in which thousands of subjects were interviewed at multiple sites across the United States, the findings are of limited use for evaluating coexistent psychopathology in substance abusers for several reasons. First, while overall lifetime rates of substance use disorders were over 5 percent, these rates were largely accounted for by marijuana, with rates for opioid and cocaine abuse/dependence at less than 0.5 percent each. Hence, out of a sample of over 9,000 subjects, the numbers of opioid and cocaine abusers were less than 60 and less than 30, respectively. Second, the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (Robins et al. 1981) was used. This instrument takes special care to insure that psychiatric symptoms were not caused by psychoactive substance use, thereby discounting the symptoms of psychiatric disorders that occurred during periods of substance abuse. Because many substance abusers never have a sustained drug-free period, diagnosis of coexistent psychopathology was not possible using this instrument without post hoc recoding of the data. Third, there was no special attempt to assure subjects of the confidentiality

of their replies regarding use of psychoactive substances. While the NIDA-sponsored household survey preserved the confidentiality of subjects both by not recording names on answer sheets and by having the subjects themselves fill out answers to questions rather than having the interviewer fill out the questionnaires (Miller et al. 1983), none of these special precautions were taken in the ECA study. Hence, there is the strong possibility that rates of substance use disorders were underreported. This possibility is especially likely considering the finding that lifetime rates of some substance use disorders actually dropped at 6-month and 1-year reinterview.

COEXISTENT SUBSTANCE ABUSE IN ALCOHOLIC, ANTISOCIAL PERSONALITY, AND DEPRESSED PROBANDS AND THEIR FAMILY MEMBERS

The evaluation of psychiatric disorders in treated opioid addicts suggests that the disorders most likely to be transmitted are alcoholism, antisocial personality, and depression. To date, studies of opioid addiction in populations with diagnoses of depression, antisocial personality, and alcoholism have been sparse. Before reviewing the evidence, it is important to note a fundamental problem which places major limitations on the types of research designs which can be used to assess familial transmission of psychopathology and opioid abuse--that is, exposure of the general population to heroin and other illicit opioids, even in recent years but especially over 20 years ago, has been relatively rare. Substance use disorders, unlike any other psychiatric disorders, have a known environmental agent which is necessary for developing the disorder; namely, exposure to the abused substance. For heroin, this means that only a small fraction of the population will place themselves at risk for having heroin addiction. Findings from the National Household Surveys from 1972 to 1984 have reported that only 5 percent of young adults and 1.1 percent of older adults had tried heroin even once (Miller et al. 1983; Rounsaville 1985). Hence, even if those with other psychiatric disorders, including depression, antisocial personality, and/or alcoholism, had a coexistent predisposition to become a heroin addict, only a small fraction of these groups are likely to have ever allowed this predisposition to influence their lives, because they were never exposed to the environmental agent of the disorder. This contrasts markedly with alcohol, which over 90 percent of the U.S. population has been exposed to at least once.

The importance of limited exposure to illicit opioids in evaluating the literature on other psychiatric disorders is that negative findings from these studies are not necessarily a severe blow to the hypothesis that underlying psychopathology is a familial-transmitted cause of heroin addiction. Studies of alcoholics tend to show rates of abuse of other substances (including opioids) higher than those expected from community levels (Grande et al. 1984; Hesselbrock et al. 1985). In addition, the preponderance of evidence suggests that nonalcoholic substance abuse is found more commonly than expected in those showing evidence of antisocial personality (Grande et al. 1984). This has not been demonstrated

for samples of treated and community depressives (Helzer, in press; Merikangas et al., unpublished).

There is little to review regarding findings which show excess rates of psychiatric disorders in the families of opioid addicts or excess rates of opioid addiction in the families of those with other psychiatric disorders. In the latter case, the lack of evidence is most likely related to the very low community rates of opioid addiction (less than 0.5 percent), so families of those with other psychiatric disorders would be required to have massively increased prevalence of opioid addiction for a statistically significant association to be found. The remainder of this chapter will be devoted to sorting through available research strategies for evaluating psychopathology rates in families of opioid addicts to obtain evidence that psychopathology is a familial-transmitted cause of opioid addiction.

RESEARCH DESIGNS FOR STUDY OF FAMILIAL TRANSMISSION OF LINKED PSYCHOPATHOLOGY AND OPIOID ADDICTION

In evaluating possible genetic transmission of opioid addiction and/or associated psychopathology, there are three general types of research designs available: Twin studies, adoption studies, and family/pedigree studies. Twin studies are frequently presented as providing evidence for a genetic component to the illness under study if it is shown that monozygotic twins have a higher concordance for the disorder than dizygotic twins. However, as Kidd and Matthysee (1978) have pointed out:

> The major value of twin studies has been that the finding of discordant monozygotic twins allows one to reject the hypothesis of complete genetic determinancy... The finding that monozygotic twins have a greater concordance than dizygotic twins does suggest the involvement of biologic factors. However, monozygotic (MZ) twins may also have greater environmental similarities than dizygotic (DZ) twins. Thus, a greater MZ concordance does not, in itself, allow rejection of either a purely environmentalist hypothesis or a purely biological hypothesis. (Kidd and Matthysee 1978, p. 927)

Strong evidence for a genetic component of a disorder can be obtained from adoption studies, which evaluate transmission of disorders from parents to children who are separated from them at birth. Hence, the excess of disorders in adopted children of biological parents with the disorder, in contrast to similarly adopted children of parents without the disorder, can most readily be explained as being related to genetic transmission of risk for the disorder.

Twin and adoption studies are absent in the study of opioid addiction or other illicit drug abuse. The major reason for this absence is, again, the relatively low prevalence of opioid addiction

or even exposure to abusable opioids in the general population. This is particularly the case in the Scandinavian countries in which the best twin and adoption registries have been kept. Finding a sample of twins who have been exposed to opioids might be feasible through a search of U.S. files of treatment-seeking opioid addicts. However, as noted above, twin studies do not really provide strong evidence for a genetic component of disorders. Moreover, twin studies tell nothing about the mode of inheritance and only provide suggestive evidence that a disorder is genetically transmitted.

The third study design available for evaluating transmission of psychiatric disorders and opioid addiction is family/pedigree studies. In these studies, families in which the disorder of interest is present are found through identified family members (probands) who have the disorder. All available relatives, including first- and second-degree relatives, are evaluated using either direct evaluation (e.g., direct interview) or the family history method, in which the psychiatric histories of all family members are obtained only from interviewed family members. Hence, a psychiatric history is available on all family members, including those who are dead or otherwise unavailable for interview. In order to reconcile divergent information from multiple informants, a "best estimate" procedure is utilized whereby two independent raters make a final diagnosis on the basis of all available information (including direct interview, interview of relatives, and medical records). Following independent review of the same data, differences between the two best estimate raters are themselves reconciled.

Family/pedigree studies have a number of advantages. First, they are comparatively feasible. Because families are identified through probands who have the disorder of interest, it is possible to identify relatively large numbers of families even when the disorder under study is relatively rare in the general population. This is clearly not the case with adoption and twin studies. Second, it is possible to obtain relatively rich and up-to-date information about probands and their families, because many family members can be personally interviewed. Again, this contrasts with many adoption and twin studies in which investigators are limited to information available from medical records kept by adoption agencies and/or records of criminality, alcoholism, or treatment for psychiatric disorders maintained in the countries in which the study is taking place. These older records contain incomplete and variable amounts of information and are frequently inadequate for determining whether subjects meet recently developed diagnostic criteria for psychiatric disorders. Moreover, the possibility that individuals with the disorder are not identified through a search of public records (e.g., whether a family member was listed with a Scandinavian temperance board) is reduced through direct interview or the family history method. Third, and most importantly, while twin and adoption studies provide comparatively little information about mode of transmission, these data can be obtained from family and multigenerational pedigree studies.

To evaluate familial transmission of psychiatric disorders that may be associated with opioid addiction, family history data must be collected from samples of opioid-addicted probands with and without the trait being evaluated (e.g., depression and antisocial personality) and from normal probands and/or those with other psychiatric disorders but no evidence of opioid addiction (e.g., depression and antisocial personality). For transmission of associated psychiatric disorders to be a plausible model, it should first be shown that (a) families of opioid addicts have an excess of the associated disorders (e.g., antisocial personality, depression, and alcoholism), and (b) within the families of opioid addicts, there is an association between the other psychiatric disorders and opioid addiction or other addictive behaviors (i.e., family members with an addictive disorder also tend to have the associated disorders). If these two conditions hold true, it is then possible to evaluate transmissibility of the different disorders and the association of transmissibility of the disorders using models developed by Reich et al (1979).

DESIGN OF THE FAMILY/GENETIC STUDY OF OPIOID ADDICTION

To pursue the hypothesis that opioid addiction is familial-transmitted through the mechanism of associated psychiatric disorders, we have, over the past 3 years, been conducting a family study of opioid addicts (Rounsaville, unpublished manuscript). The study includes male and female subjects with opioid addiction and no other psychiatric disorders, opioid addiction plus major depression, and opioid addiction plus antisocial personality. Alcoholism, while not examined separately, was associated with 40 percent of the probands in this study and was evenly distributed across cells. The age range of the proband sample was limited to 18 to 35 years, because the treated sample did not contain sufficient numbers of those over 35 to allow cohort effects of a wider age range to be taken into account. An attempt was made to interview all first-degree relatives in the parental and sibling generations. Children were excluded because very few orobands reoorted having children 16 years old or older. The direct interview included the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott et al. 1978) and the Family History Research Diagnostic Criteria (Andreason et al. 1977). Family history data were obtained for all first-degree relatives from all family members who were interviewed. Diagnostic disagreements across different sources of information were reconciled using the best estimate procedure outlined above. The comparison sample consisted of data gathered from the families of normals and depressives. The disorders evaluated included (a) addictive behaviors (defined both broadly and narrowly) and (b) psychiatric disorders covered in the Research Diagnostic Criteria (RDC) (with a special interest in depression and antisocial personality).

In the present study, it was assumed that opioid addicts are a heterogenous group and that there may be numerous pathways to addiction. If the associated psychiatric disorders play a major role in the transmission of opioid addiction (or substance use

disorders), we would expect to see the following: (a) probands with only a substance abuse diagnosis will have an excess of addictive behaviors in their families but no excess of other disorders; (b) probands with both major depression and substance abuse diagnoses will have an excess of both addictive behaviors and depression but no other disorders in their families; and (c) probands with both antisocial personality and substance abuse will have an excess of addictive behaviors and antisocial personality (but no other disorders) in their families.

Problems/Limitations With This Design

While the design of this study has many strengths listed above, there are a number of practical and conceptual limitations as well. It is difficult to evaluate the specific transmissibility of opioid addiction, per se, because the parental generation was much less likely to be exposed to opioids during the ages of 12 to 25, which is the time of greatest vulnerability to the disorder. While specific categories of drugs abused by the siblings of the addicts can be examined, studies are forced to evaluate transmission of broader categories of substance abuse. Hence, if a specific sensitivity to opioids is being transmitted, the data currently available would not address this issue. Another difficulty in explaining the specific drug sensitivity hypothesis is the fact that polysubstance abuse is the modal drug abuse pattern of today. This sequential or simultaneous abuse of multiple classes of drugs, in itself, suggests that traits being familial-transmitted are not narrowly related to the metabolism of any particular drug.

The data from this type of study can never definitively rule in or out genetic vs. environmental components of transmission of disorders in families. Although it is possible to evaluate the contribution of genetic (e.g., disorder in first-degree relatives) and environmental elements (e.g., exposure to illicit substances during teen years) using multiple threshold models, the results of this type of model testing are seldom definitive.

Sophisticated model-fitting procedures are available for assessing whether the transmission of the trait being studied within the sample conforms to known mechanisms including single locus inheritance, polygenic inheritance, multilocus inheritance, etc. (Kidd and Matthysee 1978). Likelihood ratios tests can be used to compare different hypotheses about the relationships of genotypes to phenotypes. In practice, however, factors such as incomplete penetrance and uncontrolled environmental influences usually make it difficult to rule out any of the possible genetic mechanisms of transmission of the trait. This is especially a problem if the trait under study is transmitted in numerous different ways. Hence, at best it is possible to rule out a few of the possible modes of genetic transmission using data from family studies.

As a practical matter, when probands with psychiatric disorders are being studied, it is difficult to secure the cooperation of

large numbers of family members. In the present study, only around 1.5 first-degree relatives per proband were interviewed, with similar results in studies of depressives (Weissman et al. 1982) and alcoholics (Cloninger et al., in press). Although information from multiple informants greatly reduces the insensitivity of the family history method, direct interview of all relatives remains the most sensitive method for obtaining psychiatric diagnoses. In such studies, however, it is important that interview status be entered as a covariate.

The effects of temporal trends and variable lengths of time at risk must be considered in all analyses. Across families and within families, different relatives will be in widely different age ranges, thereby having different lengths of time at risk for a psychiatric disorder. Hence, it might be anticipated that those who are older would have higher risk for disorders than those who are younger (Weissman et al. 1984). Despite this seemingly logical trend, there has been considerable evidence from community studies that rates of substance use and other disorders (e.g., depression) are becoming more common in younger age groups (Cloninger et al., in press; Klerman et al. 1985). To handle these two conflicting trends related to cohort effects and time at risk, age and year of birth must be included in all analyses.

FUTURE DIRECTIONS

The present study is currently in the phase of finalizing best estimate diagnoses, and data analysis will begin shortly. To maximize the scientific yield from the current study, it is important to: (a) obtain longitudinal information on the children of the addicts in the sample, because they represent a group at high risk for addictive behaviors, and (b) attempt to identify large, informative multigenerational pedigrees within the addict population in order to take advantage of recent, exciting advances in linkage techniques.

Study of Children at High Risk for Opioid Addiction

Because we have restricted the age range of the addict sample, the ages of their children are relatively low, with half of the children aged six and under and only a small fraction being over 15 years of age. Hence, the great majority have not completed the period of maximum risk for developing a substance use disorder. We hope to evaluate these children at multiple time periods in order to identify psychopathological, behavioral, environmental, and biological precursors of developing a substance use disorder. Evaluation of psychiatric disorders in children has been made more feasible through the development of children's psychiatric interviews like the Kiddie-SADS (Chambers et al., in press).

Linkage Studies

In just the past few years, the number of identified markers on the human genome has expanded tremendously based on the discovery

of restriction fragment length polymorphisms (RFLP) (Kidd 1982). This has made it possible to pinpoint, in the case of single major locus genetic transmission, the actual location of the gene responsible for conferring risk for a given disorder. These analyses are very sensitive to the definition of the syndrome used, which is a major stumbling block for disorders with unclear boundaries, such as psychiatric disorders. The major focus of linkage studies has been large, multigenerational pedigrees in which substantial numbers of individuals are positive and negative for the trait under study. Participation In both diagnostic assessments and donation of blood samples is needed from as many family members in the sample as possible. The discovery of such pedigrees is a rare event, but this type of research is clearly needed in the study of families of drug abusers.

