# Genetic Factors in Drug Abuse and Dependence

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## STATEMENT OF THE PROBLEM

The etiology of drug abuse/dependence is a complex interplay of psychosocial and biological factors. These factors include socioeconomic status, education, drug availability, peer pressure, childhood and adult comorbid psychiatric disorders, and specific mutant genes. The emphasis of this chapter is on the role that genetic factors play in an individual's vulnerability to drug abuse/dependence, henceforth simply referred to as drug abuse. One major point is that there are no genes unique to causing drug abuse. Instead there are genes that alter the normal function of the central nervous system as manifested by a wide range of interrelated impulsive, compulsive, addictive, affective, and anxiety behaviors. One of the outcomes or associated behaviors of attempting to cope with these disorders is substance abuse. In this light, the genetics of any one of these interrelated behaviors has relevance to drug abuse. Drug abuse is not an island unto itself.

One of the major neurophysiological players in vulnerability to drug abuse in humans is the reward system. Pathways of this system are composed of dopaminergic neurons; the administration of addicting drugs results in its stimulation. A reasonable hypothesis for the neurochemical basis of drug abuse is that vulnerable individuals self-medicate to compensate for defects in this dopamine (DA) reward system. To investigate the possibility that variations in the prevalence of different forms of the dopamine type 2 (D2) receptor (DRD2) gene in drug addicts may be involved in the vulnerability to drug addiction, the frequency of the DRD2 variants was determined in several hundred substance abusers. There was a high correlation between the frequency of the Taq I A1 variant and multisubstance abuse, based upon the number of drugs on which more than $25 per week was spent ($p < 0.006$). Using the Defense Style Questionnaire (Andrews et al. 1989), drug addicts carrying the 1haplotype, which is in linkage disequilibrium with the D2A1 variant, showed much greater use of immature defenses than non-1 haplotype carriers.

These preliminary studies support the concept that differences in the prevalence of DA receptor variants play an important role in fundamental personality traits that affect a person's vulnerability to drug abuse as well as to other impulsive, compulsive, and addictive behaviors. To verify this association, the proposed specific aims are to study 200 male substance abusers from the addictions treatment ward of a Veterans' Administration (VA) hospital, and 200 sex, age, race, and ethnically matched controls. This study will include: genetic testing of the D2A1 and haplotype variants of the DRD2 gene; genetic testing for variants of the remaining four dopamine receptor genes, D1, D3, D4, and D5; testing of all subjects with the Diagnostic Interview Schedule, Minnesota Multiphasic Personality Inventory (MMPI), Addiction Severity Index (ASI), Defense Style Questionnaire, and Axis II Personality Index; and statistical analyses to test for possible correlations between the indepen-dent genetic variables, personality variables, and drug abuse.

## BACKGROUND AND SIGNIFICANCE

### Family, Twin, and Adoption Studies

Family, twin, and adoption studies are the classic techniques for examining the role that genetic factors play in a given disorder. The greatest source of information on family studies in drug abuse comes from reports that have also examined alcoholism. Since genetic factors appear to play a significant role in risk factors for alcoholism (Cloninger 1987; Goodwin 1981; Stabenau 1990), it is a reasonable assumption that genetic factors also play a role in drug abuse. There is a high rate of comorbidity between alcoholism and drug abuse; between 30 and 51percent of drug abusers have concomitant alcohol abuse or depen-dence, and relatives of alcoholics often have problems with drug abuse, and vice versa (Dinwiddie and Reich 1991; Mirin et al. 1991; Weiss et al. 1986, 1988). In a study by Miller and colleagues (Miller et al. 1989a, 1989b), 50 percent of drug abusers had at least a first- or second-degree relative with a diagnosis of alcohol dependence. O'Donnell (1969) reported that 57 percent of fathers and 12 percent of brothers of opiate addicts were alcoholics. Ellinwood and colleagues (1966) reported that 25 percent of fathers and 15 percent of brothers of opiate addicts were alcoholics.

Two other studies (Luthar et al. 1992; Mesonero et al. 1991) examined 476 siblings of 201 opiate addicts using a structured interview. They found a marked increase in the frequency of

antisocial personality (ASP), depression, drug addiction, and alcoholism among the relatives of opiate addicts. Relevant to the theme of the interrelationship between drug abuse and other disorders, they found a variety of psychiatric disorders in the siblings even when the drug addict proband did not have the same, suggesting segregation for a genetic spectrum disorder. Some, however, have suggested that the frequency of drug addiction in the relatives of drug addicts is higher than in the relatives of alcoholics (Hill et al. 1977; Kosten et al. 1991; Meller et al. 1988), suggesting that drug addiction is the behavioral outcome more closely associated with the modified genetic substrate. In a study of relatives of probands with alcoholism and depression, Merikangas and colleagues (1985) observed a significant increase in frequency of both alcoholism and depression compared to controls.

