Disaggregating the Liability for Drug Abuse

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It is consensually accepted that the liability for developing a substance abuse disorder is not the same for all individuals in the population. Only marginal progress has been made, however, in determining the factors responsible for the variation in the liability to drug abuse, encompassing interacting biological, behavioral, and environmental processes. Since variation in the liability has a multifactorial basis, it is necessary, therefore, to identify the integral biobehavioral traits and to determine how a person's position on these traits (phenotypes) covaries with environmental influences to determine liability status. Once this can be accomplished, it will be possible to specify with a high level of precision the liability for developing a drug abuse disorder for each individual in the population.

At the outset, determining the factors contributing to the liability for drug abuse requires documentation of the pharmacological properties of compounds having abuse potential. From the multifactorial perspective of drug abuse etiology, pharmacological factors (including both kinetics and behavioral reactions), in concert with a host of other variables such as influences from family and friends, psychiatric status, drug availability, personality disposition, and beliefs about the effects of drugs, combine to determine the liability for a drug abuse disorder. This liability can be characterized as a continuous multidimensional trait ranging from a score of zero (no likelihood for the adverse outcome) to one (affected state of drug abuse disorder).

Because the liability has a multivariate basis, its distribution, as shown in figure 1, is normal in keeping with the theorem of central limits. To surpass the liability threshold for diagnosis, biochemical, physiological, and behavioral processes, through interaction with microenvironment (e.g., family) and macroenvironment (e.g., community) influences, shift or deflect the person's position (his or her liability phenotype) on the liability axis to the beyond-the-threshold region. The person is thereby deemed to be "affected" or to be a "case."

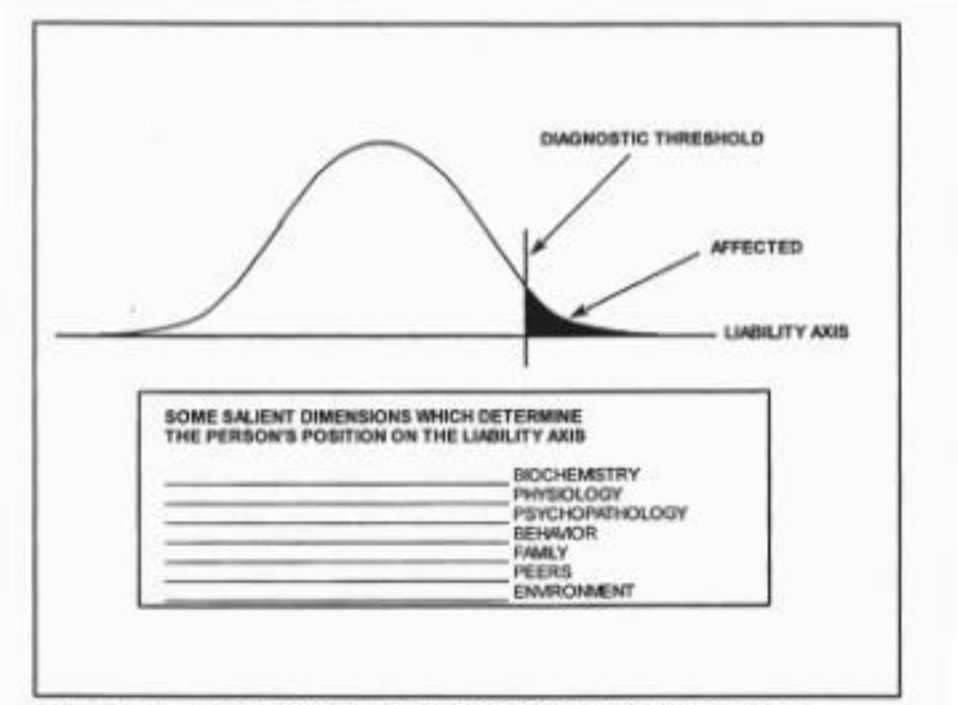

FIGURE 1. *Multifactorial model of the liability for drug abuse.*

Why does an individual's status change from noncase to case? This is the overarching question in research on drug abuse etiology. The theoretical framework guiding this line of research is discussed below.