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Methodological Issues in Family, Adoption, and Twin Research

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INTRODUCTION

A number of methodological issues must be considered when family, adoption, or twin methods are employed as research designs. Some of these issues are common to all three research strategies, while others are specific to each strategy. Failure to address these issues appropriately during study design may adversely affect the usefulness of the data obtained. It will do so either by clouding interpretation of the findings or by severely limiting their usefulness and generalizability.

This chapter will briefly discuss several of these methodological issues. The chapter is not intended as an in-depth or comprehensive discussion of these issues--the reader is referred to specific chapters in the volume or to more advanced textbooks in behavior genetics for that purpose (Fuller and Simmel 1983; Plomin et al. 1980). Instead, this chapter is intended to provide a background for the reader who may be unfamiliar with the methodological issues and assumptions involved in family, adoption, and twin research. It is hoped that it will also provide a basis for better understanding the other papers included in this volume.

COMMON ISSUES

Methodological issues common to all three study methods include: (1) appropriateness of diagnostic criteria; (2) differences in methods of data collection; (3) distinction between prevalence and incidence; (4) controlling for effects of age of risk; (5) sex differences in data analysis; (5) influence of experimenter bias; (7) influence of recruitment bias; (8) influence of assortative mating on interpretation of results; (9) comorbidity in substance abuse; (10) problems caused by abstainers in determining genetic effects; and (11) across-drug generality in interpretation of results. Some of these issues will be discussed in greater detail under each specific method considered.

Diagnosis

Criteria used to identify a disorder are of fundamental importance to clinical research and should be specified operationally. Unless such criteria are known, the generalizability of the findings cannot be determined. Differences in definitions are thought to account in part for discrepant findings across studies. For example, twin, family, and adoption studies of alcoholism have variously defined the disorder by membership in Alcoholics Anonymous, admission to an alcoholism treatment center, arrest for public drunkenness, an inability to control drinking, or meeting DSM-III criteria for Alcohol Abuse/Dependence. Other studies have failed to provide any diagnostic criteria.

Data Collection

Archival records, questionnaires, and personal interviews are three data sources typically employed in twin, family, and adoption research. Each method has certain biases, however, and results may vary as a function of the method selected. While archival records are largely unaffected by experimenter bias, these data are retrospective, are often recorded in an unsystematic manner, and may not provide sufficient detail for making psychiatric diagnoses. Questionnaires are simple to score and administer, and provide greater structure and control over item content than archival records. However, specific items may be poorly worded and ambiguous, causing subjects to misinterpret them and provide inaccurate information.

Personal interviews allow investigators to follow up on subject answers, which is not possible with questionnaires or archival records. When interviews are unstructured, data are subject to some of the same biases inherent in archival records (i.e., non-uniform data recording). With structured interviews, clarification of responses is accomplished using probes, which are specific queries concerning answers to questions. Although more time consuming, expensive, and difficult to administer than questionnaires, the structured interview offers the most accurate and comprehensive approach for obtaining information from subjects. Regardless of the data collection method, reliability and validity (corroborative) data should be obtained.

Prevalence vs. Incidence

Prevalence is the number of individuals exhibiting a disorder at any particular point in time. Lifetime prevalence determines whether the individual has ever had the disorder. Incidence, on the other hand, refers to the rate of occurrence of a disorder during a given period of time, usually one year. Thus, incidence is the number of newly discovered or diagnosed cases of a disorder (Burton and Smith 1970). For disorders such as drug abuse that are characterized by intermittent periods of drug use and abstinence, incidence and prevalence data may yield different estimates of the frequency of actual drug problems. For most studies of biological

vulnerability to drug abuse, lifetime prevalence is the most appropriate statistic to use.

Age of Risk

The age at which symptoms first appear is another issue to be addressed in twin, family, or adoption studies. If an individual has not passed through the age of risk for a disorder, he/she should not be labelled "unaffected," because a number of these individuals may eventually develop the disorder. While age of risk is frequently acknowledged, many studies fail to control for its effects. This is particularly true in family studies of alcohol or drug abuse, where children are often below the age of risk for alcohol or drug abuse. Corrections should always be made for age of risk of younger probands and other family members (Anderson 1982).

Sex Differences

Males and females show different rates of alcohol and drug problems, different ages of onset, and possibly different symptomatology as well. Therefore, caution should be exercised in generalizing data from males to females. Data collected from males and females should be analyzed separately, as important findings may be obscured by merging of the data. Such analyses, however, will require a larger number of subjects to achieve statistical significance.

Experimenter Bias

Persons collecting data may inadvertently influence responses of subjects through subtle verbal or nonverbal cues. If that person has a vested interest in the outcome of a study, this may result in a more favorable outcome. Experimenter bias, however, will not affect all subjects uniformly. Rather, certain subjects (i.e., those with a high need for approval) may be more susceptible to experimenter bias than other subjects. To the extent possible, all interviewers, research assistants, etc., should be kept blind to placement of subjects in experimental or control groups, family history, zygosity, etc.

Recruitment Bias

Another potential source of bias is the method employed to recruit subjects. In psychological research, subjects are frequently recruited on a volunteer basis. Volunteers, however, differ from nonvolunteers on many variables including intelligence, education, occupation, socioeconomic status, and need for social approval, among others (Rosenthal and Rosnow 1975). These data suggest that volunteers may not be representative of the general population, and thus caution must be used in generalizing findings from volunteers to the population at large. Also, it is important to obtain data from as many subjects in the original sample as possible.

Sample Characteristics

Prevalence is usually represented as an average for a given population. However, actual prevalence will not be uniformly distributed throughout that population. Rather, prevalence may vary as a function of age, sex, marital status, educational background, rural vs. urban setting, ethnic background, and socioeconomic status. Thus, caution should be exercised in generalizing findings from a nonstratified sample to the entire population, as data collected from a subsample may not generalize to the entire population, and vice versa.

Assortative Mating

Statistical formulae employed to calculate relative contributions of genetic and environmental factors in a disorder often assume that mating is panmictic. That is, choosing a mate is a random process with respect to the characteristic being studied. However, this assumption is often violated by assortative mating (i.e., the selection of a spouse with similar characteristics). There is substantial evidence for assortative mating among humans (Buss 1985). Several studies suggest that assortative mating plays a role in the familial clustering of alcoholism (Stabenau and Hesselbrock 1983). The influence of assortative mating should always be considered in interpretations of study results. Suggestions for controlling for the effects of assortative mating will be discussed below under each research strategy.

Comorbidity

In addition to drug abuse, many individuals show evidence of alcoholism, depression, and/or antisocial personality disorder (Meyer 1986). When more than one disorder exists in an individual, it is important to determine their interrelationship. For example, did alcohol abuse lead to symptoms of depression, or did depression lead to the development of alcoholism? Investigators typically distinguish multiple disorders on the basis of chronology. Thus, if sociopathic symptoms (e.g., stealing, fighting) predate alcohol abuse (e.g., heavy drinking, blackouts), then the diagnosis is primary sociopathy with secondary alcohol abuse. If, however, symptoms of alcohol abuse occurred prior to sociopathy, then the individual is diagnosed as a primary alcohol abuser with secondary sociopathy. It is important to distinguish between primary and secondary disorders, as evidence for a genetic factor in one disorder may, in fact, represent a genetic predisposition for the other disorder. Because multiple diagnoses are common in alcoholism and drug abuse, a thorough psychiatric evaluation should be performed on all subjects in genetic research.

Problem With Abstainers

For both alcoholism and drug abuse, a specific environmental factor must be present for the disorder to manifest itself. This factor is exposure to alcohol or drugs. Individuals who are lifetime

abstainers will never develop the disorder. When analyzing twin, family, or adoption data, it is therefore important to examine the drug and drinking histories of all nonproblematic individuals. It is an open question as to whether data from nonproblematic individuals who never used alcohol or drugs should be included in analyses. Exclusion of abstainers may enhance the magnitude of the familial/genetic effects that are found.

Across-Drug Generalities

At present it is unknown whether findings obtained with one type of drug abuse (e.g., heroin addiction) can be generalized to other types of drug abuse (e.g., cocaine abuse). Such findings may or may not generalize across drugs, or may generalize only within drug classes (e.g., opiate abuse, stimulant abuse). Whenever possible, studies should focus on specific drugs, or specific classes of drugs. However, it is recognized that this may be impractical in twin and adoption studies, where problems in finding a sufficient number of subjects may exist.

FAMILY STUDIES

Methodological issues in family studies include: (1) selection of any appropriate control group; (2) differences in methods of data collection; (3) accuracy of information supplied by family members; (4) procedures for handling unknown drug-use status of relatives; (5) importance of collecting data from both first-and second-degree relatives; and (6) influence of assortative mating on familial patterns of inheritance.

Control Group

A familial pattern is evident if a disorder occurs more frequently in relatives of probands than in relatives of controls. Selection of controls is important, as abnormally high control rates will obscure a familial effect while abnormally low control rates will falsely suggest such an effect. Ideally, control groups should be matched with probands for relevant demographic (and at times clinical) characteristics. It is an open question as to what constitutes an appropriate control group for family studies of substance abuse. In various studies, control groups have ranged from hospital employees to psychiatric inpatients (Cotton 1979). It is inappropriate to use population base rates of substance abuse as a control if proband families deviate significantly from the general population. To serve as a proper control in such cases, population base rates must be adjusted for sex, age, and socioeconomic status.

Methods of Data Collection

Two methods for collecting familial data are the family history and the family study. The family history method collects data about family substance use from a single individual, the proband. The family study method involves separately collecting data from each family member. While the family history method is economical, it

typically provides an underestimate of prevalence of disorders among family members, and its accuracy varies with types of disorders and relationship of family member to proband (Thompson et al. 1982). While more accurate, the family study method is expensive, particularly when large families are involved. A compromise approach involves interviewing the proband and one other family member (Schuckit 1981).

Accuracy of Information Supplied

To corroborate information supplied by the proband about his/her own substance use, spouses and children have been found to provide more accurate information than parents or siblings (Mendlewicz et al. 1975). When information about family members is obtained from more than one source, informants may disagree about status of a given family member. Several methods for resolving this dilemma have been proposed, including (1) use of most frequent diagnosis (i.e., consensus), (2) randomly selecting data from informants, and (3) use of most severe status reported. Since family history data have low sensitivity, that is, the modal diagnosis is not affected, the third approach may be most accurate and is thus often preferred by investigators.

Unknown Status of Relatives

Probands are sometimes unable to provide substance-use data about all family members. In such cases, responses of "no" should be clearly distinguished from "don't know," and every effort should be made to obtain the missing data. At times, when data on a family member were unknown, the status of the relative has been coded negative (i.e., not present), leading to an underestimation of familial influences In substance abuse. A more appropriate classification of such cases would be "unknown" or “data not present."

Data From Second-Degree Relatives

In many family studies, data collection is limited to first-degree relatives (parents, siblings, and children). For adult-onset disorders, data collection is often limited to parents and siblings because children may not have passed through the age of risk. While they are not genetically or environmentally as close to the proband as first-degree relatives, collecting data on second-degree relatives (grandparents, aunts/uncles, nieces/nephews, and grandchildren) allows the data base to be broadened. This is especially important for probands with no siblings.

Assortative Mating

Since substance abusers may mate assortatively with other substance abusers, it is important to collect information on substance use by the spouse, as well as by the spouse's other family members (Hall et al. 1983). Since assortative mating can also occur for other factors that may be related to substance use, such information

should be collected from proband and spouse as well, including ethnic background, socioeconomic status, other psychiatric disorders, etc.

ADOPTION STUDIES

Methodological issues in adoption research include: (1) representativeness of biological and adoptive parents to the general population; (2) influence of selective placement of adoptees on adoptive parent-child correlations; (3) informant bias; (4) influence of prenatal factors on biological parent-child correlations; and (5) effects of time spent with biological parents on biological parent-child correlations.

Representativeness of the Sample

Critics of adoption studies have contended that biological parents adoptees are not representative of parents in the general population. Therefore, heritability estimates based upon this sample may not be representative of all parents. Some studies have suggested that the biological parents of adoptees do not differ significantly from the general population in terms of personality or other characteristics (Scarr 1977, cited in Plomin et al. 1980). However, other studies have found excess rates of personality disorders in unwed mothers who give up their babies for adoption compared to unwed mothers who decide to keep their babies (Horn and Turner 1976). Apart from characteristics of the biological parents, the representativeness of adoptive or rearing parents must also be examined. Adoptive parents tend to be better educated, in higher socioeconomic groups, and less affected by psychiatric problems than biological parents of adoptees (Fuller and Thompson 1978). Caution must therefore be exercised in generalizing results from adoptees to the general population. In addition, control groups should consist of adoptees, rather than members of the general population.

Selective Placement

The rationale of the adoption method assumes that adoptees are randomly placed in adoptive homes. However, selective placement occurs when agencies attempt to match children to adoptive parents who share characteristics in common with the biological parents. When it occurs, selective placement confounds interpretation of adoption study results. If selective placement occurs for a genetically determined trait, the adoptive parent-child correlation will be increased, which will reduce the estimate of the obtained genetic effect. In contrast, if selective placement occurs for a trait that is environmentally determined, the biological parent-child correlation will be increased, thereby increasing the estimate of the obtained genetic effect. In adoption studies, attempts should be made to determine the degree of similarity between adoptive and biological parents for the characteristics being examined, in order that appropriate statistical adjustments can be made during data analysis.

Informant Bias

When the biological mother is the sole source of information about the adoptee, she may be unwilling or unable to specify paternity of the adoptee. Studies have shown that paternity is incorrectly reported in 5 to 10 percent of adoption cases (Murray et al. 1983). Also, biological mothers may deliberately or unknowingly provide inaccurate information about the biological father's occupation, education, income, etc. To the extent possible, attempts should be made to obtain corroborating information from the biological father or other family members.

Influence of Prenatal Environment

In theory, the adoption study method attempts to separate nature from nurture by establishing conditions where biological parents supply the genetic component and adoptive parents supply the environmental component to an individual's development. In reality, biological parents also contribute early environmental influences (from conception to birth and from birth to adoption). Prenatal factors are especially important in adoption studies of alcoholism and drug abuse when maternal alcoholism or drug abuse may be present. Exposure of the developing fetus to alcohol or other drugs during pregnancy may place the children at higher risk for alcoholism or drug abuse. This would result in spuriously high correlations between traits shown by the biological mother and the child, which would not be genetic in origin. These risks can be minimized by limiting studies to children of male alcoholics or drug abusers or by examining children with either the male or the female parent affected (or both). While this reduces the generalizability of the results, it does not entirely eliminate such influences as the tendency of male alcoholics to mate assortatively with heavily drinking females (Stabenau and Hesselbrock 1983). Information on patterns of alcohol and drug use by both biological parents needs to be obtained.