Childhood conduct disorder and adult antisocial personality disorder have frequently been implicated as risk factors in substance abuse (Cadoret et al. 1986; Croughan 1985; Jaffe et al. 1988; Rounsaville et al. 1982, 1991; Schubert et al. 1988; Stabenau 1984). Since genetic factors have been implicated in both conduct disorder (Comings and Comings 1987) and antisocial personality disorder (Bohman et al. 1982; Cloninger et al. 1982; Crowe 1974; Mednick et al. 1984; Sigvardsson et al. 1982), it is reasonable to suggest that these same genes can play a role in susceptibility to drug abuse.

Cadoret and colleagues (1986) reported a study of 242 male and 201-female adoptees separated at birth from their biological parents. Drug abuse was highly correlated with ASP, which in turn was predicted from antisocial behaviors in the biological parents. In addition, a biological background of alcohol problems predicted increased drug abuse in the adoptees who did not have antisocial personalities. Environmental factors such as divorce or psychiatric disturbance in the adoptive family were also associated with increased drug abuse. They concluded there were two genetic pathways to drug abuse: one through biological parents with antisocial personality, and the second from biological parents with alcohol problems who themselves were not antisocial.

While designed as a twin study of alcoholism, Pickens and colleagues (1991) also examined drug abuse. They found a concordance rate among 114 male monozygotic twins of 63.4 percent versus 43.8 percent for dizygotic twins ($p = 0.05$). They found that in males the genetic influence on drug abuse was comparable to that of alcohol abuse.

Grove and colleagues (1990) utilized the powerful approach of identical twins raised apart. This study found a high degree of heritability for drug abuse and childhood or adult antisocial behavior and a much more modest heritability for alcohol abuse. There were significant genetic correlations between drug and alcohol abuse scores ($r = 0.78$), drug abuse and childhood antisocial behavior scores ($r = 0.87$), drug abuse and adult antisocial behavior scores ($r = 0.53$), alcohol abuse and childhood antisocial scores ($r = 0.54$), and alcohol abuse and adult antisocial scores ($r = 0.75$). These correlations supported the idea that there was a common core set of genes for all these reported behaviors.

Genetic Loading Studies

While family, twin, and adoption studies provide evidence for the role of genes in drug abuse and related disorders, one of the disadvantages is that they provide no clues as to which genes are involved. An approach that does supply such clues was found in a well-defined genetic impulse disorder, Tourette syndrome (TS) (Comings et al. 1984; Pauls and Leckman 1986), and used to examine genetic factors in both alcoholism (Comings 1994b) and drug abuse (Comings 1994a). The drug use/abuse histories of 217 TS probands, 79 of their relatives who also had TS (nonproband TS), 249 relatives without TS (non-TS relatives), and 50controls were examined. Regardless of the mechanism of inheritance of TS, probands would have the highest number or genetic loading for TS (Gts) genes, nonproband TS relatives would have the next most loading, non-TS relatives would have still less loading, and controls the fewest Gts genes or least Gts gene loading. It was assumed that if there were a significant correlation between the degree of genetic loading for Gts genes and symptoms of drug abuse, then the Gts genes would be playing a role in drug abuse. This proved to be the case.

The correlation between the endorsement of eight of the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (Robins et al. 1981) symptoms, criteria for drug abuse/dependence as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed., rev. (DSM-III-R), and the genetic loading for the Gts gene(s) was significant at $p < 0.00000001$ (Comings 1994a). The correlation with alcohol abuse/dependence was also significant (Comings 1994b) but, as in the twin study of Grove and colleagues (1990), less so than for drug abuse. Of a number of comorbid disorders examined, the greatest predictor of drug abuse was

concomitant alcohol abuse, and the greatest predictor of alcohol abuse was concomitant drug abuse. This finding, plus the fact that the same genetic disorder was examined in both studies, suggests that the behavioral outcomes of alcoholism and drug abuse are related to similar genotypes.