THEORETICAL FRAMEWORK FOR DISAGGREGATING THE LIABILITY

A person's position on the liability axis is the product of the interaction between phenotypic variation on salient traits and environmental influences. As illustrated in figure 2, phenotypic variation (that is, the person's position on a trait) is the product of the interaction and covariation between genotypic variation for the trait in the population and two types of environmental influences. As the terms denote, *shared* and *unique* environments refer to aspects of the environment that are held in common with other family members or are specific to the individual. On continuous traits, there are, therefore, an infinite number of phenotypes.

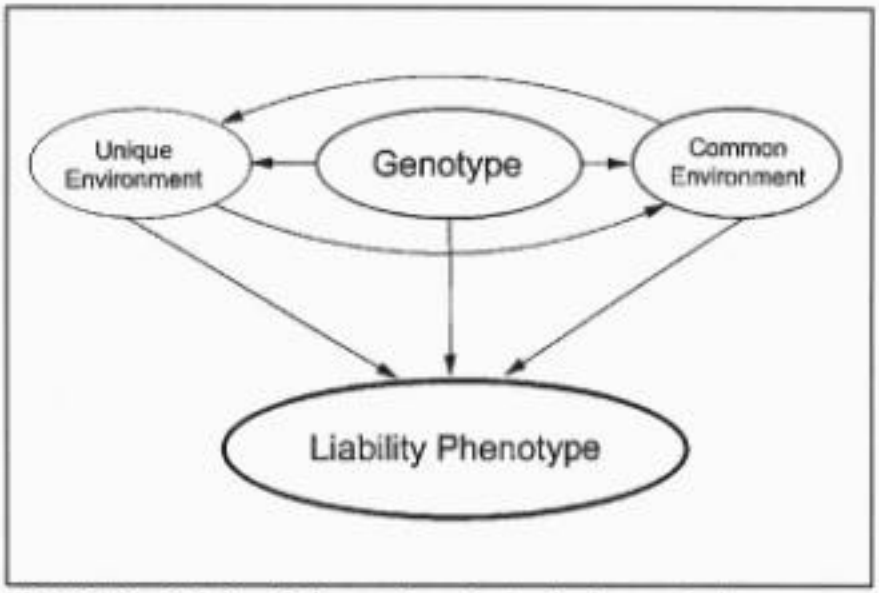

FIGURE 2. *Origins of phenotypic variation in the population.*

Inasmuch as numerous biobehavioral traits are associated with the liability to drug abuse (see figure 1), and because each trait has an infinite number of potential phenotypes, the etiological pathway to drug abuse is distinct for each affected individual. Elucidating the etiology of drug abuse thus requires determining how phenotypic individuality contributes to the outcome diagnosis of substance abuse/dependence. In other words, how are individual differences molded into a shared outcome phenotype, namely, the characteristics qualifying for diagnosis? To address this question, empirical research focuses on two main topics. First, investigations are directed at identifying the biological and behavioral traits that are salient to drug abuse liability. Second, research is conducted to determine how phenotypic variation on the putatively salient traits interact among each other so as to determine the person's position on the liability trait or axis.

Numerous biochemical, physiological, behavioral, and cognitive traits have been implicated to be associated with the liability for substance abuse/dependence. With respect to biochemical traits, neurochemical and endocrine mechanisms have been linked to the liability for substance abuse (Eskay and Linnoila 1991). Physiological evidence has been accrued pointing to the importance of intrinsic EEG rhythms and information-processing efficiency as measured by event-related potentials (Brigham et al. 1995). In addition, autonomic

reactivity has been observed to be associated with the liability for substance abuse (Finn et al. 1990). Numerous behavioral traits have also been implicated; the most frequently reported include sensation-seeking, impulsivity, coping style, and social skills. Finally, certain neuro-cognitive capacities as well as expectancies and beliefs about the effects of drugs appear to be associated with the liability for drug abuse (Hesselbrock et al. 1991). Clearly, many biobehavioral traits contribute to the variation in the liability. To date, comprehensive integrative research has not been conducted to delineate in quantitative fashion how phenotypes across multiple levels of biological organization interact to determine the person's position on the liability axis.