Influence of Early Rearing Environment

In addition to prenatal environment, adoptees also share at least part of their early rearing environment with the biological parents. The more time a child spends with the biological parents, possibly the greater will be the environmental influences provided by those parents. In an adoption study of alcoholism, Cloninger et al. (1981) found that adoptees of biological alcoholic parents who resided with their biological mother for at least 6 months were 1.5 times more likely to develop later alcohol abuse than were those adopted at an earlier age. However, other variables may also contribute to these results. Information on time spent with biological parents should be routinely collected in adoption studies.

Assortative Mating

The adoption method assumes that biological parents of adoptees mate randomly. However, studies have shown that biological parents

of adoptees mate assortatively for a number of physical and behavioral characteristics (Plomin et al. 1977). Among biological parents, assortative mating for alcohol drinking has been shown (Rimmer and Winokur 1972; Hall et al. 1983), which increases the genetic loading provided by the biological parents. Thus, the pattern of alcohol and drug use by both biological parents should be obtained, and investigators may wish to analyze their data by number of alcohol or drug-abusing biological parents, a method frequently employed in family studies.

TWIN STUDIES

When the twin method is employed to examine the role of genetic and environmental factors in the etiology of a disorder, a number of issues must be considered. These include: (1) whether twins are representative of the general population; (2) whether twins who participate in research projects are representative of twins in general; (3) validity of equal environmental similarity assumption underlying twin research; (4) accuracy of zygosity determination; (5) importance of obtaining adequate sample of twins; (6) methods of calculating concordance rates and heritability; (7) influence of assortative mating on interpretation of results; and (8) importance of obtaining population base rates in interpretation of results.

Representativeness of Twins

In the United States, the twinning rate is approximately 1 in every 83 live births. About one-third of twin births produce monozygotic (MZ) twins; half the remaining two-thirds are same-sex and half are opposite-sex dizygotic (DZ) twins. DZ twins tend to "run" in certain families, suggesting that hereditary factors may play a role in their twinning. In contrast, MZ twins occur randomly in the population (Plomin et al. 1980). Several studies have compared twins to singletons on a variety of characteristics, including cognitive abilities, personality factors, etc. While certain differences have been reported, they do not appear to influence the generalizability of the results significantly (Fuller and Thompson 1978). Nevertheless, possible differences between singletons and twins raise questions about the generalizability of twin findings, and such generalizations should be made with caution.

Recruitment Bias

Volunteer bias has been reported in twin research. Among same-sex adult twin pairs in the general population, approximately 50 percent are MZ and 50 percent are DZ, and 50 percent are male and 50 percent are female. However, volunteer subjects in twin studies are typically two-thirds MZ and two-thirds female (Lykken et al. 1978). Thus, between-pair variance for DZ twins may be restricted, resulting in an overestimate of the influence of genetic factors. Similarly, data collected from a sample of male twins should be less generalizable than data obtained from a sample of female twins. To minimize recruitment bias, efforts should be made to recruit all subjects in a sample, and to obtain data from both

members of as many twin pairs as possible. Incentives are often used to encourage subject recruitment and participation by both members of a twin pair.

Equal Environmental Similarity Assumption

An assumption underlying the twin method is that HZ and DZ twins share equally similar trait-relevant environments. Therefore, any observed differences in MZ and DZ twins must be due to number of common genes. Research suggests that the *in utero* environment is more similar for MZ than DZ twins in terms of positioning of ova within the uterus, conditions necessary for egg implantation, level of shared blood circulation, etc. (Lytton et al. 1977). However, other *in utero* differences (e.g., distribution of cytoplasm to cells) favor greater environmental similarity for DZ than MZ twins (Schuckit 1981). These early environmental differences may influence later correlations between MZ and DZ twin pairs, and may be mistaken for evidence of genetic differences.

Evidence exists that MZ twins also share more similar postnatal environments than DZ twins. They are more often mistaken for one another by parents, peers, and strangers; share more friends in common; spend more time together; and show more similar preferences in clothing, foods, etc. When degree of observed environmental similarity was determined for MZ and DZ twins, higher correlations were found for MZ than DZ twins. However, when environmental similarity was correlated with similarities in cognitive and personality traits, only low correlations (ranging from -.06 to +.06) for MZ twins were obtained (Loehlin and Nichols 1976). Thus, increased environmental similarity did not result in increased behavioral similarity, supporting the validity of the equal environmental similarity assumption. Other investigators have reported similar findings (Matheny et al. 1976; Plomin et al. 1976). While additional research is needed in this area, concern over this issue should not significantly hamper future twin research.

Zygosity Determination

Accurate zygosity assessment (i.e., determining if twins are MZ or DZ) is essential to the twin method. Misclassification of MZ and DZ twins will result in higher correlations for DZ twins and lower correlations for MZ twins for a genetically determined trait. Several methods have been employed to determine zygosity. Of these, blood-group analysis is the most accurate (and expensive), with Lykken (1978) reporting 99.8 percent accuracy for 8 blood types and 10 serum proteins and red blood cell enzymes. Unfortunately, the accuracy of self-report of zygosity is only 60 to 70 percent (Carter-Saltzman and Scarr 1977; Nichols and Bilbro 1966). In studies of substance abuse, zygosity determination based on similarity of physical appearance should be made with caution, as discordant members of MZ pairs may get misclassified as DZ due to differences in physical appearance caused by excessive alcohol or drug use.

An inexpensive yet highly accurate method for determining zygosity is use of questionnaire items such as "As children, were you and your twin as alike as two peas in a pod?" and "Did even family members have trouble telling you apart?" This approach has been found to be 90 to 96 percent accurate in distinguishing MZ and DZ pairs (Cederlof et al. 1961; Cohen et al. 1973). We have obtained 95 percent accuracy in use of the approach to classify alcoholic twins (results confirmed by blood-group analysis).

Adequate Sample Size

Twins are rare compared to singletons, and twins with specific disorders (e.g., alcoholism, drug abuse) are even more rare. Further, some twins will refuse to be recruited, or have cotwins who cannot be located. Thus, it is sometimes necessary to screen large numbers of individuals to obtain an adequate sample size for a study. Power calculations are used to determine the number of twin pairs needed to distinguish between various MZ/DZ concordance rate differences.

Concordance and Heritability

If a trait is dichotomous (i.e., either present or absent), concordance rates are computed. For pairwise concordance, number of concordant pairs is divided by total number of pairs. Probandwise concordance is computed similarly, except if both members of a pair are ascertained in a sample they are counted twice (Gottesman and Shields 1972). Concordance rates range from .00 (none of the pairs were concordant) to 1.00 (all of the pairs were concordant). While there are advantages to both methods, probandwise concordance is usually preferred from a sampling perspective (Plomin et al. 1980). A comparison of MZ and DZ concordance rates will provide an estimate of the role of genetic factors in the etiology of a disorder.

For continuous traits, heritability is calculated by Falconer's or Holzinger's formula (Plomin et al. 1980), but Falconer's (1960) formula is thought to give a more accurate estimate of heritability (h^2). As a population statistic, heritability possesses no absolute value and varies as a function of the specific environmental factors operating upon a selected sample (Vernon 1979). Heritability estimates may also vary as a function of the population base rates for a particular disorder. (For a more comprehensive review of this topic, see Gottesman [this volume]). Numerically, heritability estimates range from 0.00 (solely environmental) to 1.00 (solely genetic). Assortative mating can confound interpretation of heritability and must be adjusted for in the calculation.

For a discrete trait (i.e., drug abuse, alcoholism), concordance rates may be used to provide a measure of heritability. The formula for estimating heritability for a discrete phenotype is $(C_{MZ} - C_{DZ})/(100 - C_{DZ})$, where C_{MZ} is the probandwise concordance rate for MZ twins and C_{DZ} is is the probandwise concordance rate for DZ twins (Allen et al. 1967; Smith 1974).

Assortative Mating

Assortative mating by parents of twins is an important issue in twin studies of alcoholism or drug abuse, because it violates an assumption on which heritability calculations are based. Assortative mating affects heritability estimates by increasing the additive genetic variance shared by DZ twins, but produces no change in that for MZ twins (Plomin et al. 1980). For DZ twins, this increase in additive genetic variance will result in higher phenotypic correlations (i.e., DZ twins will appear more similar), thereby reducing the magnitude of MZ and DZ differences. If twins have parents who are heavy alcohol/drug users, it is important to control for the effects of assortative mating in calculations of heritability.

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ACKNOWLEDGMENTS

Matt McGue, Ph.D., of the University of Minnesota reviewed the manuscript and provided helpful comments.

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Analytical Approaches to Twin and Family Data

Matt McGue

INTRODUCTION

Theories of genetic and environmental transmission provide a basis for predictions about the nature, magnitude, and pattern of familial resemblance. The relevance of these theories and their associated predictions extends beyond the mere demonstration that genetic and/or environmental factors play a role in the etiology of a given disorder. They also provide a framework for both identifying relevant research questions and developing efficient research designs and analytical methods.

The supposition that a disorder may "run in families" implies the need for a systematic approach to resolving the basis of this familiality. Initially, it must be determined whether there is familial resemblance for disease status. Next, is familial resemblance the result of genetic factors and/or common environmental circumstances, and what are the magnitudes of their effects? Finally, what are the nature and characteristics of the genetic and environmental factors that contribute to disease etiology? For genetic factors, this might involve resolving the mode of inheritance and, if evidence of a major gene effect is found, linkage studies in order to associate the gene with a specific chromosomal location. For environmental factors, this might involve an assessment of the relevant factors and a demonstration that they do, in part, account for environmental similarity among relatives.

In the area of substance abuse, virtually nothing is known about the existence of familial resemblance let alone the relative importance and characteristics of genetic and environmental factors. Consequently, speculation about the existence of genetic mutations that result in specific forms of human drug abuse and discussions about analytical methods (such as segregation and linkage analyses aimed at their characterization) are premature. Rather, the focus here will be on research designs and analytical methods that can provide necessary and basic information about familial resemblance. Specifically, models of genetic and environmental

transmission will be briefly described, and the designs and methods used for establishing familial resemblance, resolving the components of familial resemblance, and characterizing the nature of genetic and environmental factors will be outlined.

MODELS OF TRANSMISSION

Phenotypic Specification

In general, both genetic and environmental factors are assumed to influence the development of a phenotype (i.e., characteristic of interest). It is convenient, when considering their effects upon familial resemblance, to characterize the different types of genetic and environmental factors. Genetic factors include additive genetic effects as well as intralocus (i.e., dominance) and interlocus (i.e., epistasis) nonadditive genetic effects (Falconer 1960). Environmental factors include familial environmental factors (i.e., social class and diet that are shared among family members) and nonfamilial environmental factors (i.e., accidental occurrences and peer groups that are not shared by family members) (Jinks and Fulker 1970).

A general model of phenotypic determination is given by the structural equation

$$\underbrace{P = hG + dD + iI}_{\text{Genetic Effects}} + \underbrace{cC + eE}_{\text{Environmental Effects}} + \underbrace{w(GE)}_{\text{Interaction Effect}}$$

where capital letters are used to denote variables, and lower case letters denote the effect of that variable on the phenotype. In the equation, P denotes the phenotype; G, additive genetic factors; D, genetic dominance factors; I, epistasis factors; C, familial or cultural environmental factors; E, nonfamilial or residual environmental factors; and GE, the interaction of genetic and environmental factors. Although models that incorporate, for example, interaction terms (Lathrop et al. 1984) or epistasis (Williams and Iyer 1981) have been applied in the analysis of family data, the general model is usually too complex and the available family data not sufficiently informative to allow simultaneous consideration of all possible factors (Heath et al. 1984). In practice, then, one initially adopts a reduced or simpler form of the general model with the hope that, even in the general case, it will still provide an adequate approximation. This model can and should be extended if the simpler model does not account for the family data.

A basic linear model that has been widely applied in human and behavioral genetic research (Rao et al. 1984; McGue et al. 1983)

is given by the structural equation

$$P = hG + cC + eE.$$

The reduced model is achieved by assuming that all genetic effects are additive and that there are no genotype-by-environment interactions. By imposing (without loss in generality) the additional constraint that all variables are standardized to unit variance and (with some loss in generality) the assumption that all variables are independent, the variance of the phenotype can be expressed as

$$1.0 = h^2 + c^2 + e^2$$

which gives a partition of the phenotypic variance into proportions due to genetic (h^2), familial environmental (c^2), and nonfamilial environmental (e^2) factors.

The model assumes that these three factors contribute to differences among individuals. Two of the factors (genetic and familial environmental) also contribute to familial resemblance. But, as their contributions differ depending on the particular familial relationship involved, their separate influences can be resolved as described below. The third factor does not influence familial resemblance and includes systematic but nonfamilial environmental influences as well as the unreliability associated with the assessment of the phenotype. Although the three factors are, in general, unobserved, a goal of twin/family studies and genetic analyses is to identify these factors with specific observable entities.

Liability Threshold Model

The stuctural equation models given above provide specifications for quantitative phenotypes only. Many of the phenotypes of interest are, however, qualitative or categorical (e.g., substance abuse. schizophrenia. breast cancer. etc.). Falconer (1965) introduced the notion of a threshold character and provided a unified framework for theories about the transmission of both quantitative and qualitative phenotypes. A threshold character is assumed to be an expression of an underlying continuously distributed quantitative character termed "liability." The character is expressed whenever an individual's combined liability exceeds a fixed threshold value along the liability distribution (figure 1).

Wright (1934), in a series of classic breeding experiments on polydactyly in the guinea pig, provided strong empirical support for the threshold concert by demonstratino that a discontinuous character (in this case an extra toe) could be the result of the operation of many genes (in this case eight). The threshold model

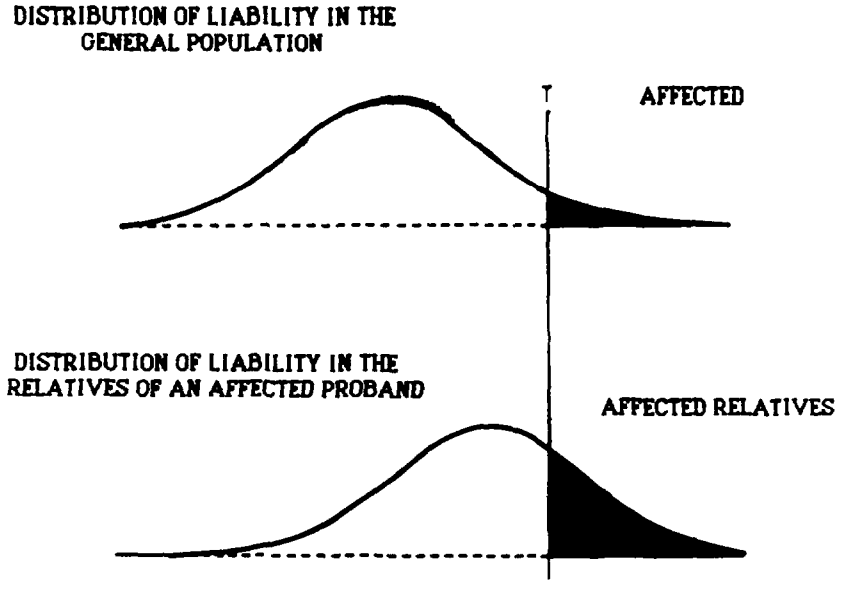

FIGURE 1. *Liabitity threshold model*

NOTE: Affected individuals have liabiIity values that exceed the threshold value T. Relatives of an affected individual are expected, if the disorder is familial, to have higher mean liability values and thus greater risk than the generaI population.

has now been applied to the analysis of family data from a wide range of human disorders including schizophrenia (Gottesman and Shields 1967), diabetes (Falconer 1967), and cleft lip and cleft palate (Fraser 1970).

