Introduction: Individual Differences in the Biobehavioral Etiology of Drug Abuse

Harold W. Gordon and Meyer D. Glantz

STATEMENT OF THE PROBLEM

Research into substance abuse tends to be divided into two general conceptual approaches to understanding the etiology and nature of drug abuse. One major direction focuses on psychological/behavioral and social/environmental variables and their interactions leading to the abuse of psychoactive substances. The second approach focuses on the neurobiological mechanisms affecting, or affected by, the chemical action of drugs. Studies following the psychological/environmental approach are commonly descriptive, have a strong behavioral orientation, and typically attempt to understand individual behaviors or the behavior of specified subgroups. Individuals are compared and contrasted on such characteristics as psychopathology, self-esteem, and attitudes in order to explicate the nature and development of drug abuse in terms of the individual differences in these variables. In a variation of this approach, culturally, ethnically, and often demographically defined groups are assumed to be homogenous and studied in terms of their experiences within differing family environments, peer group interactions, cultural influences, and community settings. More sophisticated versions of this psychological/environmental approach embed the study of intra-individual characteristics within the context of extra-individual influences. For example, personality and attitudes are assessed in relation to peer group influences and cultural standards. The most comprehensive and successful studies have incorporated a longitudinal or developmental strategy that allows for more powerful causal inferences. These trajectory models are not only becoming more widely accepted, but also produce valuable data as the quality of the assessment and sophistication of the studies increase (see Glantz and Pickens 1992 for a comprehensive review).

These psychological/behavioral and social/environmental variables and the models that emerged from the studies have significantly contributed to the understanding of individual differences in resistance to, and risk for, drug involvement. They have not only illuminated the critical contributions of behavioral and environmental

factors; they also have demonstrated both the complexity and multifactorial nature of the drug-taking behavior. The research has also been valuable because significant studies are conducted with a more systemic and developmental approach. The focus of behavioral/environmental studies can be characterized as an attempt to address the questions: "What characteristics of people and their environments account for the enormous variability in individuals' involvement with drugs?" and "What is the behavioral nature of drug abuse?"

On the other hand, these studies have been incomplete. For example, it may be asserted that drug abusers with psychopathologies and/or low self-esteem are self-medicating their condition. Conclusions based on behavioral characteristics hint at, but virtually ignore, the biological aspects of drug use by failing to incorporate these factors into the person environment models.

Studies following the biological, and especially the neurobiological, approach include those that measure the heritability of drug involvement, identify drug receptor sites, determine the effects of psychoactive drugs on neurotransmitter systems, or attempt to identify the areas of the brain where activity is changed by an action of the drug. Major accomplish-ments in the study of neurobiological systems have facilitated under-standing of the neurochemical mechanisms underlying the action of drugs of abuse, provided insight to the mechanisms associated with drug taking, and contributed to the conceptualization of what determines a drug's abuse liability. Neurobiological studies have provided critical informa-tion about the short-term biological, and long-term medical, effects of drug abuse, laying the foundation for the development of chemical agents that may be effective in the treatment (and perhaps even the prevention) of drug addiction and craving.

While these studies have been taken to the molecular level, the neurobiological approach has given little consideration to individual differences; to the contributions of developmental, behavioral and environmental resistance and disposition factors; to the systemic interactions of these determinative factors; to the heterogeneity of drug abuse patterns and factors; and to the ways in which the neurochemical mechanisms associated with drug involvement translate into or manifest in the larger context of behavior. In summary, neurobiological studies focus on the questions: "What are the biological influences which are determinative of drug abuse?" and, in

particular, "What are the effects of abusable drugs on the neurological systems of the user?"