Research into the multifactorial determinants of the liability to substance abuse requires a developmental focus. Epidemiological research has demonstrated that the age at which a substance abuse diagnosis is first manifest is not equally distributed across the lifespan among the population of individuals who develop this disorder. This is not surprising since biological and behavioral processes change with age consequent to ongoing interactions with multiple environments (e.g., family, peers, work.). Consequently, the factors influencing one's position on the liability axis are not the same throughout life. For example, in youth, the factor of peer affiliation is likely to be a more important contributor to the liability for substance abuse than in adults, since adolescents are especially susceptible to the influence of friends. In contrast, among older adults, reactions to the pharmacological properties of analgesic and hypnotic drugs may be more important determinants of the liability because chronic pain and sleep disorders are uncommon in youth. It is thus important to research drug abuse etiology within a developmental framework inasmuch as the particular traits contributing to the liability and their constituent phenotypes change throughout the lifespan. Because the components of the liability change during life, the person's position on the liability axis fluctuates over time. Consequently, depending on the changing dynamic between phenotypes and environmental influences, a drug abuse disorder can occur at any time in life subsequent to initial drug exposure. As depicted in figure 1, the shift from nonaffected to affected status corresponds to the person surpassing the diagnostic threshold on the liability axis.

This lifespan perspective is illustrated in figure 3. It can be seen in the hypothetical developmental pathway that the person's position on the liability axis changes with age. At the moment of conception,

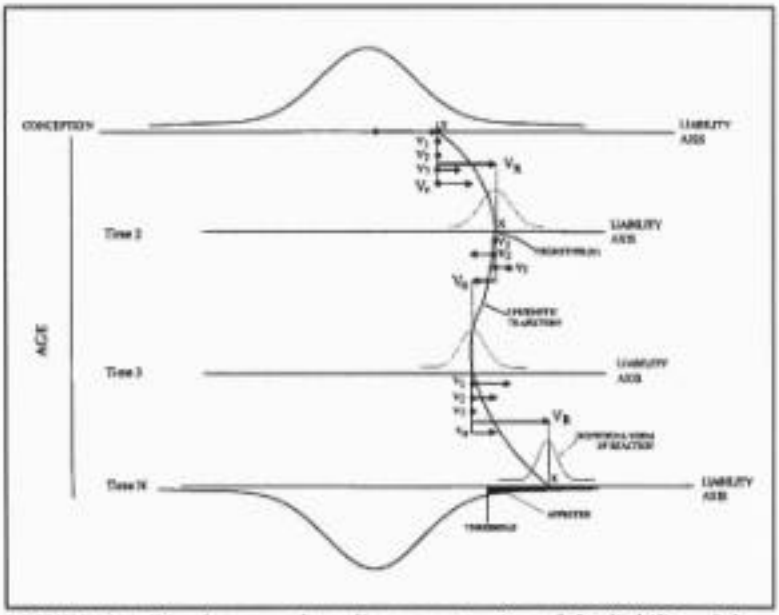

FIGURE 3. *Developmental nonlinear patterning of the liability of drug abuse.*

everybody's liability phenotype is subthreshold, as the whole age-specific liability distribution, reflecting predominantly genotypic variation, contains no substance abuse phenotypes. The mode of the age-specific liability distribution shifts to the right as age progresses. Concomitantly, the individual phenotype may change in its absolute value and with respect to its relative position within the liability distribution. The upper and lower limit of phenotypic change that is possible within a particular environment is genetically determined; this range is termed the norm of reaction. In effect, the potential for modification of behavior has limits which, in a given environment, is genetically determined. (For example, a baby's future height in adulthood, or for that matter any complex phenotype, has an upper and lower limit controlled by genetic factors; however, within that range environmental factors influence variation.) In the example shown (see figure 3), following a series of events occurring during the lifespan, the person satisfies criteria for a drug abuse diagnosis; this is shown by the person's position in the affected range on the liability axis in the distribution at the bottom of the figure. One of the cardinal issues in etiology research is to clarify the developmental trajectory linking the outset and outcome positions on the liability axis.

As previously discussed, one's liability phenotype is determined by the interaction among the phenotypes on salient traits spanning biobehavioral organization and shared and unique environmental influences. This is designated on the liability axis by $\underline{X}$ in figure 3. $\underline{X}$ is the product of the interaction of all phenotypes V_1, V_2, V_3...V_N on traits associated with the liability. Their resultant product is a vector designated V_R. This vector, consisting of all salient phenotypes and in the context of shared and unique environmental factors, influences the direction of the developmental trajectory toward either a good or poor outcome. In figure 3, this is manifest as a shift in the position on the liability axis toward either the normative (left side) or toward the affected (right side) segment of the population distribution.