The liability threshold model can be used to derive familial risks as a function of the heritability of liability (Smith 1971) and has been extended to allow for multiple graded expressions of a single liability distribution (e.g., in the case of substance abuse, the gradation of cigarette smoking to marijuana use to hard drug abuse) (Reich et al. 1972). The threshold model can also be used to resolve the heterogeneity and association between related diagnostic categories (e.g., between substance abuse and anti-social personality) (Cloninger et al. 1978). The liability

threshold model explicitly assumes that the transmission of a qualitative phenotype is due to the transmission of the underlying quantitative liability. The goal of twin and family studies of qualitative phenotypes is, then, to identify and characterize the genetic and environmental factors that contribute to this liability.

FAMILIAL RESEMBLANCE

For qualitative phenotypes, familial resemblance is established by demonstrating that relatives of an affected individual are at increased risk for developing the disorder, compared to the general population. There are two general research designs used to establish familial resemblance. The proband method involves first selecting a sample of affected individuals (i.e., the probands), then studying the probands' relatives to determine whether the risk to relatives exceeds a known population prevalence value or a baseline risk estimated from a simultaneously studied control group. The family method involves observing a representative sample of families to determine whether there is a nonrandom distribution of disease status within families. For relatively rare disorders (prevalence less than 10 percent), the proband method yields observations on substantially more affected individuals than the family method and will thus provide a more sensitive test of the existence of familial aggregation. As substance abuse is relatively rare (Robins et al. 1984), the remaining presentation will focus on the proband method.

Table 1 gives the expected risks to first-degree relatives as a function of the population prevalence of the disease and the heritability of underlying liability. To simplify, all familial resemblance is assumed to be due to genetic factors. Two characteristics of the table are worth comment. First, for rare disorders, low levels of familial risk may be consistent with high levels of genetic involvement. For example, a risk to first-degree relatives of only 2.9 percent is consistent with a heritability of liability of 80 percent if the disorder has a population prevalence of .1 percent. Second, familial risks are functions of both population prevalence and heritability of liability. Statistics such as relative risk that are based on familial risk figures are, consequently, ambiguous concerning the strength of familial resemblance. For example, the risk for developing a disorder among the first-degree relatives of affected individuals relative to the risk among the first-degree relatives of unaffected individuals is 7.06 if the prevalence of the disorder is .001 and the heritability of liability is .40, but only 4.31 if the disorder has a population prevalence of .10 and the heritability of liability is 1.0. The ambiguity of familial risks underscores the importance of describing the familial resemblance for qualitative phenotypes in terms of the tetrachoric correlations among liability values. Calculation of the tetrachoric

TABLE 1. *Expected risks to first-degree relatives of an affected individual as a function of the population prevalence and the heritability of liability*

		Population Risk				
Heritability	Correlation	.001	.010	.050	.100	.500
.20	.10	.003	.019	.074	.133	.532
.40	.20	.007	.034	.105	.172	.564
.60	.30	015	.056	.143	.216	.597
.80	.40	.029	.087	.188	.267	.631
1.00	.50	.054	.129	.244	.324	.667
----	.60	.095	.188	.311	.390	.705
----	.80	.263	.378	.495	.562	.795

NOTE: Correlations greater than .50 for first-degree relatives are not consistent with complete genetic determination but are included to provide examples of what the MZ twin risk might be in certain cases.

correlations, which are of course constant for varying prevalence, requires knowledge of the familial risk as well as the population prevalence and can be obtained using standard numerical approximations (Kirk 1973) or published nomographs (Smith 1970).

For a proband study, table 2 gives the number of first-degree relatives one must observe in order to assure a statistical power of .95 for detecting a significant increase in familial risk relative to a known population prevalence. For rare disorders of known prevalence and moderate heritability, a large number of first-degree relatives must be observed to assure adequate statistical power. This number is greatly increased if the prevalence must be estimated in a simultaneously studied control group (not shown in the table but derived using sample size calculations for comparing two independently estimated proportions). For example, for a liability heritability of .40 and a prevalence of .001, in order to assure a power of .95, 994 first-degree relatives would need to be studied if the prevalence is known, while 2,391 first-degree relatives and 2,391 controls would be required if the population prevalance were unknown. For more common disorders that are at least moderately heritable, the required sample sizes are moderate when the prevalence is known but remain large for unknown prevalence. For example, for a known population prevalence of .05 and a liability heritability of .80, only 53 first-degree relatives are required to achieve a power of .95. To achieve the same level of statistical power when the prevalence is unknown, however, 114 first-degree relatives and 114 controls are needed.

TABLE 2. *Number of independent relatives who must be studied to detect an increase in familial risk*

Liability Correlation	Population Risk .001	.010	.050	.100	.500
.10	5,039	1,862	1,082	1,017	2,638
.20	994	371	247	240	656
.30	324	139	101	102	283
.40	138	67	53	54	153
.50	64	37	31	32	92
.60	33	21	19	20	59
.80	9	7	8	9	26

NOTE: The table shows the number of independent relatives who must be studied to detect. with a statistical power of .95, an increase in familial risk over a known population prevalence, using a one-tailed test at p=.05.

RESOLVING THE SOURCES OF FAMILIAL RESEMBLANCE

The basic linear model for the specification of a phenotype can be extended to the phenotypes of several family members. If the subscript "i" is used to denote the individual, then

$$P_i = hG_i + cC_i + eE_i.$$

The correlation between the phenotypes of any two relatives (denoted by the subscripts "i" and "j") can be expressed as:

$$cor(P_i,P_j) = h^2cor(G_i,G_{j)} + c^2cor(C_i,C_j)$$

where $cor(G_i,G_j)$ and $cor(C_i,C_j)$ are, respectively, the correlations between the genotypes and familial environments of the two relatives. Precise specification of these two correlations will depend on the assumed model of phenotypic transmission.

Figure 2 provides a schematic representation or path diagram of one model of phenotypic transmission that has been widely applied in human and behavioral genetic research (Rao et al. 1979; McGue et al. 1983). The path diagram depicts transmission within a nuclear family consisting of a father, mother, and two children. Using the basic rules of path analysis (Li 1975), one can derive model-based correlations as functions of the four parameters of

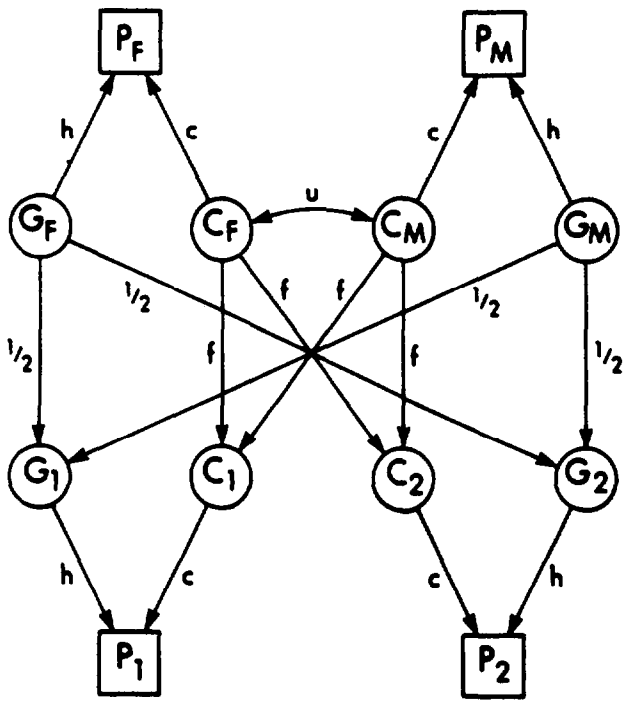

FIGURE 2. *Path diagram for the transmission of a quantitative phenotype in nuclear families*

NOTE: G, C, and P denote genotype, familial environment. and phenotype, respesc-tlvely. Subscripts F, M, 1, and 2 denote father, mother, and two children, respectively. Parameters of the model are genetic heritability (h^2), cul-tural heritability (c^2), effect of parental familial environment on off-spring's familial environment (f), and correlation between the familial environments of spouses (u).

the model: the genetic heritability (h^2), the cultural herit-ability (c^2), the effect of parental familial environment on off-spring's familial.environment (f), and the correlation between the familial environments of spouses (u).

Table 3 gives the model correlations for various familial rela-tionships for both the general four-parameter case and the case where environmental transmission mimics genetic transmission; f=1/2 and u=0 (i.e., the pseudopolygenic model) (Rice et al. 1978). The model correlations under the pseudopolygenic model clearly illustrate that, if both genetic and environmental factors

TABLE 3. *Model familial correlations*

Degree	Relationship	Familial Correlation: General Model	Familial Correlation: Pseudopolygenic Model
Identical	MZ Twins	$h^2 + 2c^2f^2(1 + u)$	$h^2 + 1/2c^2$
First	DZ Twins	$1/2h^2 + 2c^2f^2(1 + u)$	$1/2(h^2 + c^2)$
	Siblings	$1/2h^2 + 2c^2f^2(1 + u)$	$1/2(h^2 + c^2)$
	Parent-Offspring	$1/2h^2 + c^2f(1 + u)$	$1/2(h^2 + c^2)$
Second	Half-Siblings*	$1/4h^2 + 2c^2f^2(1 + u)$	$1/2h^2 + 1/4c^2$
	Aunt/Uncle-Niece/Nephew	$1/4h^2 + 2c^2f^3(1 + u)^2$	$1/4(h^2 + c^2)$
	Grandparent-Grandchild	$1/4h^2 + c^2f^2(1 + u)^2$	$1/4(h^2 + c^2)$
Third	Cousins	$1/8h^2 + c^2f^4(1 + u)^3$	$1/8(h^2 + c^2)$
---	Spouses	$c2_u$	0

*Reared by common parents.

NOTE: The model familial correlations were derived as functions of the model and the four parameters given in figure 2.

contribute to familial resemblance, the study of intact and typical familial relationships (e.g., parent-offspring, cousins, etc.) will not resolve the two sources of familial aggregation (i.e., the weighting of h^2 and c^2 is the same within each relationship).

To examine the genetic and environmental contributions to familial aggregation, three general approaches can be employed. First, twin studies and their derivatives (e.g., twin families (McGue et al. 1984)), as well as half-sibling studies, resolve genetic and environmental influences by comparing the magnitude of phenotypic resemblance between two relatives where the degree of genetic but not environmental similarity varies (e.g., monozygotic (MZ) vs. dizygotic (DZ) twins or full- vs. half-siblings). Second, adoption studies (Cloninger et al. 1984) allow direct estimation of the importance of genetic and environmental factors through the assessment of phenotypic similarity among biological relatives who share no environmental factors and among adoptive relatives who share no genetic background with the proband. Finally, the study of intact nuclear families allows resolution of genetic and environmental influences if a measure of the familial environment is available (Rao et al. 1984). For most behavioral traits, however, the presumed complexity of the familial environment precludes general application of this third approach.

The number of relatives one must observe in order to achieve a given level of power for the detection of the influence of genetic factors will, of course, vary depending on the design used (Moll

and Sing 1979; Heath et al. 1985). In the present paper, only the two most basic designs--adoption and twin studies--will be considered. In an adoption study, establishing the significance of genetic factors is equivalent to demonstrating familial resemblance among biological relatives who were reared apart. Therefore, table 2 can be used to determine the number of first-degree relatives one must observe in order to achieve a statistical power of .95. In a twin study, genetic factors are implicated if the MZ concordance rate is greater than the DZ concordance rate. Assuming equal numbers of MZ and DZ twin pairs, table 4 gives the number of twin pairs of each type that would be needed to assure a statistical power of .95 for the detection of genetic influences. Note that, even for moderate levels of heritability, a sufficiently large twin sample will provide powerful tests for the existence of genetic factors.

TABLE 4. *Number of MZ and DZ twin pairs needed to detect significant genetic effects*

Model		Population Risk				
h^2	c^2	.001	.010	.050	.100	.500
.40	.00	788	436	391	409	1,158
.40	.20	287	249	266	313	875
.60	.00	174	131	132	149	439
.60	.20	64	64	78	92	258
.80	.00	47	43	49	58	162
.80	.10	25	26	32	38	107

NOTE: The table shows the number of MZ and DZ twin pairs which must be studied In order to achieve a statistical power of .95 for detecting significant genetic effects, using a one-tailed test at p=.05.

It is worth while to compare the relative efficiency of twin and adoption studies for detecting the influence of genetic factors. If the population prevalence is unknown, then, relative to a twin study, an adoption study requires fewer observations for low values of the heritability and an approximately equal number of observations at higher values to achieve the same level of statistical power. For example, for a character with a population prevalence of .01 (h^2=.40 and c^2 =.00), a twin study requires 872 relatives (i.e., 2 times 436), while an adoption study requires only 371. For the same prevalence, when h^2=.80 and c^2=.00, the twin study requires 86 relatives and the adoption study, 67.

Factors such as variable age of onset and unknown population prevalence will reduce the efficiency of the adoption study relative to the twin study, An example is the above case, where the population prevalence is .01 (h^2=.40 and c^2=.00). If the population prevalence must be estimated, however, an adoption study would

need to observe 804 first-degree relatives and 804 controls in order to achieve the same level of power as 371 first-degree relatives with known prevalence and 872 twins with either known or unknown prevalence.

Quantification of the magnitude of genetic and environmental influences can be accomplished through analysis of the estimated familial (tetrachoric) correlations (Rao et al. 1981; Rice et al. 1981). To illustrate, for schizophrenia the MZ and DZ twin concordance rates are, respectively, 44.3 percent and 12.1 percent (Gottesman and Shields 1982). In the absence of additional information, all that can be concluded from these figures is that genetic factors play a role in the etiology of schizophrenia. Knowing that the population prevalence for schizophrenia is .85 percent (Slater and Cowie 1971) permits calculation of the MZ and DZ twin liability correlations as .853 and .501, respectively. These correlations can be further analyzed to yield estimates of the parameters of the model. From table 3, the model-based twin correlations are

$$r_{MZ} = h^2 + 2f^2(1 + u)c^2$$

and

$$r_{DZ} = 1/2h^2 + 2f^2(1 + U)c^2.$$

An estimate of genetic heritability is then given by

$$h^2 = 2(r_{MZ} - r_{DZ}) = .704.$$

Observations on additional familial relationships are required to identify the remaining parameters of the model and to test the goodness-of-fit of the model to the family data. General likelihood methods have been developed to estimate parameters and test hypotheses from categorical family data (Rao et al. 1981; Rice et al. 1981). However, these methods require, in addition to family data, information on the population prevalence of the disorder.