Development of drug abuse, addiction, or dependency as a result of genetic and biological determinants alone or in interaction with behavioral and environmental factors is in its infancy of study. It is important to focus on the ways in which the neurochemical mechanisms associated with drug involvement translate into or manifest in the larger context of drug-taking behavior. In order for research to continue to make the progress necessary for a thorough understanding of drug abuse, as well as a means for its prevention and treatment, greater concentration is needed on studies of individual differences in neurobiological factors and on studies that focus on the integration of neurobiological systems with behavioral and environmental factors. It is with this perspective that the National Institute on Drug Abuse (NIDA) is supporting research initiatives in this area. As part of this effort, NIDA sponsored a workshop in 1993 on "Individual Differences in the Biobehavioral Etiology of Drug Abuse." The chapters presented in this monograph are updated versions of those originally developed for that meeting.

PURPOSE OF THIS MONOGRAPH

The primary purpose of this monograph is to provide a platform of ideas from which new directions for research in the biobehavioral etiology of substance abuse can be developed. Researchers from a variety of neurobiological disciplines were invited to develop innovative approaches to the study and understanding of individual differences in neurobiological risk and resistance factors for drug abuse. While the researchers were encouraged to be creative and speculative, they were also asked to tie their ideas to available data and to translate their hypotheses into concrete methodology suitable for empirical investigations.

To facilitate the immediate application of these innovative research ideas to pragmatic research projects, the researchers were asked to make presentations as if they were writing a proposal for a research grant. This approach required that the presenters not only propose a creative idea, but that they also show its relation to the extant relevant research and findings, translate it into a feasible project, and demonstrate the worth and utility of the expected results. At the meeting, each proposal was presented, commented upon by a designated referee and then discussed by audience participants.

Revised and updated versions of these proposals and commentary were submitted for inclusion in this monograph. Both the commentary and audience participation were edited and are also included. Some of these proposals have been formally submitted and funded; others are still being developed. All are designed to stimulate further thought and implementation.

TOPIC AREAS

In organizing the workshop and this monograph, the editors selected three research areas on which to focus: genetic bases, neurophysiological correlates, and neurochemical factors underlying drug-abuse risk or resistance. These areas were selected for their importance and research potential as established by innovative and promising research that was already being developed in drug-abuse and nondrug-abuse fields (e.g.,mental health). The researchers who contributed to this monograph have generously agreed to share their ideas at early stages of their work in order to stimulate further research and to communicate their enthusiasm for the potential of integrative biobehavioral research on drug abuse.

Behavioral Genetic Factors

Several years of family, adoptee, and twin studies have demonstrated the likelihood of a genetic contribution underlying drug-abuse risk behaviors including, but not limited to, drug abuse itself. For example, substance abuse in a biological parent has been shown to be associated with drug abuse in adopted-away offspring even when environmental factors are controlled by statistical analysis. This observation suggests that at least one of the determinative variables for drug abuse is related to genetically coded traits. One of the concepts regarding the genetic aspect of drug abuse is emergenesis, which posits that substance abuse as an outcome (behavior) variable is not determined by one specific gene or gene set, but is a behavioral consequence of any of a number of genetically influenced but nonspecific maladaptive functions of the individual (Lykken et al. 1992). From this perspective, substance abuse may be one of many possible behaviors in a dysfunctional system and related in different individuals to differing configurations of genetic variations. Available research does not point to a single drug abuse gene; this gives credence to the emergenesis hypothesis.

One implication of the emergenesis concept is that if a variety of genetically influenced maladaptive functions may lead to substance abuse, then the identification of these gene patterns and maladaptive functions must distinguish their involvement from environmental influences. Twin studies provide one of the best means to separate environmental and genetic contributions to an outcome behavior. For example, monozygotic (MZ) nonabusing cotwins of substance abusers (i.e.,abuse disconcordant) should have high biological risk factors not present in nonabusing cotwins of nonsubstance abusers (i.e., nonabuse concordant). Discovery of these factors will aid in selecting the genetic, and possibly the biological, basis leading to drug-taking risk or, alternatively, resistance. While consideration of nongenetic (familial/ environmental) factors should continue to be incorporated in genetic research, the focus of research should shift to allelic variations analyzed within the context of these nongenetic factors that contribute to individual differences in risk behaviors. Although environmental factors serve to modify the expression of gene differences, discovery of underlying gene variations and their respective functions in context will dramatically increase the power of models tracing the etiology of drug abuse.