Numerous factors operate during development that determine the course and direction of the trajectory. For example, changing environmental circumstances impact on the individual to change behavior and physiology, thereby either augmenting or decreasing the person's liability. Also, the acquisition of liability-enhancing or liability-attenuating behaviors is influenced strongly by prior behaviors. This process is referred to as epigenesis. The main point to be made, however, is that the developmental pathway to a drug abuse outcome is nonlinear, complex, and idiosyncratic.

Prevention interventions involve methods that shift one's liability position toward the left side of the liability axis. Treatment involves shifting an affected person toward the subthreshold side of the distribution. Whether the intervention is prevention or treatment, effectiveness depends on identifying and disaggregating the unique components of each person's liability and applying methods that are capable of deflecting the person's position toward the left side of the axis. Because no two individuals in the population have the same developmental history, composition of phenotypes, or environment, it follows that it is necessary to adopt an individualized approach to prevention and rehabilitation.

A lifespan developmental approach has potential for clarifying the etiology of substance abuse. This perspective emphasizes the influence of cumulative prior experience as the major determinant of the emergence of each successive phenotype. This epigenetic process allows understanding of the etiology of drug abuse in the context of an orderly process in which the outcome is the culmination of an ongoing developmental trajectory concomitant to person-environment interactions. It is important to note, however, that other outcomes (e.g., AIDS, criminality, dementia) can likewise be

investigated through continued monitoring of the trajectory across the lifespan. Thus, drug abuse is not necessarily the only or final outcome of interest but instead is commonly intermediary to other negative outcomes. The epigenetic approach enables, therefore, the integration and sequencing of adverse outcomes associated with drug abuse as well as quantitative analysis of the patterning of other outcomes.

In order to fully understand how a segment of the population succumbs to drug abuse/dependence, it is essential to characterize and be able to predict the course of both normal and deviant development. Upon completing this task, the liability to drug abuse will be elucidated; however, the magnitude of this task is daunting considering the manifold biobehavioral traits that appear to be salient components of the liability. For example, it is universally recognized that exposure to particular environments influences the liability. Equally important is the fact that individuals with particular phenotypic features seek out specific environments. For example, shy youth are less inclined to form the same social relationships as aggressive youth. Thus, to understand how the person's position on the liability axis shifts during development, a central task is to analyze the quality of person-environment interactions as an ongoing bidirectional process.

A developmental approach also provides the theoretical foundation for understanding termination of drug abuse. For example, it is well established that only a small segment of the drug-using population become "affected"; that is, develop a diagnostic disorder. Among those who qualify for a diagnosis of abuse/dependence, a substantial proportion spontaneously remit. In effect, their position on the liability axis shifts from the suprathreshold to subthreshold location (see figure 1). Understanding person-environment interactions during the lifespan affords the opportunity for researchers to determine which factors foster nontreatment-based recovery. By identifying the factors that facilitate the transition from a diagnostic disorder of substance abuse/dependence to nondrug abuse, it may be possible to devise more imaginative and effective therapies that encompass an understanding of liability-attenuating influences. By extension, the developmental approach is suitable for detecting the factors associated with resiliency and primary prevention.

The multifactorial perspective aligns with research directed at determining how individual variation interacts with variations in multiple environments (e.g., family, peers, school, work, retirement community, etc.). Investigations of drug and alcohol preference and

consumption patterns in animals are informative to the extent that the distinguishing characteristics among different strains studied comprise components of the liability in humans. For example, what is it about alcohol-preferring rodents, apart from a propensity to drink alcohol, that predisposes to developing a pattern of habitual consumption and its consequences (e.g., tolerance)? Obtaining this type of information from animal research is important in clarifying the liability to substance abuse in humans.

To date, systematic research has not been conducted to determine how phenotypic variation in animals covaries with specific facets of environmental variation to determine the liability for substance use. For example, temperament in subhuman primates and the opportunity during infancy to acquire affectional bonds with parents are critical determinants of future alcohol consumption when the monkeys are adolescents (Higley et al. 1987, 1988). Unfortunately, this interactional approach has not been widely adopted by researchers who use animal models to investigate drug abuse liability.