CHARACTERIZATION OF GENETIC AND ENVIRONNENTAL FACTORS

The goal of any twin/family study is ultimately to identify those genetic and environmental factors that contribute to disease etiology. For genetic factors, this would involve resolution of the mode of inheritance and, if evidence of a major gene effect is found, linkage studies and analyses in order to associate the gene with a specific chromosomal location, For environmental factors, this would involve an assessment of the relevant environmental factors and determination that the factors contribute to disease liability.

Behavioral pheontypes do not usuallly show simple Mendelian patterns of inheritance (e.g., recessive, dominant, etc.). For non-Mendelian categorical characters, genetic methods such as segregation and linkage analyses appear to have only limited power (Risch and Baron 1984). In order to resolve complex patterns of inheritance and genetic heterogeneity for such qualitative characters, it may be necessary to identify and use as alternative phenotypes the quantitative factors that contribute to disease liability.

The relationship between a quantitative risk factor and the expression of the disease can be characterized by observing both the risk factor and disease status of each individual. The basic linear model can be extended to allow for two or more observations (i.e., phenotypes) as

$$P_i = h_i G_i + c_i C_i + e_i E_i$$

where the subscript now denotes phenotype. The correlation between phenotypes "i" and "j" is given by

$$cor(P_i,P_j) = h_i h_j cor(G_i,G_j) + c_i c_j cor(C_i,C_j) + e_i e_j cor(G_i,G_j).$$

The correlation between two characters is thus partitioned into genetic, familial environmental, and nonfamilial environmental components. Multivariate genetic methods seek to resolve the components of phenotypic covariation through analysis of multivariate family data (DeFries and Fulker 1986). A quantitative risk factor with a high environmental but low genetic correlation with the disease status phenotype should provide insights concerning probable environmental mechanisms in disease etiology, while a quantitative risk factor with the reverse pattern of correlation should suggest possible genetic mechanisms.

The relationship between immunoglobulin E (IgE) and the inheritance of allergies illustrates the utility of multivariate genetic analyses. Briefly, allergies affect a sizeable proportion of the population, are familial, and genetic factors appear to play a major role in their etiology (Marsh et al. 1981). It has been hypothesized that the inheritance of allergies is mediated by the inheritance of IgE (Willcox and Marsh 1978). Indfviduals who inherit high levels of IgE possess a generalized hypersensitivity for developing allergic responses which may be expressed in several ways depending on early exposure.

The hypothesized relationship between IgE and the inheritance of allergies can be tested by analyzing family data where both allergies and IgE levels have been assessed in all individuals. As part of the Tucson Epidemiologic Study of Obstructive Lung Disease, Lebowitz et al. (1975) assessed IgE levels and responses to

skin prick tests for five different aeroallergens in 332 Caucasian nuclear families (1,313 total individuals). The within-person (biserial) correlation between positive response on the skin prick test and log IgE is .403 for adults and .471 for children (both significant at $p<.05$). Table 5 gives the familial correlations for positive skin prick response, log IgE, and between positive skin prick and log IgE. Note that there are substantial and significant between-phenotype familial correlations. If the inheritance of IgE accounts for the transmission of allergies, then the between-phenotype familial correlation should equal the square root of the product of the two within-phenotype familial correlations. The correlations in table 5 are generally consistent with this expectation. For example, for mother-offspring, the square root of the product of the two within-phenotype correlations is .234, a value that does not differ markedly from the between-phenotype correlation of .206. These data suggest, then, that the genetic transmission of allergies may be due to the transmission of IgE, which can now be the focus of future attempts to understand the genetics of allergies. Indeed, recent studies have shown that a recessive gene that influences IgE levels also contributes to risk for developing allergies and may explain the familial aggregation of allergies (Borecki et al. 1985).

TABLE 5. *Familial relationahip between allergies and IgE in the Tucson Epidemiologic Study of Obstructive Lung Disease*

	Familial Correlations		
Relationship	Positive Skin Prick	Log (IgE)	Between Skin Prick and Log (IgE)
Father-Offspring	.147	.146	.162*
Mother-Offspring	.243	.226	.206*
Siblings	.250	.266	.167
Father-Mother	.076	.055	.082

*Average of parent skin prick minus offspring log (IgE) and offspring skin prick minus parent log (IgE).

CONCLUSION

Substance abuse is a relatively rare disorder. Epidemiologic Catchment Area estimate of the lifetime rate for drug abuse/dependence is slightly greater than 5 percent (Robins et al. 1984). Little is known about its familial aggregation. This presentation focused on the types of twin/family designs needed to determine whether substance abuse is familial and, if so, the characteristics of the factors that contribute to familial risk. Several conclusions are warranted.

Family studies allow one to determine whether there is familial aggregation for the disorder, but not whether that aggregation is due to genetic and/or familial environmental factors. The power of a family study for identifying familial aggregation depends on whether the population prevalence of the disorder is known. If the prevalence is unknown, a much larger study is required to achieve the same level of statistical power than if it is known.

Twin and adoption studies allow one to resolve the genetic and/or environmental sources of familial aggregation. If the prevalence is known, an adoption study will provide a more powerful test for the existence of genetic factors than a comparably sized twin study. The reverse is true, however, if the prevalence is unknown. From a practical perspective, at least in the United States, twin studies may be easier to execute than adoption studies. The twinning rate of approximately 1.2 percent insures that there will be a sufficiently large population of substance-abusing twins to make a large twin study feasible. Twin and adoption studies should be undertaken in the drug abuse area.

Concordance rates in the absence of prevalence data are not fully informative concerning the basis of familial resemblance. Availability of prevalence data allows one to: (1) fit and test the adequacy of various models of phenotypic transmission and (2) quantify the magnitudes of genetic and environmental influences through estimation of statistics such as the genetic heritability. The power of genetic analysis is greatly enhanced by population prevalance information.

Characterizing the genetic and environmental factors that contribute to disease etiology will require twin/family designs where disease status as well as quantitative genetic and environmental risk factors are assessed for all participants. Multivariate designs and analyses will be needed.

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Exploring Drug Abuse With Genetic Strategies: Cautionary Tales

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INTRODUCTION

Sir Francis Galton could hardly have imagined that his suggestion in 1875 that the relative powers of Nature and Nurture could be uncovered by the study of twins would have led to the proliferation of twin studies in the 20th century. During the last quarter of the 19th century, Galton had noted the occasional appearance of twins with similar forms of insanity as well as a greater similarity in intellect and personality in same-sex twins than in opposite-sex twins. Great advances have been made from these crude beginnings, but it was not until 1930 that Luxenburger, a German psychiatrist, put twin research on a firm scientific footing with the requirement that sampling of the twin types be systematic and unbiased. He could easily show that case reports from the psychiatric literature were overloaded with identical twins and that most of them were concordant for whatever disorder was reported. Data gathered in such a fashion could not reveal the truths about the contribution of genetic and environmental factors to the etiology of psychiatric disorders. Nowadays, we recognize that familiality of psychopathology can arise from the sharing of genes and/or environments. Most often, some combination of genetic and environmental factors does the best job in accounting for the observed facts, even when the problem, disorder, or disease has a primary cause known to be nongenetic.

For the past half century of research on twins with mental disorders, the results have usually been reported in the form of concordance rates for identical and fraternal twins, with separate rates for the two sexes. Our thesis is that such concordance rates leave much of the meaning unextracted from the twin data. Furthermore, alternative hypotheses and additional perspectives about social, ecological, and biological (but <u>not</u> genetic) contributors to the likelihood of developing psychiatric disorders can be generated by twin data and by contrasting twin data with those from family and adoption strategies.

Our intent is not to criticize the literature in this area, but rather to show how additional meaning may be extracted from the data reported, once probandwise concordance rates (Allen et al. 1967) have been transformed into tetrachoric correlation coefficients and evaluated within the framework of multifactorial-threshold-polygenic (MFTP) models (Falconer 1965; Falconer 1967; Gottesman and Shields 1967; Reich et al. 1972; Reich et al. 1975a). Such a model has been found useful in the analysis of such diseases as diabetes, schizophrenia, alcoholism, coronary heart disease, and tuberculosis. These conditions are familial, common in the general population, i.e., not rare like the mendelizing diseases, and do not lend themselves to easy explanations in terms of mendelian genetics. We shall use the MFTP model to examine twin studies of schizophrenia, affective disorders, alcoholism, criminality, tuberculosis, and dyslexia in a search for models that may be most useful for adaptation to drug abuse and dependence. Alternative models are not excluded by our analyses, but they are not considered further in this paper.

Nothing said here should be construed as antagonistic to the idiographic (Allport 1937), descriptive psychiatric (Jaspers 1963; Slater and Roth 1969) approach to twin studies. Careful case histories and descriptions are of paramount importance to understanding the etiology of psychopathology. A number of twin researchers have provided detailed case histories supplementing their summary statistics and permitting an appreciation of the nuances and subtleties of psychopathology that cannot be gathered in any other way (Essen-Moller 1941; Kringlen 1967; Rosenthal 1963; Slater and Shields 1953; Tienari 1963). In our view, twin studies are a means to an end and not an end in themselves. Additional observations from spouses, adoptees, siblings, parents, and offspring are required to reduce the ambiguities inherent in the study of twins "in a vacuum."

PRELIMINARY PRECAUTIONS

Certain precautions are required before the twin method can even be suggested for the study of various types of psychopathology. After all, twins are studied to enable researchers to generalize to the general population of nontwin patients exhibiting those pathologies studied. If twins are not representative of the general population of patients, or if twinship per se correlates with certain kinds of psychopathology, the method will generate results that cannot be generalized. Unlike many other research strategies, the adequacy of the twin sample can be verified by internal checks on the proportion of the two sexes, the proportion of various zygosities, and whether twins are overrepresented in the reference population of schizophrenics, criminals, or drug addicts. Racial factors are important in these determinations as well (Bulmer 1970).

After infancy, about 2 out of every 100 Caucasian individuals in the United States and Western Europe are twins. This fact should encourage government-supported researchers to begin twin registers in their own settings; it also provides a benchmark against which

to evaluate the possible excess of twins with any particular diagnosis. Among individuals with mental deficiency, about 4 percent are twins, twice the expected rate. Twins comprise 6.7 percent of cerebral palsy cases (Hanson 1960).

Some common complications of pregnancy are even more common among twins and may have an effect on studies of psychopathology with differential effects by race. Relevant information can be found in Price (1950), Bulmer (1970), and Parisi (1974). Given the explicit and implicit sources of central nervous system (CNS) damage to twins, together with confounding factors such as organic mental disorders, mental retardation, and pervasive developmental disorders, it would be difficult to conduct a twin study of early infantile autism (EIA) and have results generalizable to the general population of autistic children. It is uncertain, but likely, that twins occur in excess in populations of autistic children (Hanson and Gottesman 1982). Using computerized tomography (CT) scans, Campbell et al. (1982) showed that 11 of 45 young autistic children had significantly enlarged ventricles. Folstein and Rutter (1977) reported that 11 pairs of EIA monozygotic (MZ) twins contained 4 concordant pairs, all probands, for a probandwise rate of 53 percent; none of 10 dizygotic (DZ) pairs were concordant; 13 of 25 EIA twins experienced significant biological hazards ranging from delay in delivery of the second-born to neonatal convulsions. The point is that traits or disorders confounded by obstetrical complications associated with twinship should be analyzed cautiously (Reveley et al. 1981).

One fact established about twinning that is relevant to some aspects of psychopathology is the relationship between maternal age and DZ twinning. MZ twinning is not associated with maternal age and appears to be a relative constant at 3 to 4 deliveries per 1,000. DZ twinning, however, is dependent on maternal age, parity, and race (Bulmer 1970; Parisi and Caperna 1981). At age 20, 3 per 1,000 deliveries among Caucasians are DZ twins; in the midthirties, 15 per 1,000 deliveries are DZ twins. The net effect of this phenomenon is to insure that maternal age in a random sample of fraternal twins will be higher than in a random sample of identical twins. For disorders in which maternal age at time of birth is considered relevant to psychopathology, for example, antisocial personality (Aichorn 1935) and its legal consequences, and possibly drug abuse and alcoholism, we might expect a difference in the prevalence of such behaviors in samples of fraternal compared to identical twins (Cloninger et al. 1978). Older, more mature mothers may be better disciplinarians for their sons than younger mothers (Johnson 1959). A diminished prevalence of criminality, delinquency, or drug abuse, if observed in fraternal twins, is the phenomenon to be explained, not something peculiar about identical twins, such as "identification," which leads to an excess of pathology in identical twins.

THRESHOLD DISEASES, PSYCHIATRIC DIAGNOSES, AND CORRELATIONS IN LIABILITY

The seminal paper by Falconer (1965) on the inheritance of liability to certain diseases, estimated from the "incidence" among relatives, permitted-the joining of the methods for quantitative genetics, with its long history in agriculture and biometrics, to the clinical genetic observations about apparently qualitative differences between the relatives of normals and the relatives of affected probands, i.e., starting index cases. The methods require the assumption that the disorder, such as dependence on substance X, has an underlying, continuous, normally dfstributed liability that is, conceptually, the final common pathway for all relevant genetic and environmental contributors. The qualitative information about the proportion of proband relatives similarly affected is transformed into a correlation in the underlying liability by means of the tetrachoric correlation coefficient or its equivalents. Bivariate normality is also assumed. The prevalence or the lifetime risk in the general population specifies the threshold point. Some biases inherent in the methods of Falconer were modified by Edwards (1969), Smith (1970), and Smith (1974).

If one were to make the unsafe assumption of no trait-relevant environmental similarities between relatives,the correlation in liability derived from Smith (1970), equals Rh^2 (R = the coefficient of genetic relationship; 1.0 for identical twins, and 0.5 for fraternal twins and other first-degree relatives in the absence of assortative mating) multiplied by h^2 (heritability of liability). Thus, it follows that the heritability for any set of relatives is equal to the phenotypic correlation coefficient divided by the genetic coefficient of relationship, but only after a number of simplifying assumptions. The graphical solution to r will contain some error, especially when the population risk exceeds about 5 or 6 percent, as it will for many forms of drug and alcohol abuse. We also caution that heritability estimates have very large standard errors with the usual twin sample sizes (Martin et al. 1978), so that we offer these techniques in the context of discovery and hypothesis generation. The heritability derived from these procedures is narrow sense heritability, which refers only to the proportion of total variance associated with additive genetic factors. Broad sense heritability, on the other hand, includes variance associated with dominance, assortative mating, and epistasis (i.e., gene x gene interaction) (Falconer 1981). If we set the variance in total liability equal to V, it can be decomposed into all genetic variance, V_G, + V_U + V_C, where V_U is the within-family environmental variance that makes siblings unique, and V_C is the between-family variance that siblings share in common and that makes them alike. We use the notations V_U and V_C rather than E_1 and E_2 associated with the Jinks and Fulker (1970) and Eaves et al. (1978) approaches to avoid the implication that an analysis of variance has been conducted for the correlations derived from the MFTP approach.