Another approach to studying the genetic contribution to drug abuse propounds the possibility that a single gene or a small number of genes do not code specifically for drug abuse per se, but rather code for a particular behavior or characteristic (e.g., stress)which is a risk factor for, or an intermediating determinant of, substance abuse instead. Research following this approach must focus on identifying these mediators and their underlying genetic components. Such behaviors and characteristics include those accompanying (comorbid with) drug abuse or those that likely underlie an abuse liability.

Historically, a serious obstacle has been to define the drug-abuse phenotype, or even an at-risk phenotype. Without a good definition of the phenotype, the search for the associated genes is near impossible. But based on the broad assumption that some of the risk behaviors are derived from genetically controlled mechanisms, the task has been to employ association studies where candidate gene polymorphisms are compared across groups of individuals who have, in common, patterns of the putative risk behaviors. One expectation is that genes will be discovered that increase the manifestations of certain behaviors or psychological states which, in turn, increase or decrease the propensity to take and abuse psychoactive substances.

The chapter by McGue, Lykken, and Iacono follows the emergenesis approach and seeks to outline traditional behavioral genetic methodology to determine the interaction of genetically influenced psychological characteristics and experiential factors leading to a path of drug abuse. The challenge is to separate the biological/environmental contributions, on the one hand, and to determine the incremental effect of their interaction, on the other. Using a twin-family approach, the authors propose to determine the relative degree of genetic or environmental influences that lead to drug abuse, determine the degree to which individual differences are affected by exposure to an adverse environ-ment, and show how these differences are enhanced or potentiated by interaction with the environment. The sample will include a number of families in which there is high drug-abuse risk for the child due to the drug-use pattern of the parents. This powerful design, coupled with well-validated assessment instruments, is the model offered for behavioral genetic research.

Tsuang and Lyons also plan to use twins, but theirs are to be selected from a registry of Vietnam veterans. Given their large sample, they will be able to compare concordant and discordant (for drug use and abuse) MZ pairs for a variety of biological and behavioral variables. For example, variables present in the nonabusing cotwin of a discordant pair, and not present in a cotwin of a concordant nonabusing pair, would be indicative of vulnerability variables. This powerful design allows one to explore whether the presence of the variable is due to drug use or rather to the genetic connection to the abusing twin. Again, with such a large sample, subjects may be segregated into specific drug abuse patterns. Additionally, this design can potentially distinguish variables that may be associated with, for example, opiate addiction as compared to barbiturate addiction.

Comings' proposal employs the mediator approach and directly explores the genotype of the drug-abusing individual. The best candidate genes, it is hypothesized, are related to the reward system in the brain. Specifically, these would be genes associated with dopamine receptors. Therefore, the search for candidate genes will look for particular allele(s) more prevalent in severe drug abusers. It is assumed that it is not likely that such mutations or variations would be direct causes for drug abuse, but rather might be responsible for modifying behavior that increases the vulnerability to either seek drugs in the first place and/or continue and escalate use once there has been initial exposure. Therefore, the proposed study will attempt to not only determine the association of the polymorphic genes among

drug abusers, but try to tease out the personality or behavioral characteristics that may more closely result from action of the gene itself.

Neurophysiological Factors in Behavioral Etiologies

Postulating that drug abusers have a biological predisposition to continue from use to abuse of psychoactive substances, and to dependence and addiction, implies that there must be measurable premorbid individual differences in neurophysiological variables. Examples would include differences in regional brain responsiveness, metabolism, or activation patterns that are associated with vulnerability to drug abuse itself or with risk behaviors leading to drug abuse. Substantial basic (animal) research has already identified many of the important neurotransmitter systems affected by various licit and illicit psychoactive substances. Missing, however, is information about the differentiating features among human abusers that make their critical brain systems particularly more vulnerable in a way that leads some individuals to abusive drug involvement. From what has been learned, it seems logical that among the possible differences would be cerebral distribution of function, metabolic efficiency, or neural activity associated with those putative systems that underlie abuse liability.