In summary, delineating the liability to drug abuse requires analysis of the covariation between salient phenotypes in the context of interaction with multiple environments. This interactional approach is well established in human-based research but has not yet been widely adopted by researchers who utilize animal models to elucidate the liability for drug abuse.

RESEARCH PARADIGM

The National Institute on Drug Abuse (NIDA)-funded Center for Education and Drug Abuse Research (CEDAR) has the primary mission of identifying the traits associated with the liability to drug abuse and delineating the covariation among phenotypes on these traits and environments during the period between late childhood and middle adulthood. Subjects are prospectively tracked and biannually reevaluated to characterize liability status. This longitudinal investigation thus enables discovering the determinants of the liability for substance abuse among youth prior to exposure to abusable compounds. Thereafter, the factors that contribute to first use, habitual use, and ultimately the affected condition of drug abuse or dependence can be elucidated.

Probands in this research are adult men who either do or do not have a lifetime diagnosis of drug abuse or dependence. It is well established

that the population of offspring of men with drug abuse are at higher than average risk to develop drug abuse or dependence. Hence, identifying and tracking boys whose fathers have a drug abuse disorder according to DSM-III-R or DSM-IV criteria provides an efficient method for accruing a sample in which the likelihood of experiencing the adverse outcome is higher than average. Contrasting these youth at high risk with children who do not have a parental history of drug abuse thereby enables detecting the discriminating factors that are influential determinants of the liability. And, by tracking these two groups of youth into adulthood, it is possible to ascertain the relative and potentially changing impact of these variables on developing a drug abuse disorder at different stages of life.

Figure 4 illustrates the paradigm. The comparison groups consist of children at high average risk and low average risk for drug abuse; both groups are drawn from the population in which the father is either affected (substance abuse/dependence) or nonaffected (normal). Importantly, it should be noted that this paradigm does not specify whether a particular individual in each group is at high or low risk; rather it is the group that is at higher or lower risk. For example, as can be seen in figure 4, it is possible that some offspring in the high-risk group, although having an affected father, are not at the high end on the axis of the liability distribution.

Employing this paradigm, one aspect of CEDAR's current activities focuses on the role of temperament as a key determinant of the liability to substance abuse or dependence. Researching the contribution of temperament is heuristic for several reasons. For instance, certain temperament phenotypes have been shown to distinguish prepubertal male offspring of alcoholics (Tarter et al. 1990*a*) and other types of drug abusers (Blackson 1994; Blackson et al. 1994) from children of normal fathers. Magnitude of deviation on temperament traits has also been shown to be associated with severity of substance use involvement among adolescents (Tarter et al. 1990*b*; Windle 1991).

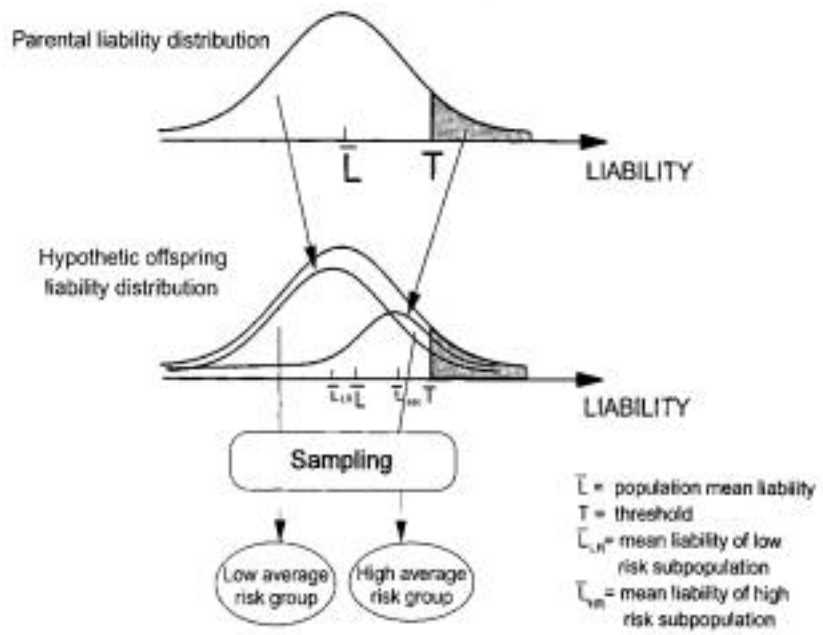

FIGURE 4. Sampling strategy in the high-risk paradigm.