We shall extract some of these components of liability from twin data below. First, we must make the important point that concordance rates disembodied from the associated population risk lead to ambiguous conclusions in regard to the etiology of a disorder. Table 1 selects two representative concordance rates for identical twins: 50 percent and 80 percent. The body of the table shows that the meaning attached to the concordance rate is completely dependent on the associated population risk. Thus, a concordance rate of 50 percent in identical twins can be an indication of either a highly heritable trait (given a low population risk) or a disorder with trivial genetic contributions as the population risk increases, such as for marijuana use in young adult twins. Concordance rates in identical twins as high as 80 percent are difficult to interpret in isolation, but they imply high correlations in liability even with very high population risks. As we shall show shortly, however, very high correlations in liability for identical twins may occur in the context of disorders with no heritability. The quantity known as relative risk is calculated from the risk in relatives divided by the population risk. We show this quantity to make the point that it is not a useful indicator to the kinds of problems we deal with in psychiatric genetics. Although very high relative risks point toward something genetic, low relative risks do not exclude high heritability.

TABLE 1. *MZ correlations in liability to a multifactorial disorder with fixed concordance rates**

Population Risk (%)	At r=50%	Relative Risk	At r=80%	Relative Risk
.1	.92	500.0	.99	800.0
1.0	.87	50.0	.98	80.0
5.0	.80	10.0	.96	16.0
10.0	.72	5.0	.95	8.0
20.0	.62	2.5	.95	4.0
50.0	.00	1.0	.80	1.6

*Correlation in liability from graphical solution in Smith (1970)

SOURCE: Derived from Gottesman and Carey 1983.

The correlations in liability for identical and fraternal twins cannot be used as two independent estimators of heritability in the broad sense, because they contain other variance components. Besides genetic variance, it is reasonable to suspect a priori. that, for behavioral traits, nongenetic familial effects (V_C) contribute to the phenotype correlation. The equations below show the basic twin correlations in terms of variances as well as the general equations for total variance in liability and h^2_B and h^2_N.

1. $V = \underbrace{V_A + V_D + V_{Ep}}_{V_G} + \underbrace{V_C + V_U}_{V_E}$

   1.1 Heritability (h^2_B) in the broad sense $= V_G/V$

   1.2 Heritability (h^2_N) in the narrow sense $= V_A/V$

2. $r_{MZ} = (V_A + V_D + V_{Ep} + V_C)/V = (V_G + V_C)/V$
3. $r_{DZ} = (1/2V_A + \rho V_A + 1/4V_D + <1/4V_{Ep} + V_C)/V$
4. $2(r_{MZ} - r_{DZ}) = (V_A - 2\rho V_A + 3/2V_D + >3/2V_{Ep})/V$
5. $2r_{DZ} - r_{MZ} = (2\rho V_A - 1/2V_D - >1/2V_{Ep} + V_C)/V$
6. $1 - r_{MZ} = V_U$

With twin data, we only have two observations, the MZ and DZ correlations in liability, plus the constraint that the proportions of variance components must sum to 1 (equation 1). From the equations there are six unknowns, but we can only estimate three of them. For our purposes, we make the assumptions of no dominance (V_D) and no epistasis (V_{Ep}). In general, this simplification should not be too critical,since additive genetic variance is the largest component (Morton 1982). We also assume no assortative mating **(ρ),** recognizing that its presence will result in an underestimation of genetic effects and an overestimation of common environment. The need to make these assumptions demonstrates how important it is to complement twin data with data from other types of relationships, to reduce uncertainty. For substance abuse (Reich et al. 1975b) as well as for affective disorders, known values for assortative mating can be entered.

By taking two times the difference in correlation coefficients, we obtain, via equation 4, an estimate of the magnitude of genetic effects that will be an overestimate if dominance (V_D) or epistasis (V_{Ep}) variance is important, or an underestimate if assortative mating **(ρV_A)** is important. We can estimate the quantity V_C via equation 5, by subtracting the identical twin correlation coefficient from two times the fraternal twin coefficient. We can estimate the quantity V_U, the unique environmental influences, by subtracting the identical twin correlation from 1. Whenever the fraternal twin correlation exceeds .5, it is a clue to the need to search for V_C and/or assortative mating. The assumptions one wants to make about the sources of genetic variance other than V_A in equations 4 and 5 are critical for their application to twin data for any particular psychiatric disorder or trait (Carey and Rice 1983).

Unlike table 1, which fixed concordance rates, table 2 fixes the heritability as high (.8) or low (.2) and shows various combinations of identical and fraternal twin concordance rates that will yield such high or low heritabilities. Once again, the general population risk for the disorder similarly defined is critical. It is clear that low absolute levels of concordance either for identicals or for fraternals is still compatible with high heritabilities

for disorders with the kinds of population risks observed for the so-called functional psychoses. As the population risk for a disorder increases toward 20 percent, as it will for alcohol and drug abuse in some sectors of society, the moderate concordance rates generated in twins do not yield evidence for appreciable genetic contributions. In this table, the relative risks as well as the ratio of the MZ:DZ concordance rates are given. Both quantities are ambiguous indicators of facts better determined directly from the correlations in liability. Notice that both high and low relative risks are compatible with high heritability and that considerable variability in the ratio of concordance rates occurs, despite the fixing of the heritability at .8.

TABLE 2. *Expected concordance rates for high (.8) and low (.2) heritability disorders*

	High Heritability				Low Heritability			
Population Risk (%)	MZ (%)	DZ (%)	Relative Risk*	Ratio MZ%/DZ%	MZ (%)	DZ (%)	Relative Risk*	Ratio MZ%/DZ%
.1	26	2.8	260/28	9.3	.65	.28	6.5/2.8	2.3
1.0	38	8.5	38/8.5	4.5	5.30	1.90	5.3/1.9	2.8
5.0	50	19.0	10/38	2.6	10.50	7.50	2.1/1.5	1.4
10.0	55	26.0	5.5/2.6	2.1	17.00	13.00	1.7/1.3	1.3
20.0	65	35.0	3.2/1.8	1.8	28.00	23.00	1.4/1.2	1.2

*Concordance/population risk, MZ/DZ.

SOURCE: Derived from Gottesman and Carey 1983.

THE LIABILITIES TO PSYCHIATRIC DISORDERS AND ALCOHOL DEPENDENCE/ABUSE

As noted earlier, one of the biggest deterrents to interpretation of twin concordance rates for different psychiatric disorders is the absence of risks in the general population for disorders similarly defined and diagnosed. Twin data were selected where population risks are presented or easily determined to reevaluate twin data in the literature. Table 3 presents a reanalysis of the classical twin study on alcoholism conducted by Kaij (1960) in Sweden. Kaij's findings included census data on the general population of Swedish males indicating various levels of alcohol abuse. Only information from official records is presented and used, although Kaij analyzed the data based on his personal followup of most of the twins. Although the total sample consisted of 59 MZ probands and 146 DZ probands, some of the definitions lead to small sample sizes. For example, only seven MZ probands were chronic alcoholics. Again, our analysis is meant to be exploratory. All definitions for alcohol abuse in terms of severity result in substantial heritabilities, although it does appear that

chronic alcoholism may be more heritable than the others. One fact that emerges from this analysis is the trivial contribution to the liability to chronic alcoholism from common familial effects, V_C, which would include such factors as social class and family attitudes toward drinking. As the definition for alcohol abuse is broadened in the cotwins, such common environmental factors take on considerable weight. One clue to this phenomenon is the correlation in liability for fraternal twins exceeding .50. One analysis was derived from selecting as probands those twins who were defined only at level b, that is, having a single conviction for alcohol abuse during their careers. By using any definition of alcohol abuse in cotwins, we found a 36 percent concordance rate for both MZ and DZ pairs. The resulting correlations in liability were both .60, which guarantees a zero heritability. In this kind of analysis, for what may be called mild alcohol abuse, it appears that all the variance in liability is nongenetic, with V_C equal to .60 and VU equal to .40. Our cautions above, about the assumptions required before using the equations, should be stressed. Many other lessons relevant to the drug abuse field can be gleaned with the information in table 3.

In table 4, we present reanalyses using the methods above for some conditions to stimulate drug abuse researchers interested in genetic possibilities. The data on affective disorders are taken from the important twin study by Bertelsen (1979) and Bertelsen et al. (1977) conducted with the Danish Twin Register. His total sample consisted of 110 pairs. We use his best guess as to the population risk for manic-depressive psychosis (bipolar + unipolar), 1.2 percent, and then estimate the population risk for bipolar psychosis as a proportion of that total risk using data given by Bertelsen. The credibility of our reanalyses for the data in table 4 would be undermined by using population risks gathered in different countries by clinicians with differing orientations toward diagnosis. By restricting ourselves in this fashion, we believe we can make more sense of the data. Our expectation that bipolar psychosis would be more heritable than manic-depressive psychosis as a whole could not be confirmed. The bipolar probands are nested within the manic-depressive probands; the remaining cases are unipolar. Although both categories of affective psychoses are highly heritable, there is considerable room left for common family variance, V_C.

The data tables for schizophrenia come from a pooling of the modern studies on schizophrenia in twins (Gottesman et al. 1982). All concordance rates are probandwise (Allen et al. 1967). The criteria for diagnosing cotwins can be equated with the population risks for definite (.85 percent) and for definite plus probable (1.17 percent) reported by Slater and Cowie (1971) for Western European psychiatric epidemiology, coinciding with the location of the twin studies. Schizophrenia appears to be as heritable as the affective psychoses despite the lower concordance rates for identical and fraternal twins. Unlike the affective psychoses, the liability to schizophrenia appears to be little influenced by common family variance. However, the total nongenetic variance is .30,

TABLE 3. *Severity thresholds for alcoholism and the consequences for concordances and heritabilities in Kaij's Swedish twin study*

Definition for Proband (1)	Definition for Cotwin	Population Risk (%) (2)	Probandwise Concordance MZ%	Probandwise Concordance DZ%	r_{MZ} (3)	r_{DZ} (3)	h^2 (4)	V_C/V (5)
e	e	.57	86	10.0	.99	.50	.98	.01
cd+e	e	.57	24	7.5	.71	.44	.54	.17
b+cd+e	e	.57	15	4.1	.59	.30	.58	.01
e	cd+e	1.90	100	30.0	1.00	.70	.60	.40
cd+e	cd+e	1.90	53	26.0	.87	.65	.44	.43
b+cd+e	cd+e	1.90	46	23.0	.82	.60	.44	.38
e	b+cd+e	7.70	100	30.0	1.00	.50	1.00	.00
cd+e	b+cd+e	7.70	79	41.0	.97	.68	.58	.39
b+cd+e	b+cd+e	7.70	61	39.0	.85	.64	.42	.43

(1) Definitions of severity from Kaij (1960): e = chronic alcoholism for 10 years, cd = multiple convictions for intoxication, b = single conviction.

(2) Actual population prevalences reported by Kaij (1960) from a census of all Swedish men in 1947--7.7 percent were noted to have alcohol abuse.

(3) Correlation in liability from graphical solution in Smith (1970).

(4) Broad sense heritability from equation 4.

(5) Variance in liability from shared environmental influences from equation 5.

SOURCE: Derived from Gottesman and Carey 1983.

the balance being made up of idiosyncratic or unique environmental variance, or V_U. With regard to schizophrenia, path analysis using other degrees of familial relationship is convergent with the analyses from twins (McGue et al. 1985; Rao et al. 1981).

The data on male and female criminality in twins represent a final update on the initial sample for Christiansen's Danish twin study (Cloninger and Gottesman 1987; Christiansen 1977). The probandwise concordance rates shown in table 4 are not in need of age correction, as all the twins are through the risk period. The population risks shown for felony offenses are the lifetime risks using the total twin population from the Danish Twin Register for all twins born in the eastern half of Denmark between 1881 and 1910, in which both twins survived at least until age 15, the age of criminal responsibility. The risks were calculated only from same-sex pairs registered in the National Police Register and are very similar to data for nontwins (Wolf 1965). The base population of twins from which the offenders were identified consisted of 1,462 male pairs

TABLE 4. *Twin data for disorders with population risks determined by equivalent homotypic criteria*

Disorder	MZ%	DZ%	Population Risk (%)	Relative Risk MZ/DZ	MZ:DZ Ratio	r_{MZ}	r_{DZ}	h^2	V_C/V
Manic-Depressive Psychosis	69	22	1.20	58/18	3.1	.95	.63	.64	.31
Bipolar Psychosis	79	19	.32	247/59	4.2	.99	.69	.60	.39
Schizophrenia (S)	44	12	.85	52/14	3.7	.85	.50	.70	.15
Schizophrenia (S+?S)	46	14	1.17	39/12	3.3	.85	.50	.70	.15
Male Criminality (Felony)	51	30	10.00	5/3	1.7	.74	.45	.58	.16
Female Criminality	33	13	1.60	21/8	2.5	.74	.45	.58	.16
REading Disability	91	45	14.00	6/3	2.0	.99	.61	.76	.23
Tuberculosis	87	26	1.37	64/19	3.3	.99	.66	.66	.33

and 1,580 female pairs. The male probands consisted of 73 MZ and 146 DZ twins, while the female probands consisted of 15 MZ and 28 DZ twins. The data on criminality provide a striking example of how quite different concordance rates between the sexes still reduce to the very same correlations in liability and the consequent heritabilities. For adult crime, as defined within this particular sample over this particular time period (the twins were last followed up in 1977), we find marked heritability, a trivial contribution to liability from common family variance, but an appreciable contribution from unique environmental factors (perhaps bad luck and temptation). V_U amounts to .26. Preliminary evaluation of twins who are juvenile delinquents yields very different results: no genetic variance and large V_C estimates (Gottesman et al. 1983).

The results of these kinds of analyses are shown for two further disorders: reading disability, with a population risk relevant to drug use (14 percent); and tuberculosis, a known infectious, i.e., environmental, disease. The twin-based heritability for the liability to tuberculosis is wrong; it is presented in order to embarrass the method in this instance where we know that a bacillus is the primary causal agent.

The information in table 5 from the risks to other relatives, including spouses and half-siblings, can be fitted to path models (McGue et al. 1985) to determine the heritability (h^2) and the environmentability ("cultural transmissibility" or c^2) of the liability to this infectious disease. The results reveal that c^2 is .62 and h^2 is .06 for this classical data set (Kallmann and Reisner 1943) on the relatives of cases. The twin-based value of h^2.66, is misleading and incorrect. The path model results reveal a role for genetic factors, albeit small at .06, in determining resistance to the bacterial/environmental vector. Could

such a model be relevant to understanding the role of genetic factors in drug abuse/dependence?