Several newly developed techniques have been successful in displaying the effects of drugs on addicts' brains. Cerebral metabolism and activation can be measured by positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), cortical evoked potentials, and several other modern advances in technology. These techniques can predictively differentiate among certain performances on neuropsychological tests, some of which have predictive value for drug abuse liability. Individual differences in brain function may also be distinguished for other related risk or intermediary behaviors including anxiety, stress, and aggression. Differentiating cerebral functioning for these behaviors in people without behavioral pathologies as well as in individuals who exhibit clinical psychopathology may point to underlying neurobiological contributions for behavior leading to drug abuse.

For example, in research at the Addiction Research Center (the NIDA Intramural Program), aggressive delinquent males showed delays in auditory cortical evoked potentials as well as a decreased slow wave amplitude of cognitive event-related potentials (ERPs) during mental processing (Herning et al. 1989). This suggests that there are

individual premorbid differences in brain organization for nonabusing at-risk adolescents. In rhesus monkeys, there was greater activation of the left frontal lobe in response to diazepam (Davidson et al. 1992) and the magnitude of the asymmetry was highly correlated (r= 0.82) with a measure of anxiety (Davidson et al. 1993). Finally, several studies in humans have shown localized (regional) changes in blood flow as measured by single photon emission computerized tomography (SPECT) (Miller et al. 1992; Pearlson et al. 1993) cerebral metabolism following chronic use (Volkow et al. 1992) or withdrawal (Holman et al. 1993; Volkow et al. 1992) from psychoactive drugs such as cocaine. Research using these types of approaches could be strengthened by the utilization of more sophisticated neurotransmitter tracers, and by behavioral conceptualizations and assessments. For example, it has been shown that the number of dopamine type 2 (D2) receptors are reduced in cocaine abusers compared with controls (Volkow et al. 1993), suggesting that the dopamine dysregulation caused by chronic use may be related to some of the behavioral changes in these individuals. Application of these technologies to research on the biobehavioral etiology of drug abuse may yield critical information.

Iacono, Lykken, and McGue propose that psychophysiological vulnerabilities could be assessed to the degree to which these traits are inherited and relate to substance abuse. They hypothesize that the traits would be associated with behavioral undercontrol or disinhibition exhibited in externalizing disorders. Furthermore, they assert that these traits may be found in, and predictive of, affected individuals and their families, and would be stable over time. It is proposed that these traits can be assessed by electrocortical potentials, either evoked (e.g., P300) or resting electroencephalogram (EEG). Both have been modestly shown to be associated with substance abuse severity or with risk behavior symptomatology leading to substance abuse. Other prime physiological measures that would potentially point to disinhibition are those that assess reactivity to aversive stimuli. Such studies would focus on habituation, or conditioning to distraction.

Similarly, the Herning proposal will use ERPs to study children at risk for substance abuse due to specific personality or diagnostic characteristics including attention deficit disorder, aggressive-ness, and/or depression. Children will be studied before and during a methylphenidate challenge, and retested after 3 years. Since these children, at first assessment, will likely be too young to have engaged in a drug-abuse experience, the ideal result will be an electrocortical

or neuropsychological profile obtained at the first testing that will be predictive of later substance abuse.

Moss's proposal is based on the same general hypothesis that physiological measures can be associated with behavioral risk factors, but this proposed study is more specific. In particular, it is hypothesized that the risk behaviors observed in children of substance abusers are related to dysfunction of the frontal lobes. Accordingly, children of substance- abusing fathers with and without conduct disorder will be compared on prefrontal phospholipid metabolism as measured by 31P magnetic resonance spectroscopy. This methodology is relatively new; it takes advantage of the fact that specific phosphorus-containing molecules can be detected, which, in turn, can be used to assess the degree of metabolism. The ratio of phosphocreatine to inorganic phosphates may be indicative of the synthesis of adenosine triphosphate, an important energy-transporting molecule. While this technique has its limitations in terms of cortical localization, it is a relatively inexpensive, noninvasive assessment that potentially can identify at-risk children.