In addition, several cogent theoretical reasons prompt investigating the contribution of temperament to the overall liability for drug abuse. First, phenotypic variation on temperament traits is determined to significant extent by genotypic variation in the population (Buss and Plomin 1975). These psychological propensities thus afford the opportunity to clarify the heritable contribution to the liability and provide the framework for linking genetic and behavioral processes. Second, temperament traits are reliably measurable within the first month or two after a child's birth (Buss and Plomin 1975). Hence, it is possible to initiate research into drug abuse etiology from the beginning point of the developmental trajectory. Third, a poor "fit" between the child's temperament and the environmental context substantially augments the risk for psycho-pathology and behavior disorder by late childhood (Thomas and Chess 1984). Thus, particular phenotypes are neither "normal" nor "abnormal" but rather are adaptive or nonadaptive depending on the environmental context. And fourth, temperament phenotypes tend to be temporally stable. In effect, temperament phenotypes reflect dispositional features of the individual, although the topography of expression changes during the lifespan. High emotionality in childhood, for example, is expressed in childhood as tantrums and intense, sudden crying spells. In adulthood, this same

temperament trait is usually (but not always) expressed differently. Typically, high emotionality is manifest as anxiety-spectrum reactions.

Temperament is measured at CEDAR using the revised Dimensions of Temperament Survey - Revised (DOTS-R) (Windle 1992). Youth and adult versions of the DOTS-R are administered to each child in the sibship and to each parent. The DOTS-R was selected to measure temperament because it has sound psychometric properties, and the traits measured are relevant for understanding the emergence of psycho-pathology and behavior disorder among youth and adolescents. The temperament traits evaluated are as follows: General Activity, Flexibility/Rigidity, Approach/Withdrawal, Mood Quality, Daily Rhythms, Eating Rhythms, Sleep Rhythms, Distractibility, and Persistence. In addition to these primary scales, the DOTS-R yields aggregate indices that multidimensionally characterize temperament makeup. Of particular interest is the constellation of traits referred to as the difficult temperament. This configuration consists of high scores on the primary traits measuring activity level and low scores on the traits measuring mood quality, rhythmicity, and sociability.

Consistent with the prospective paradigm, investigative efforts focus on clarifying the role of temperament in the development of drug abuse. However, rather than search for direct causal effects, the association between temperament and other putative risk factors with drug abuse liability is examined within a mediational framework. In this manner, the multifactorial liability for drug abuse can be decomposed into its components and the relative contribution of the constituent factors can be determined.

RESULTS

Figure 5 illustrates a structural path model depicting the relationship between difficult temperament, history of substance abuse disorder in the father, and socioeconomic status with three parameters reflecting nonnormative social behavior. These six variables were measured in 92 boys when they were 10 to 12 years of age. Alcohol and drug use was measured 2 years later when the boys were 12 to 14 years of age. The coefficients that are statistically significant are depicted by the