TABLE 5. *Rates of tuberculosis in relatives of tuberculosis index cases, observed tetrachoric correlations, and expected correlations under each of three path models*

			Tetrachoric Correlations			
				Model Expectations		
Relationship to Proband	BZ*	Affected (%)	Observed	General	Environ-mental	Genetic
Spouses	197.5	7.1	.314	.281	.291	.00
Parents	676.0	16.9	.541	.558	.552	.50
Siblings	534.0	25.5	.663	.647	.649	.50
MZ Twins	55.0	87.3	.992	.992	.992	1.00
DZ Twins	164.0	25.6	.665	.647	.649	.50
Half-Siblings (Reared by Common Parent)	33.5	11.9	.445	.611	.649	.25

*BZ = age-corrected sample sizes

NOTE: Family data were reported originally in Kallmann and Reisner (1943), age corrections were made using the abridged Weinberg method, and tetrachoric correlations were calculated using a lifetime risk for tuberculosis at that time estimated by Kallmann and Reisner to be 1.37 percent.

SOURCE: Derived from McGue et al. 1985.

CONCLUSIONS

We have shown that the common practice of simply reporting proband-wise concordance rates for psychiatric disorders leaves much of the meaning unextracted from the data. We recommend that appropriate population risks be determined and that the concordance rates be converted into correlations in the liability toward developing the disorder. Further manipulations of correlation coefficients result in statistics that can be interpreted within the discipline of quantitative genetics and may provide directions for further research. Many other innovations and developments have taken place over the past decade of twin research and should be consulted by those contemplating the use of twin strategies (Eaves et al. 1978; Fulker 1978; Liston et al. 1981; Rose et al. 1980).

Twin strategies are alive and well but, like all strategies in research, require an awareness of their limitations, assumptions,

and appropriateness. Our nation's current and future twin registers are an untapped gold mine for exploring the feasibility of multifactorial genetic and environmental models for drug abuse/addiction.

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ACKNOWLEDGMENTS

Preparation of this paper was aided in part by grants MH 31302, AA 03539, and MH 36517 to Washington University School of Medicine and a fellowship to the Center for Advanced Study in the Behavioral Sciences, Stanford, CA, supported by the John D. and Catherine T. MacArthur Foundation. This paper draws on earlier work (Gottesman

and Carey 1983; McGue et al. 1985), which presents some of these ideas in greater detail.

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Biological Vulnerability: Treatment Implications/Applications

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INTRODUCTION

When this conference was being planned, we agreed to provide comments on the implications of biological vulnerability issues for treatment of drug abuse. In some subsequent listings of the conference program, our topic, "implications," was changed to "applications." This change led to some anxiety on our part, as we felt that treatment application in this area would be premature at this time. Clearly, though, utilization of biological vulnerability information to improve treatment efficacy and patient-treatment matching is a desirable long-term goal. Thus, while we are perhaps not yet able to proceed with valid therapeutic applications, certainly the developing data and issues in this area do have implications for how studies of biological vulnerability might proceed. While this distinction between implications and applications may seem like a trivial matter of semantics, we believe it is important; the words we select can carry with them unintended suggestions of what we believe to be the current developmental status of our understanding of biological vulnerability issues.

To suggest that we can productively discuss treatment applications of differences in biological vulnerability would be to imply that we are fairly advanced in our understanding of this area. The applications goal in studying biological vulnerability is that we might ultimately be able to match appropriate treatments to individual characteristics. At present, however, we are far from such a capability. To achieve this goal, we need to understand the nature of and the differential processes inherent in individual differences in biological vulnerability, as well as the elements and processes of effective substance abuse treatment. Unfortunately, our knowledge in these critical areas remains in its infancy.

Thus, we offer at the outset our general conclusion that, at the present time, our knowledge about the processes involved in biological vulnerability and effective drug abuse treatment are too rudimentary to allow us to use this information about individual differences to guide differential treatment.

While we suggest that vulnerability differences and processes are not yet developed or understood enough to have major application in treatment delivery, we certainly believe that the data are strong enough and the relationships important enough to have major implications for treatment. However, much more research is needed before it will be possible to translate these data and relationships into practical therapeutic application.

The general organization of our discussion will be:

- What is biological vulnerability?
- How might it influence treatment?
- How has it influenced treatment of disorders/diseases other than drug abuse?
- What is needed to achieve application in the drug abuse field?

INDIVIDUAL DIFFERENCES IN BIOLOGICAL VULNERABILITY

The concept of biological vulnerability refers to the entire range of innate individual difference characteristics that might be associated with increased likelihood of an individual's developing a drug dependence disorder. This innate biological vulnerability should not be viewed as a dichotomous variable--with an individual being either vulnerable or not--but rather as a multifaceted construct which varies along a continuum from high vulnerability to low vulnerability. By definition, all drug abusers must have some degree of biological vulnerability, otherwise they would be biologically invulnerable and could not have become drug abusers. The multifaceted nature of biological vulnerability is evidenced, for example, in Oriental populations, which, despite the biological protective factor of the flushing response to alcohol, continue to display some degree of vulnerability to alcoholism. It is at present unclear whether complete biological invulnerability exists.

It should be abundantly clear that there are great individual differences in vulnerability to substance abuse disorders. Some individuals become substance abusers, and others do not; some become dependent, and others do not. The other presentations at this conference indicate that a wide range of variables might serve as markers of these individual differences in drug abuse vulnerability. Perhaps most prominent among these putative markers of biological vulnerability is family history of substance abuse or psychiatric disorder, but such markers might also exist in the domains of personality characteristics, mood and affect, and neuropsychological or behavioral responses to drugs. A major scientific challenge remains in determining the extent to which these various markers of vulnerability represent biological (or genetic) as opposed to acquired factors. Also, it remains unclear whether the different markers all relate to the same vulnerability process or whether there might be multiple, independent biological vulnerability processes operating.

POTENTIAL INFLUENCES

Regardless of how it is assessed and regardless of whether it is a unitary or multifactorial construct, there are two general ways in which an individual's biological vulnerability might influence treatment decisions. These are in the areas of whether to treat and how to treat. If knowledge of a patient's biological vulnerability status were to influence either one of these factors, this would certainly represent an application of this knowledge to substance abuse treatment.

Diagnosis

Diagnosis is the process of determining whether a specific disorder is present. Thus, it is the critical step in deciding whether or not to treat. Individuals with diagnosed disorders presumably warrant treatment; intervention in the absence of a diagnosed disorder presumably falls into the domain of prevention rather than treatment. If biological vulnerability information were to influence the diagnostic evaluation of individual patients, this would clearly have a direct and major impact upon treatment decisions. This is not used at present. Current DSM-III/IIIR diagnostic criteria for substance abuse disorders do not include individual vulnerability factors, e.g., family history of substance abuse, in the process of diagnostic determination. If this were to be done, it is possible that two patients with identical clinical presentations but with differing vulnerability characteristics might be differently diagnosed and, consequently, differently treated.

The most likely context within which biological vulnerability assessments might influence diagnostic decisions is that of the patient with mixed symptoms, e.g., the case of the depressed alcoholic with a positive family history for either depression or alcoholism (but not both). In such a case, it is likely that the patient's primary diagnosis would be that for which there was a positive family history. Thus, although such diagnostic roles for family history information do not appear in the official criteria of the Diagnostic and Statistical Manual, practical clinical realities are likely to result in this type of diagnostic application. Data concerning the validity of such applications are lacking at present.

Treatment Methods

The clearest way in which biological vulnerability information might affect treatment would be if different treatment modalities or different treatment goals were prescribed for individuals with differing biological vulnerability characteristics. This ability to practice effective patient-treatment matching so as to maximize therapeutic outcomes is perhaps the ideal applications goal for studies of biological vulnerability. At present, data do not exist to guide such differential treatment. However, as with diagnostic applications, we need to recognize that practical clinical realities will likely result in treatment applications of biological

vulnerability information even in the absence of supporting data. A likely application would be the prescription of more intensive or intrusive treatments to patients with positive family histories, or perhaps the prescription of those specific modalities to which the patients' relatives responded.

Prognosis

A third way in which biological vulnerability factors might be related to treatment deserves mention. This is as a possible prognostic marker. For example, data from the alcoholism field indicate that alcoholics with positive family histories, i.e., genetic loading, for alcoholism follow a more rapid and more severe course of deterioration. A prognostic marker would not necessarily have any influence at all upon the therapist's diagnostic and treatment decisions. Thus, while it might be a correlate of treatment outcome, biological vulnerability status as a prognostic marker might have no influence upon recommendations for patient care. It is likely, however, that therapists would be more adamant and aggressive in prescribing the usual therapies to individuals whose prognostic markers indicate that they are at greater risk of adverse outcome. This is a potential subtle influence upon treatment; the nature of recommended treatment is not altered, but the therapist's motivation to deliver it might be.

OTHER DISORDERS

In order to obtain some framework or reference point with which to discuss how biological vulnerability might influence drug abuse treatment, it seems worthwhile to consider the examples of other disorders or diseases for which biological predisposition has been demonstrated. Perhaps examination of the historical examples provided by these other disorders might tell us what applications we could expect to see in the drug abuse treatment field. For this exercise, we have chosen to consider the examples provided by a selection of disorders for which a positive family history is known to be a marker of increased biological vulnerability. Thus, we discuss six different disorders with significant heritability: three medical disorders and three psychiatric/behavioral disorders.

For the medical disorders, we have chosen to consider hypertension, diabetes, and coronary heart disease (CHD). For each of these three, a positive family history of disease is a significant risk factor for an individual's developing the disease. The questions we want to ask concerning these disorders are the following: Is diagnosis of the disorder influenced by knowledge of the individual's family history? And, once an individual is diagnosed as having the disorder, are any treatment decisions influenced by whether or not the patient has a positive family history of the disorder? For all three disorders, it appears that the answers are "No." For none of these medical disorders does family history have a significant impact upon either diagnosis or treatment decisions. Rather, diagnosis is based upon objective aspects of the patient's clinical presentation, and treatment decisions are based upon that

diagnosis and upon the clinical presentation of the individual patient, regardless of the individual's family history of disease.

Thus, overall, the historical examples provided by these three medical disorders suggest that biological vulnerability may have little impact upon treatment. The diagnostic criteria for, and the therapeutic response to, elevated blood pressure, elevated blood glucose, or cardiac ischemia have been unaffected by family history factors indicative of elevated biological vulnerability.

What about psychiatric/behavioral disorders? Is their diagnosis and/or treatment affected by individual vulnerability considerations? As historical examples of the impact of biological vulnerability for psychiatric disorders, we have chosen to consider schizophrenia, depression, and alcoholism. Again, as with the medical disorders, we find no evidence that either the diagnostic criteria for, or the therapist's response to, these disorders is influenced by biological vulnerability/family history factors. Rather, treatment decisions are based on the characteristics and presentation of the individual patient, independent of family history factors.

Thus, the historical examples provided by these six other disorders tell us that we must be prepared for the possibility that biological vulnerability issues will similarly have little or no treatment impact in the drug abuse area.

The primary area in which genetically loaded vulnerability factors have affected the handling of medical disorders is that of prevention--primarily through the mechanism of early detection and intervention. Thus, individuals with family histories of hypertension, diabetes, or CHD are typically advised to have periodic diagnostic assessments to detect potential onset of disease as early as possible. It may be the case that similar preventive or early detection activities may be the chief domains in which biological vulnerability factors will influence our handling of substance abuse disorders.

Also, though we are aware of no data on this issue, we suspect that a close examination of the treatment of these other biologically loaded diseases would reveal subtle influences upon therapist behavior resulting from the prognostic implications of positive family histories of the diseases. For example, a normal and appropriate therapeutic recommendation for cases of ischemic heart disease or adult-onset diabetes is a regular regimen of physical exercise. We suspect that the likelihood and firmness with which such an exercise prescription is made will be greater in patients carrying the added risk factor of a positive family history. A similar subtle effect on the therapist seems likely to occur in the drug abuse treatment area.

PREREQUISITES FOR TREATMENT APPLICATION

The experience discussed above with other, non-drug-abuse disorders suggests that biological vulnerability information may have little if any impact on treatment. However, we think it is possible that this information may come to have a very significant impact on drug abuse treatment. Before such treatment applications can occur, it will be necessary to have both scientific and practical advances in several areas.

Recognition/Detection

Improved methods for identifying individuals with heightened vulnerability are needed. The emphasis in current efforts to identify vulnerable individuals is upon family history. Yet it remains unclear exactly what family history factors confer risk. Family histories of drug abuse, alcoholism, antisocial personality, and other psychiatric disorders are all among the candidates. We need to determine which familial factors confer risk, and, if there are multiple familial factors, we need to determine whether they all confer risk of the same type or through the same mechanism. For example, does a family history of one type of substance abuse/dependence, e.g., alcoholism, confer increased risk for other types, e.g., opiate abuse? Does a family history of multiple types of disorder confer a different or greater risk than a family history of only one type of disorder? Once we know what the relevant risk factors are, we need adequate methods for assessing those risk factors. The methods used for assessment of vulnerability status must possess adequate sensitivity and specificity; schemas with high rates of false positives or false negatives will generally be unacceptable for clinical application. Ideally, these methods should yield a quantitative evaluation rather than a categorical labelling of vulnerability status; quantitative evaluations permit more precise differential assessments among individuals.

Unfortunately, the family history method has substantial weaknesses on both of these last two points: it is imprecise, and it is categorical. In the family history method, patient vulnerability status is categorized based upon the characteristics of the patient's blood relatives. Since we do not yet know how to identify the vulnerability characteristic in an individual patient, we look for markers in his/her relatives. However, there is substantial imprecision due to the facts that not all vulnerable individuals have positive family histories and not all individuals with positive family histories display the vulnerability. Clearly, it would be preferable if the vulnerability characteristic could be directly detected and assessed within individual patients. Thus, our major recommendation in this area is that efforts to identify vulnerable individuals begin to focus upon characteristics of the individual in coordination with characteristics of his/her family members. These efforts will move us beyond the stage of using family history as a rather global marker or risk factor and should yield new information about the pathophysiological processes and

mechanisms involved in elevated substance abuse risk. This information will permit the design of treatment strategies specifically targeted to those processes and mechanisms and is more likely to yield acceptable levels of sensitivity and specificity of detection.

At present, while we must continue to rely upon the family history method for detection of biological vulnerability, improvements to this methodology would be desirable. Different investigators use different methods and it is not yet clear which methods for assessing family history are most valid and appropriate. Some investigators rely upon patient interviews, while others also interview other family members. The severity of prior disorder required for classification as family history positive varies across studies. Evaluation and scientific consensus on techniques for assessing family history would be useful.

Alternative Treatments

For differences in patient vulnerability characteristics to have an effect on treatment, it is necessary that there be some variety among treatment approaches. Assessing individual differences can have little practical import if all patients are treated the same regardless of that assessment. Alcoholism provides an example of a field in which it is clearly documented that biological vulnerability plays a significant role but in which the available treatment methods and goals are generally rather homogeneous--the major difference being whether treatment is delivered on a residential or an outpatient basis. In the absence of significant treatment variety, determination of the presence or absence of a positive family history of alcoholism has no major impact on treatment delivery. The situation with respect to treatment variety is only slightly better in the drug abuse field, where the specific modality of methadone maintenance is used with a significant number of patients. If treatment is to be influenced by biological vulnerability assessments, it is necessary that a variety of treatments be developed and that these treatments bear some meaningful relationship to specific, identified pathophysiological processes or mechanisms associated with the heightened vulnerability.