Neurochemical Factors in Behavioral Etiologies

Identification of individual differences by electrocortical and imaging techniques (which are related to systematic and variable findings in measurements hypothesized to be related to specific behaviors) implies there are differences in underlying neurohumoral substances that give rise to the neurophysiological measurements. While potentially very informative, these neurochemical system factors are impossible to directly assess in humans because current techniques would require assays of live human brain tissue to evaluate the concentrations of neurotransmitter systems. Examination of postmortem tissue in humans is possible and may give indications of consequences of certain drug-related effects and perhaps even etiological factors leading to substance abuse. For example, nicotinic receptors can be quantified with [3H]cytisine, a nicotinic receptor ligand in smokers, according to smoking history (Hall et al. 1993). Nevertheless, there are limitations to the possibilities of this approach. In the past, the extensive development of animal models has defined each of the neurochemical systems critical for maintenance of a drug-taking behavior. However, in the final analysis, human neurosystems are the principal concern because animal models can never represent the psychological aspects of abusive drug taking. Given the difficulty of such research in humans, progress has been limited to date.

Fortunately, human models for behaviors associated with drug abuse as well as new neurochemical assay techniques are leading the way for study in this area. Individual differences in neurotransmitter levels can now be detected and related to behavioral function. This has been accomplished methodologically by observing individuals with behaviors at risk for substance abuse and obtaining appropriate samples from plasma or cerebrospinal fluid that are indicative of central nervous system metabolic activity. For example, low levels of cortisol are correlated with increased aggression in animals (Politch and Leshner 1977) and hypo-mania in nondrug-abusing humans (Ballenger et al. 1983). Also, since the reward system of the brain is largely dependent on the neuro-transmitter dopamine, individual differences in the efficiency of this system in the reward areas of the brain may underlie abuse liability for certain psychoactive substances. Use of these types of indirect indicators may lead to critical new information.

King and Flowers, in their proposal, intend to examine the relationship between neurochemical and behavioral factors in order to predict vulnera-bility to drug abuse. To do this, they propose to assay for dopamine metabolites in cerebrospinal fluid and relate these measures to cocaine craving in addicts after long-term abstinence. A behavioral check of this same relationship will be made with motor activity that is believed to be related to central nervous system (CNS) dopamine activity. Illuminating the nature of craving is a key element in these studies, because if a reliable correlation can be established between craving and a neuro-chemical substance, progress can be made toward treatment and prevention.

The dopaminergic neurotransmitter system has dominated research and theory on the involvement of neurotransmitters in drug abuse. However, the serotonergic neurotransmitter system may also be implicated in psychological behaviors at risk for substance abuse. Similar to dopamine's association with certain behavior, reduced serotonergic activity appears to correlate with aggression and inability to control impulse behavior (Coccaro 1992) while increased activity is associated with inhibition (Spoont 1992). The interaction of serotonin and dopamine is evident in studies of habituation to environmental stimuli where higher serotonin levels result in reduced startle activity in animals (Geyer and Tapson 1988). In spite of the well-established connection of dopamine to pleasurable experiences, research relating the serotonergic, dopaminergic, or other endogenous systems to vulnerability to drug abuse has been very limited. This is

largely due to the complexity of the issue and lack of unifying theory, and is compounded by methodological difficulties.

As proposed by Kaye and Wisniewski, one solution to this dilemma for drug abuse may lie in drawing on research models of eating disorders. Patients diagnosed with bulimia nervosa (BN) are more likely to develop drug abuse and have many more substance abusers in their families compared with patients with restricting type anorexia nervosa (RAN). One current model of these related disorders is a faulty serotonergic system in each group—in one case acting to potentiate impulse control; in the other, to overcontrol or restrict actions. The authors' proposal addresses this observation and related hypotheses, first exploring whether behavioral factors of control, novelty seeking, and emotionality (unstable mood states) are associated with eating-disordered women (normal weight bulimics (NWB) and those with RAN). Then, once the relation-ships of these characteristics are established, the contribution of the serotonergic system to these behaviors and to substance abuse or avoidance can be studied.