Genetic loading studies were also performed with a smaller number of probands and relatives with attention deficit-hyperactivity disorder (ADHD), a disorder with strong genetic links (Faraone et al. 1991, 1992). Again, there was a significant correlation with genetic loading for the ADHD genes. Except for the presence of tics, TS and ADHD are virtually identical disorders with similar clinical symptoms, comorbid disorders in probands and their relatives, genetics, and treatment (Comings and Comings 1993). Previous studies had already suggested that children with either ADHD (Cloninger et al. 1988; Gittelman et al. 1985; Goodwin et al. 1975; Hechtman and Weiss 1986; Loney et al. 1981, 1983; Mannuzza et al. 1991; Mendelson et al. 1971; Tarter et al. 1977) or TS (Comings 1989, 1990a; Comings and Comings 1990) are at significant risk to develop substance abuse disorders as adults.

The DRD2 Gene in Substance Abuse and Related Impulse Disorders

Blum and colleagues (1990) reported that the Taq I A1 variant of the DRD2 gene was present in 69 percent of severe alcoholics compared to 20 percent of controls. Subsequent studies have been mixed, with some supporting (Arinami et al. 1993; Blum et al. 1991; Comings et al. 1991a; Cook et al. 1992; Parsian et al. 1991) and some not supporting (Bolos et al. 1990; Gelernter et al. 1991; Schwab et al. 1991; Turner et al. 1992) this association. One avenue of research is to determine if the D2A1 allele might correlate better with impulsive, compulsive disorders than with alcoholism per se for the following reasons: One of the major theories of TS is that it involved defects in DA metabolism; haloperidol, a DRD2 agonist, is one of the more effective medications for treating TS; and there is an increase in the prevalence of alcoholism among TS probands and relatives (Comings 1990a; Comings and Comings 1990).

A significant increase was found in the prevalence of the D2A1 allele in subjects with ADHD, TS, conduct disorder, and posttraumatic stress disorder (PTSD) (Comings et al. 1991a), all of which have significant associations with drug abuse (Comings 1990a; Comings and Comings 1990; Gittelman et al. 1985; Kulka et al. 1990). In these association studies, intragroup comparisons were used and the subjects and

controls were restricted to a single racial group to help eliminate gene frequency as a confounding variable. Fifty-nine percent of non-Hispanic caucasian, "battle-hardened" Vietnam veterans with PTSD carried the D2A1 allele, while only 5percent of those without carried the D2A1 allele ($p < 0.001$) (Comings et al. 1994). Within the group of TS probands, the prevalence of the D2A1 allele was 29 percent in 763 controls (Comings et al. 1994), 35.0percent for 20 mild cases, 40.4 percent for 146 moderate cases, and 55.5percent for 54 severe cases (Comings 1992).

These observations suggest that the D2A1 allele is in linkage disequilibrium with physiologically important variants of the DRD2 gene. Since drugs such as cocaine and dextroamphetamine produce a greater perturbation of the dopaminergic reward pathways than alcohol (DiChiara and Imperato 1988), it is hypothesized that the D2A1 allele would correlate more strongly with drug addiction than alcohol per se. To test this, 200 caucasian subjects on a VA inpatient addiction treatment unit were examined. Compared with controls, this group showed a significant increase in the prevalence of the D2A1 allele in individuals with polysubstance abuse (42 percent) ($p < 0.006$), but not in individuals with alcohol abuse only (21 percent) or alcohol dependence only (32percent) (Comings et al. 1994). Of those who spent more than $25 a week on two or more drugs, 57 percent carried the D2A1 allele versus 28.2 percent of those abusing only a single drug ($p < 0.0005$). Smith and colleagues (1992) have also reported a significant increase in the prevalence of the Taq I B1 allele of the DRD2 locus in drug addicts; Noble and colleagues (1993) reported a significant increase in the prevalence of the Taq I A1 allele in cocaine addicts.

Additional within-group comparisons were also informative. For those on the addiction treatment ward who had been jailed for nonviolent crimes only, such as driving under the influence (DUI), 29 percent of 111subjects carried the D2A1 allele. By comparison, 53 percent of 32subjects who had been jailed for violent crimes (e.g., assault, armed robbery), carried the D2A1 allele. In a subset of 13 subjects who had been arrested for violent crime and been expelled from school as children for fighting, 69 percent ($N = 9$) carried the D2A1 allele.

Pathological gambling is a disorder that combines the elements of impulsive, compulsive, and addictive behaviors. In preliminary studies of 96 pathological gamblers, approximately half carried the D2A1 allele (Comings et al., unpublished results). This study and others

reviewed above suggest that drug abuse, alcoholism, ADHD, TS, conduct disorder, antisocial personality disorder, PTSD, and pathological gambling have genetic substrates in common, and that the DRD2 gene is one of the genes involved.