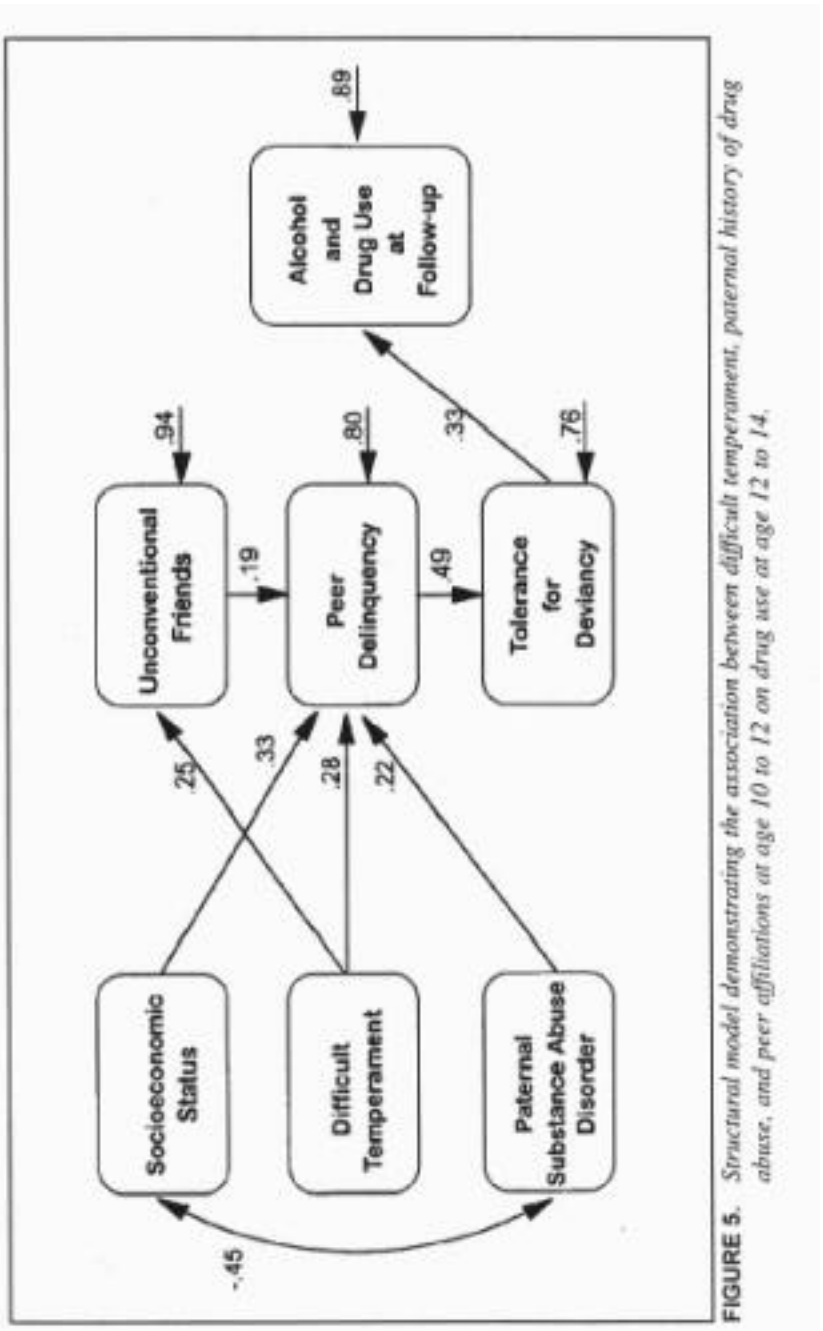

FIGURE 5. *Structural model demonstrating the association between difficult temperament, paternal history of drug abuse, and peer affiliations at age 10 to 12 on drug use at age 12 to 14.*

arrows connecting the variables. Nonsignificant pathways are not shown in order to illustrate only those relationships that are relevant to under-standing the association among the factors at age 10 to 12, which predict alcohol and drug use 2 years later.

Three aspects of the results are noteworthy. First, it can be seen from the significant path coefficients that difficult temperament is directly related to affiliation with unconventional friends and delinquency among peers. Second, these latter two variables are directly associated with tolerance for deviancy which, in turn, is the only factor that predicts alcohol and drug use at 2-year followup. Third, socioeconomic status mediates the relationship between paternal substance abuse disorder and delinquency in the child's peer network. The data fit this model quite well (chi-square with 11 degrees of freedom = 9.24 (p = 0.057). The goodness of fit index = 0.097. The normed fit index = 0.90.

From the analysis summarized in figure 5, difficult temperament, paternal history of substance abuse, and socioeconomic status are directly associated with level of delinquency among the boys' friends. However, this latter factor is not directly associated with drug and alcohol use 2 years later. Rather, delinquency among peers predisposes to acceptance or tolerance of deviancy that in turn leads to drug/alcohol use. Within the framework of this chapter, difficult temperament in the child is thus an important contributor to the initiation of alcohol/drug use by age 12 to 14; however, its influence is mediated by peer affiliation and tolerance of deviancy.

Biological Substrate of Temperament

As noted previously, phenotypic variation on temperament traits is explained to significant extent by genotypic variation in the population. A question having important ramifications for understanding the biological mechanisms underlying drug abuse liability pertains to whether biochemical or physiological processes can be detected that covary with temperament phenotype. Preliminary analyses conducted at CEDAR indicate that plasma GABA is unrelated to difficult temper-ament. Neither plasma homovillic acid (pHVA) nor MHPG, a dopamine metabolite, nor MHPG, a noradrenaline metabolite, correlates with difficult temperament in 10- to 12-year-old sons of substance-abusing fathers. Thus, the biochemical substrate of difficult temperament remains obscure.