Another approach to studying the neurochemical aspects of vulnerability to substance abuse is reflected in the proposal by Volkow, Fowler, Hitzemenan, and Wang which investigates individual differences in dopamine reactivity to psychostimulants. It is hypothesized that these differences in reactivity will reflect differences in brain biochemistry and predisposition for drug abuse. The basis for this hypothesis is the assumption that behavioral responses to a drug as well as one's personality characteristics and disposition reflect the neurochemistry of the individual. The study design includes assessment of the subjects' behavioral response symptomatology after methylphenidate (or placebo) exposure, and the use of PET to determine the relationship of these symptoms to dopamine activity. The dependent variable is 11C-raclopride binding, which is a measure of D2 receptor activity.

PUBLIC HEALTH SIGNIFICANCE

It seems likely that there are multiple pathways leading to an individual’s first trying and then, in a limited number of cases, escalating the use of psychoactive drugs to abuse, dependence, and/or addiction. The majority of theories and research on humans about the etiology and nature of drug involvement have omitted extensive consideration of individual differences underlying biological or

physiological components of these pathways. The result of this omission is that psychological/environmental research and models have been incomplete.

Conversely, neurobiological components of drug effects and abuse liability have been studied extensively in animal models where psycho-logical and environmental factors are either controlled or irrelevant. Human neurobiological research has been largely confined to verifying the animal work, largely omitting consideration of psychological and environmental factors. In humans, as in animals, individual differences were considered "noise" in this research approach, to be controlled or minimized so as to provide clear answers about neurochemical mechanisms underlying the neurosystems involved with psychoactive drugs. Accordingly, this approach has failed to explain the variability of human drug involvement not only as a result of individual differences in these neurobiological systems, but also as these systems co-occur and interact in varying environmental contexts.

It is believed that drug abuse is not only a heterogeneous phenomenon but also a multiply determined one involving the interaction of biological, psychological, and environmental determinants; research and theory must incorporate this multiplicity. Inclusive consideration of these deter-minants is already being initiated by some researchers, but the field in general has not embraced a multidimensional approach to drug abuse research. The concepts and studies presented in this monograph focus on biological factors underlying vulnerability to (and by implication, variability in) human substance abuse. Most incorporate, either explicitly or implicitly, a more integrated consideration of biological and behavioral factors than is generally found in the drug abuse field. Similarly, the power of most of these studies is enhanced by their recognition of the importance of individual differences in biological and behavioral factors and by their consideration of biological mechanisms within this larger context.

The hypothesis of a genetic contribution to substance abuse behaviors has been gaining acceptance for some time, but only now, with rapidly evolving methodology, can researchers hope to corner the derelict genes. It will be a challenge to determine how these genes modify human behavior to increase drug abuse risk, but neurophysiological measures that differentiate such individuals will provide clues. As imaging (especially) and neurochemical models of human behavior are studied, the all-important breakthrough to associate drug abuse

vulnerability to neurochemical mechanisms will be differentiated. Such discoveries will inevitably open currently unavailable avenues for treatment and prevention. The time is ripe for these researchers to broaden their scope and include drug abuse as the disease focus. It is certainly fair to argue that the best methodology and design are essential to success of such speculative research, but it is also essential that such work be started. While many may argue that more basic research in animal models is needed, such as finding better candidate genes of substance abuse, it is argued there is never a guarantee of recognizing the "right time." Researchers must seize the moment, taking advantage of advances in technology that make the task less formidable. Even if there is argument that some studies are "fishing expeditions," good fishermen know where to fish.

NIDA would like to thank the researchers who have been both generous and courageous enough to share, through the original conference and in this monograph, their speculations and their research in such early forms. The Institute joins with these innovative researcher leaders in encourag-ing others to adopt a biobehavioral approach to the study of drug abuse.

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AUTHORS

Harold W. Gordon, Ph.D.
Program Director
Biobehavioral Research Program
Etiology and Clinical Neurobiology Branch
Division of Clinical and Services Research

Meyer D. Glantz, Ph.D.
Associate Director
Division of Epidemiology and Prevention Research

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

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