## Oligogenetic Disorders in Psychiatry

Even though the D2A1 allele was significantly more prevalent in a number of impulsive, compulsive, and addictive behaviors, most affected individuals did not carry the allele, and the relative increase in carrier rate compared with controls was only modest. These and other observations (Comings, in press; Comings and Comings 1992) led to the suspicion that, unlike single gene disorders such as Huntington's disease and cystic fibrosis, psychiatric disorders are oligogenetic in nature (i.e.,caused by a clustering of several major and modifying genes). The disorders are common because the mutant alleles themselves are common, as are the chances of acquiring a sufficient number of genetic variations that modify behavior to clinically diagnostic levels. These considerations led to the speculation that each of the DA receptor genes might possess functional allelomorphic variants and thus play a role in psychopathology.

## The DRD3 Gene in Impulse Disorders

The DA type 3 (D3) receptor is described (Lannfelt et al. 1992) as a polymorphism that alters the coding sequence in the first exon resulting in the substitution of a glycine for serine and producing a Msc I polymorphism. In 139 TS probands, there was a significant decrease in the presence of D3A1A2 heterozygotes and an increase in D3A1A1 homozygotes and, to a lesser extent, D3A2A2 homozygotes (Comings et al. 1993). Crocq and colleagues (1992) reported virtually identical results in 141 schizophrenic patients versus controls in samples from England and France. But the results in TS were not confirmed in a small number (N= 19) of TS cases all from the same large pedigree (Brett et al. 1993). However, this was not a suitable test; only a single proband was examined and all subjects were mildly affected individuals from a single pedigree (Comings et al. 1993; Hebebrand et al. 1993).

Hebebrand and colleagues (1993) examined a larger number of probands (N= 66) from Germany and found no decrease in D3A1A2 heterozygotes compared with 100 controls. This prompted the examination of additional cases. Of 350 TS probands, 38.3 percent were D3A1A2 heterozygotes versus 49.7 percent D3A1A2

heterozygotes in a total of 358 caucasian controls ($p < 0.002$). In addition, structured interviews were available on a subset of these, allowing stratification by severity. There was a progressive decrease in heterozygosity, from 48.3 percent for 29 mildly affected TS subjects, to 39.5 percent for 119 moderately affected TS subjects, to 31.3 percent for 48 severe TS patients ($p < 0.005$, Cochran-Armitage linear rank test). It was suggested that the D3 receptors in D3A1A1 homozygotes were relatively hypofunctional, since previous studies in a series of Hispanic females showed that D3A1A1 homozygotes had higher prolactin levels than D3A1A2 homozygotes; hypothalamic DA neurons inhibit prolactin secretion. Ongoing studies have found a significant deficiency of D3A1A2 heterozygotes in pathological gamblers. These findings concerning the DRD3 receptor support those with the D2A1 allele, in that there was an increasing prevalence in TS patients with increasing severity.

## The Dopamine Transporter

The DA transporter is responsible for the reuptake of DA at the synapse. It plays a critical role in the regulation of synaptosomal DA levels and is the pharmacological site of action of cocaine (Usdin et al. 1991). The cloning and sequencing of the DA transporter gene (Carroll et al. 1992; Kilty et al. 1991; Usdin et al. 1991; Vandenbergh et al. 1992) and demonstration of a polymorphism at the 3' end of the gene due to a variable length tandem repeat provided the potential for uncovering an exciting gene effect in cocaine and other forms of substance abuse. Studies are underway in a number of laboratories to determine if there is an association between this polymorphism and susceptibility to substance abuse.

## Serotonin in Psychiatric Disorders

Defects in serotonin metabolism have been implicated in a wide variety of psychiatric disorders including alcoholism, drug addiction, depression, suicide, aggressive behaviors, antisocial borderline personality disorder, phobias, panic attacks, eating disorders, ADHD, and TS (Brown and van Praag 1990; Comings 1990a; Murphy 1991; Whitaker-Azmitia and Peroutka 1990). Because a similar spectrum of disorders was present in TS probands and their relatives (Comings 1990a), the blood serotonin and tryptophan levels were examined in 1,440 TS probands, their relatives, and controls (Comings 1990b). There was a significant decrease in both platelet serotonin and blood tryptophan in TS patients and their parents. A likely candidate gene responsible for this combination of defects would affect the synthesis

of tryptophan 2,3 dioxygenase (TDO2). If a mutation resulted in the constitutive hyper-induction of this enzyme, it would result in a relative deficiency of both tryptophan and serotonin.