Patient-Treatment Matching

The ultimate treatment applications goal for studies of biological vulnerability is to be able to match patient subgroups to the specific treatment approaches that are most successful for individuals with their identified characteristics. Therefore, once we are able to identify the patient with a significant loading on biological vulnerability, and we have alternative treatments to choose from, the final step to achieving treatment application is to develop a data base justifying such patient-treatment matching. This will require a great deal of careful clinical research. Unfortunately, at present most clinical therapeutics research in the substance abuse field does not involve assessment of biological vulnerability status or analysis of its relation to treatment response. The

studies that are needed must do more than examine the relation of vulnerability status to treatment outcome. It is likely that heightened vulnerability will be a correlate or predictor of poor prognosis, but that simple correlation cannot justify differential treatment decisions. What is needed are data indicating that the relative efficacies of treatments A and B are reversed for patients with and without high biological vulnerability, i.e., treatment A is better for one group, while treatment B is better for the other. If it should turn out that there are different types of biological vulnerability operating through different mechanisms, then it would be necessary to conduct similar research for each type.

CONCLUSION

At present, our understanding of biological vulnerability issues in substance abuse remains in a primitive stage. Further understanding of the bases for individual differences in substance abuse vulnerability offers considerable promise for improving the efficacy of substance abuse treatments. As our science advances, we will understand better how to recognize or detect the individual with heightened biological vulnerability, we will understand better whether this biological vulnerability is a unitary or multifactorial construct, we will understand better the specific pathophysiological processes and mechanisms involved in expression of this vulnerability, and we may understand better how to select treatments that are specifically appropriate to the characteristics of individual patients. The last of these steps--that of actual application via patient-treatment matching--is the only one about which we have significant uncertainty. While we feel certain that our understanding will advance, we are less certain that this improved understanding will yield treatment applications. Our consideration of other medical and psychiatric disorders with significant biological vulnerability loadings failed to reveal instances of treatment application of vulnerability information for those disorders. Applications in the prevention field seem certain to accrue from studies of biological vulnerability; applications in the treatment field remain a scientific challenge and a yet-to-be-fulfilled hope.

ACKNOWLEDGMENTS

Preparation was supported in part by U.S. Public Health Service grants DA-00050 and AA-07026.

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The Applications of Biological Vulnerability Research to Drug Abuse Prevention

Edward Kaufman

INTRODUCTION

Alcoholism studies are well ahead of drug abuse research in the understanding of biological vulnerability to substance abuse and dependence. The papers that are presented in this monograph attest to the disparity of knowledge between the two fields. There are several as yet unanswered questions about the relevance of existing alcoholism findings for drug abuse. These questions include: (1) How much of the conclusions based on alcoholism studies of biological vulnerability are directly applicable to drug abuse? (2) Which studies should or can be replicated? (3) In view of the high prevalence of alcohol abuse among drug abusers and of drug abuse in alcoholics, to what extent are the two groups made up of the same persons? (4) How often is the family of procreation of one generation's alcoholic the family of origin of the next generation's drug abuser? (5) What can we learn from studies of biological vulnerability to alcoholism, and from alcoholism prevention efforts, that is applicable to the prevention of drug abuse?

Several difficulties in comparability between alcohol and drug abuse studies readily come to mind. Scotch, bourbon, or beer, alcohol is the same drug. Valium is different from heroin and even more different from cocaine. Amphetamines are neither PCP nor amyl nitrite. Thus, with hundreds of drugs of abuse, we should expect more heterogeneity in drug abusers and difficulties in tracing patterns over generations, which shift from one drug to another. Another clear difference is that alcohol is legal, and most drugs of abuse are not. Thus, drug abusers are more likely to commit illegal acts and therefore more likely to be diagnosed as antisocial personalities (ASPs), validly or not.

Meisch and George (this volume) presented animal studies demonstrating that strains of rats that are selectively bred for high alcohol intake are the same strains that show high morphine intake. Also, Pickens and Svikis (this volume) found evidence to suggest that the pattern of inheritance for drug abuse is similar

to that for alcoholism. This suggests a predisposition to drug taking in general rather than to any one specific substance. It is unknown, at present, if this phenomenon provides evidence for a combined receptor site or a final common pathway of drug satiation, craving, etc.

Animal research has shown that monkeys will continue to self-administer cocaine (unlike any other drug) until death. This is the only commonly used example of an animal study cited by teachers, therapists, and prevention specialists in an attempt to dissuade vulnerable individuals from ever trying cocaine (Cohen 1981). It would be interesting to know if dissemination of knowledge such as this is helpful in preventing cocaine abuse. Perhaps animal researchers should attempt to breed selectively for high- and low-cocaine-seeking animals; such research might help prevent cocaine abuse by providing knowledge about the genetics or neurobiology of cocaine-resistant individuals.

Stabenau (this volume) cited studies that show increasing risk for alcoholism and antisocial personality (ASP) with increasing number of alocholic parents. If neither parent is alcoholic, the risk for alcoholism in progeny is 6.5 percent, and the risk for ASP is 2.8 percent. If one parent is alcoholic, the risks are 15 percent and 10 percent, respectively, and if both parents are alcoholic, the risks are 36 percent and 31 percent, respectively. Cloninger et al. (1986), in their Swedish adoption study, found 22.8 percent of adopted-out sons of biological fathers registered for alcohol abuse were themselves alcohol abusers, as were 28.1 percent of adopted-out sons of alcoholic biological mothers. If we trace alcoholic or drug-abusing sons back to their fathers, we find a very high prevalence of drug and alcohol abuse and dependence. These data have potentially broad implications for prevention, which may or may not be implementable. An alcoholic should be aware that the risks of his or her child's becoming an alcoholic are four to five times greater than those of the nonalcoholic. If two alcoholics are married to each other, they should be aware that the odds of bearing an alcoholic child are far greater. Although most children are born before their parents' alcoholism becomes recognizable, the onset of parental drug dependence generally occurs before children are born. Thus, it is of considerable importance and possibly greater utility to demonstrate the role of genetic transmission in drug abuse so that drug abusers could be made aware of the possible consequences, should they have children. The comunity at large could be made aware of the vulnerability of these children, as could the children themselves.

Rounsaville (this volume) emphasizes the present difficulty in assessing the genetic transmissibility of opioid dependence because the parents of today's opioid addicts were extremely unlikely to have been exposed to opioids. In my own earlier work (Kaufman 1981) and that of Zeigler-Driscoll (1979), rates of parental alcoholism in opioid abusers were found to be 33 percent and 63 percent, respectively. In 1976, I treated one family of a heroin addict where four of his five children were also heroin addicts.

Over the next decade, many children of the heroin addicts of the 1960s and early 1970s will be entering the age of drug vulnerability. Thus, this is an important time to perform studies of substance abuse disorders in the parents and children of opioid addicts.

We know that many of the children of severe drug abusers are at risk for substance abuse and psychiatric dysfunction. However, we have not yet established the extent of the risk for drug abuse, as we have for alcoholism. Not all children of alcoholics are dysfunctional; in fact, some appear to be highly functional. These apparently overfunctioning children of alcoholics may do so at the expense of gratifying their own needs, because they have become accustomed to meeting everyone's needs except their own as a result of growing up within an alcoholic family. The data on the various roles of the children of alcoholics have not been well documented by scientific studies. However, there is presently an opportunity to perform state-of-the-art family system research on the roles of children of adult drug abusers. We must also search for the mechanism that enables some children of substance abusers to function overcompetently. Is their apparent health explained by genetic, societal, or family system factors?

Another factor that needs to be researched in these families is sibling birth order. In my own preliminary studies of heroin addicts, the youngest sibling was often heroin addicted. There was frequently a highly competent oldest sibling, who took over the role of the early-departed father (Kaufman 1981). Addiction, in my study, appeared to be related to the parents' need to have a perennial child to care for in order to avoid focusing on their own relationship. Studies of birth order and sibling roles need to be further defined and quantitatively demonstrated.

Wegscheider's (1974) descriptions of different sibling patterns in alcoholism should be quantitatively assessed to see if comparable roles exist in children of drug abusers. Studies done by Black et al. (1986) of the consequences of being the child of an alcoholic also need to be replicated with children of drug abusers. If definitive, problematic roles in children of drug abusers can be clearly described, then the detrimental aspects of these roles can be prevented through education of parents and children. There is also a need to determine if certain childhood roles lead to specific adult psychopathology. For example, are youngest siblings most vulnerable? Are oldest siblings spared? Does the "family hero" become the overachieving adult? Does the family scapegoat become the drug-dependent adult? Does the lost child become schizoid or schizophrenic? Long-term, prospective followup studies can give us the answers to these key questions in the prevention of substance abuse and psychological disability in the progeny of substance abusers.

Studies by Cadoret et al. (1985) suggest that male/female differences in alcoholism rates reflect socially determined greater exposure to alcohol rather than different genetic transmission. In

part because of the low rate of female alcoholism, the genetics of this group has not been well studied. Preliminary studies suggest different etiologic factors for males and females (Pickens and Svikis, this volume; Cloninger, this volume). However, with women's increasing exposure to drugs and alcohol, we can expect higher rates of female drug and alcohol abuse and dependence. With female dependence on some drugs, e.g., benzodiazepines, higher than male dependence, it is critical that the interaction of genetics and environment be studied in the progeny of drug-dependent females. Over the past few years, we have begun to develop trait markers for substance abuse risk (Tarter, this volume). These include: (1) low platelet serotonin and low monoamine oxidase with related sensation seeking; (2) decreased amplitude of the P300 wave of the event-related potential; (3) increased truncal ataxia; (4) decreased intensity of reaction to modest doses of ethanol; (5) possibly diminished alpha-wave activity (slow waves) in EEGs, with a greater possibility of alpha waves after drinking; and (6) intense changes in cortisol and prolactin secretion in response to an acute ethanol challenge. Another high-risk group are those children with attention deficit disorder and early antisocial behavior. These markers, if carefully shown to be replicable in demonstrations of individual. vulnerability, could, if combined with family pedigree data, help predict who is at high risk for alcohol abuse and perhaps for drug abuse. Certainly investigation of these phenomena in male children of male drug abusers is warranted, to determine if the findings parallel those reported for alcoholism.

However, even if we identify a high percentage of children at risk for drug abuse, we must consider to what extent our prevention efforts should target this group. If we do target high-risk groups, it should never be at the expense of diminishing comprehensive prevention efforts. Perhaps these studies of markers could be used to discourage certain types of advertising that might appeal to potential substance abusers, particularly those who have high sensation-seeking traits. Substance abuse by individuals with proclivities for sensation seeking might also be prevented by encouraging drug-free sensation-seeking activities such as Outward Bound. There is sufficient evidence that a general prevention effort should be made to encourage children of alcoholics, drug abusers, and ASPs to choose a path of total abstinence from drugs, alcohol, and cigarettes. How to communicate this message effectively is another potential area for research. It would be helpful to know what proportion of the children of substance-dependent individuals and ASPs can use substances moderately without eventually becoming dependent. Can some of these children be taught that the first time they use substances to intoxication or in any other problematic way should be the last time they use or use immoderately? How can we determine which of these children can use drugs or alcohol without becoming addicts or alcoholics? Certainly children of substance abusers and ASPs who are in a pattern of recurrent substance use should be informed of their high-risk status and encouraged to work toward a lifetime of abstinence. They must learn that they cannot drink, smoke, or take drugs like other children. Another problem in targeting high-risk children is

the risk of stigmatizing them. Although our concern about stigmatizing them should never be an excuse for doing nothing, we must try to help these children without their becoming the subject of damaging peer ridicule or critical teacher scrutiny.

One proposal would be to educate all school children about factors associated with vulnerability and give them the opportunity to volunteer for services that are provided in a discreet way. In most communities, there are no support groups for children of drug abusers that function in the way Alatot and Alateen do for children of alcoholics. There is no movement at all in drug abuse comparable to the apparently effective Adult Children of Alcoholics group. The National Institute on Drug Abuse should support the development of these groups as well as evaluate their effectiveness. Chemical dependency groups are still continuing to function; these could be used to seed Narcotot and Narcoteen.

Communities could be encouraged to begin an "Adult Children of Drug Abusers" movement. The effectiveness of these groups with drug abusers should be researched more thoroughly than they have been with alcoholics. A child-of-a-drug-abuser questionnaire should be developed, which can identify these children before they manifest overt problems, so that problematic behavior can be prevented.

There is no single method of prevention that can, in isolation, make a dent in the substance abuse problem. Prevention must be comprehensive and deal with all aspects of the problem. We must work with the three-generational system of the children of drug abusers. Their parents need help in parenting skills and communication, whether they be intact families, single parents, blended families, common-law relationships, or extended family networks. The entire family system needs substantial assistance, whether the drug abuser is still living with them, drops in occasionally, or has abandoned them totally. This assistance should be provided without stigmatizing these families. Thus, services must be offered voluntarily and discreetly.

Perhaps the knowledge we have gained at this meeting and the knowledge about alcoholics as it is replicated with drug abusers can be utilized to target high-risk schools where the majority of students are at risk. Another high-risk group are children in juvenile facilities and group homes. Comprehensive attempts at prevention could be universally implemented with these high-risk children, and should include the following.

(1) Training of high-risk children should include how to "say no" and the building of self-esteem.

(2) Counselling should be performed by an effective, well-trained, student-respected, readily available staff counsellor. This counsellor should come from within the educational system. Staff can be supplemented by peer counsellors, who should be well trained, given school credit for their training and counselling time, and well supervised.

(3) Parents should also be involved in the effort, including the use of educational groups, directive multiple family therapy, and parenting and communication classes. Self-help groups for children of all ages and for parents should be made available.

(4) Training should be provided for all teachers to help them recognize substance abuse problems and deal with students who present these problems.

This comprehensive approach to prevention in a high-vulnerability school could be matched with a comparable "school as usual" and would be an interesting research project, which could substantially affect future prevention efforts. Separate aspects of school-based prevention programs could also be evaluated individually. These modalities could be compared across approaches or to a matched "school as usual" having little or no prevention activity.

Recent studies on biological vulnerability in schizophrenia have been very helpful in shifting the thrust of family therapy efforts with this group to a more educative approach. The techniques that have been developed to diminish hostility, criticism, and over-involvement on the part of the families of schizophrenics have been found to be very helpful (Goldstein et al. 1978; Anderson 1983). These techniques developed only after the concept of biological vulnerability to schizophrenia was accepted. The more we can demonstrate biological vulnerability in the progeny of drug abusers, the more we can shift our family treatment approach to an educational model. My presentation certainly raises more questions than it answers. However, the relative absence of studies on biological vulnerability in the children of drug abusers and the total absence of any work on the application of this concept to prevention support the need for questioning our approach.

It is hoped that this technical review will raise many critical questions in this rapidly emerging field that can be answered with appropriate, relevant, scientific methodology.

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DHHS Publication No. (ADM)90-1590
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1988, Reprinted 1990