RECOMMENDATIONS FOR FUTURE RESEARCH

Research employing animal subjects is informative to the extent that important questions about the liability to drug abuse can be addressed that are not otherwise amenable to investigation. In the context of the theoretical perspective discussed herein and the data presented, several innovative opportunities are noteworthy.

1. Recognizing that the focus of research on humans is to elucidate the covariation between organismic and environmental variables as determinants of the liability, it would appear important to conduct studies on animals in which phenotypes and environments are systematically manipulated. The advantage of using animal models is the opportunity to experimentally control the phenotypes and environments. In this manner, the conditions contributing to drug abuse liability in animals can be established, which then allows for confirmation in humans. Significantly, certain inbred strains of rodents have phenotypes that in humans have been linked to drug abuse liability. These phenotypes include behavior activity level, emotionality, and aggressivity. In addition to studies comparing inbred strains, it is potentially heuristic to investigate the role of liability-enhancing phenotypes in unselected animal subjects. The association between particular phenotypes and environmental factors that promote or mitigate drug self-administration can be measured. Each strategy provides the opportunity to systematize the relation-ship between specific phenotypes and specific environmental conditions underlying the liability for drug abuse.

2. As reported in this chapter, temperament traits are heuristic for elucidating certain of the early-age contributors to drug abuse liability. Research on animals allows for an objective determination of the role of temperament as a contributor to the liability because of the opportunity for rigorous control over environmental conditions. Significantly, several temperament phenotypes that are pertinent to the liability to drug abuse in humans have been inbred in rodent strains. Using these animals, the neurobiological substrate of temperament phenotypes can be determined.

3. Although research traditionally has aimed to exercise control over environmental conditions, it is dubious whether the range of environments that have been investigated in animals are relevant to understanding the liability for drug abuse in humans. For example, unlike animals maintained in the abnormal circumstance of social isolation, drug use by humans usually occurs in a social context. Research with animals could potentially make an important advance to understanding drug abuse liability by expanding the range of paradigms to include systematic manipulations of the social environment so as to delineate phenotype-environment covariation.

4. Prevention intervention is a powerful method for informing about etiology. For example, poor parent-child attachment augments the liability for drug abuse. A huge literature has developed in the past six decades regarding the importance of affectional bonding for normal development in humans and animals. Similarly, other well-established traits (e.g., aggression) are known to be associated with drug abuse liability. In effect, this line of research would be directed at modifying putative liability-enhancing phenotypes toward norma-tive expression and their determining whether this intervention alters drug preference.

5. It was argued in this discussion that the pharmacological properties of a given compound need to be considered in the framework of comprising a single liability factor, not as the main or only causal determinant. Hence, the importance of pharmacologic properties in relation to other liability enhancing and attenuating variables remains to be determined before there can be a comprehensive understanding of drug abuse etiology. Furthermore, broad-based research of this type needs to be undertaken within a lifespan perspective inasmuch as a compound's pharmacologic effects may not be constant throughout life. It is recommended, therefore, that researchers expand pharmacological investigations into the liability for drug abuse in humans and animals to also encompass the critical factor of age-specific pharmacologic effects as a contributor to drug abuse liability.

CONCLUSIONS

This chapter outlined the general theoretical framework for conducting research into the liability of substance abuse/dependence within a multifactorial perspective. The central research goal in this perspective is to determine how individual uniqueness is transformed through the course of ontogeny into a pattern of substance abuse or dependence. Because the liability is hypothesized to have multiple determinants, integrative research having a multidisciplinary focus is required. Investigations using animal models are necessary to test hypotheses not possible to test in humans. Drug abuse is invariably preceded by a period of no drug use and a stage of casual and often nonproblem use. This sequencing of increasing involvement and deleterious consequences argues for an ontogenetic perspective and, accordingly, for the use of longitudinal paradigms. A lifespan approach focusing on understanding changing person-environment interactions affords the opportunity to delineate the developmental trajectories to a substance abuse outcome. Once it is possible to disaggregate these interactions to reveal the determinants of the liability, empirically sound prevention and treatment will then be possible.

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