To test this association, the human TDO2 gene was cloned and sequenced for over 8,400 base pairs of exon, intron, and regulatory deoxyribonucleic acid (DNA). Since many restriction endonucleases failed to produce any polymorphisms, large regions of the gene were sequenced in TS patients and controls. This procedure resulted in the detection of three intron polymorphisms. Two are testable by allele-specific polymerase chain reaction (PCR), and to date only one is detectable by denaturing gradient gel electrophoresis (DGGE) of a PCR product. Preliminary results with these polymorphisms suggest that this gene may play a role in impulsive, compulsive, and addictive behaviors.

Conclusions

1. Genetic factors play an important role in the vulnerability to drug abuse; the more severe the abuse, the greater the role of genetic factors.

2. Drug abuse is the result of a complex interplay of environmental, social, comorbid psychiatric, biochemical, and genetic factors.

3. Childhood impulsive disorders such as ADHD, conduct disorder, and TS are associated with vulnerability to drug and alcohol abuse.

4. Adults with drug abuse have a high frequency of other comorbid psychiatric diagnoses including alcoholism, ADHD, TS, antisocial personality disorder, depression, panic attacks, anxiety disorders, and others.

5. There are no genes unique to drug abuse. The genes involved are likely responsible for modification of the neurotransmitter balance resulting in a life-long spectrum of impulsive, compulsive, addictive, affective, and anxiety disorders.

6. There is no single gene responsible for this spectrum of disorders; rather, a small number of major genes and a larger number of modifying genes play a role. Genes affecting the serotonin-DA balance in the brain are particularly important. Since a number of genes are involved, the effect of each one is modest and is best identified by comparison of a large number of probands stratified by

severity against a large number of racially (and if possible, ethnically) matched controls.

7. The allelomorphic variants at the DRD2 locus play a role in a wide range of impulsive, compulsive, and addictive behaviors.

8. Other candidate genes for a role in this spectrum of behaviors are the DA D1, D3, D4, and D5 genes; the DA transporter gene; DA ß-hydroxylase; TDO2; serotonin; and other receptor genes.

9. The identification of an important role of genetic factors and comorbid disorders in drug abuse has important implications for treatment. While abstinence from street drugs is the goal in treatment, abstinence from all drugs may be counterproductive. The potential role of the serotonergic and dopaminergic agonists or reuptake blockers as adjuncts in the treatment of the biochemical defects underlying substance abuse needs attention and continued study.

## EXPERIMENTAL METHODS

### Clinical Studies

In the proposed study, two major groups of subjects will be evaluated: 200 adult male caucasian substance abusers, and 200 adult caucasian male healthy controls who do not meet criteria for lifetime drug abuse, but may have had minor to moderate degrees of drug use. In addition, to prepare for future studies of drug abuse in females and in other races, 25to 50 male blacks, 25 to 50 male Hispanics, and 25 to 50 female caucasians will be examined.

### Setting

The clinical section of the study will be undertaken on the addiction treatment unit (ATU) of a VA medical center. The ATU contains a 30-bed inpatient program and a large outpatient program (1,600 patient visits per month). The patient population is made up of 65 percent polysubstance abusers, 20 percent alcohol-dependent patients, and 15percent single-drug abusers. The majority are considered chronic and severe in their addictive patterns, with lengthy treatment histories at numerous other facilities. Additionally, roughly 40 percent of the treatment population has a second psychiatric diagnosis (in order of frequency: unipolar depression, PTSD, and bipolar affective disorder). The multidisciplinary treatment team includes a

full medical staff (psychiatrist, internist, psychiatry resident) as well as psychologists, social workers, addictions therapists, and nurses.

Sample Acquisition

The principal component of the proposed investigation will study 200adult white male admissions to the 28-day ATU inpatient program who meet DSM-III-R criteria for diagnosis of psychoactive substance abuse disorders. All subjects will be between the ages of 25 and 55. Fourteen days after the hospital admission (to ensure clearance of ethanol and drug neurotoxicity), subjects will be asked to participate and their written informed consent obtained. Randomly chosen subjects in the ATU are routinely given, at admission, a urine drug screen for the commonly abused substances. This information will be used to verify statements concerning drug use reported by research subjects.

Ethnicity

The ethnic origin of all four grandparents of the test subjects and controls will be determined. This will allow stratification of the subjects and controls by major ethnic groups to determine if this factor plays a role in accounting for differences between subjects and controls.

Psychiatric-Psychological Testing

DIS-III-R. A trained interviewer will administer the Diagnostic Interview Schedule, Version III Revised (DIS-III-R) to obtain lifetime DSM-III-R diagnoses. The computerized version will be employed. However, since subjects are able to learn the branching system of the DIS and develop shortcuts, the interviewer will read the contents of the screen to the subject and input the responses, thereby increasing the validity. All interviews will be reviewed by a staff psychiatrist to verify and finalize the diagnosis.

Drug Use Survey. The Drug Use Survey, developed by the Addiction Research Center (ARC) of the National Institute on Drug Abuse (NIDA), indexes both the quantity and frequency of use of all major psychoactive drugs including cigarettes and alcohol. Trained interviewers will assess the amount, frequency, and/or dollar cost of the time of lifetime peak use for drug classes used more than five times. Blinded ratings of lifetime peak use of each individual substance will subsequently be made on a four-point scale: 0 = absent, 1 = minimal,

2 = moderate, or 3 = heavy use. The Drug Use Survey was chosen for two reasons: it is a standardized test used by the ARC of NIDA; and information on all aspects of substance abuse is needed for this study, since variants of different DA receptors may also be related to cigarette smoking.

Minnesota Multiphasic Personality Inventory (MMPI-2). The computer-administered version of the MMPI-2 will be used to assess personality dimensions. The MMPI was chosen for two reasons: it gives quantitative scores of various clinically relevant variables, such as depression, while the DIS gives only dichotomous diagnostic results; and it is a well-standardized, reproducible, and validated test.

Addiction Severity Index (Hodgins and Guebaly 1992). The ASI is a semistructured interview that collects data from substance abusers in seven problem areas: medical, employment, legal, alcohol, other drug use, family-social functioning, and psychological status. In each area, the subjects provide an estimate of the seriousness of the problem and their need for treatment. This test was chosen because it is a standardized test for estimating addiction severity.

Defense Style Questionnaire (Andrews et al. 1989). This 188-item, paper-and-pencil test allows assessment of the degree of reliance upon mature, neurotic, and immature ego-defensive operations. This test was chosen because it provides information concerning basic defense styles, and because preliminary studies indicate that carriers of haplotype 1 of the DRD2 gene use significantly more immature defense styles than noncarriers.

Axis II Personality Inventory. To further access the role of axis II personality disorders on the distribution of the various genetic variants, the Computerized Personality Disorder Interview (C-PDI) will be self-administered.

Controls

The study will recruit 200 controls matched by age, sex, and race from the staff of the VA hospital (physicians, nurses, medical students, secretaries, janitors, others) and from those attending routine screening clinics for diabetes, hypertension, cholesterol, and blood lipid testing. The ratio of hospital personnel to screening clinic controls is expected to be 1 to 3.

Genetic Studies: Genotyping of the DRD2 Gene

The details of the method for testing the Taq A1 allele of the DRD2 gene have been presented elsewhere (Comings et al. 1991b). The allele-specific oligomers and haplotyping procedure for the DRD2 gene are described by Sarkar and Sommer (1991).

Other Dopamine Receptor Gene Polymorphisms

The necessary probes are available and synthesized, and the necessary DNA primers for genotyping all the other DRD1, DRD2, DRD3, DRD4, and DRD5 polymorphisms have been tested. The molecular biology of these additional genes was described above.

Statistics: Sample Size Calculation

One of the specific aims is to determine if the subjects with multi-substance abuse will show a higher prevalence of the genotype and haplotype 1 variants of the DRD2 gene than those with single substance abuse or alcoholism alone. Based on preliminary studies, the prevalence rates of D2A1 alleles were 27.8 percent in single drug abusers (usually alcohol) and 55.9 percent in multiple substance abusers. A power analysis indicates that a sample size of 200 drug abusers and 200 controls will be sufficient for all the polymorphisms to be studied.

Statistical Analysis

Data analyses will be done with the use of Statistical Packages for the Social Sciences (SPSS), Statistical Analysis Software (SAS), Biomedical Data Processing Program (BMDP), or Fortran language programs. The significance of association between two categorical variables (e.g., the relation between DA receptor alleles and haplotypes and a specific diagnostic category) will be assessed by the chi-square test, and the magnitude of association will be measured by

the odds ratio. Significance test of the association between categorical and continuous variables (e.g., the association of DRD2 alleles and haplotypes and various clinical scores) will be done with the t-test, analysis of variance, or nonparametric tests such as Wilcoxon tests and Kruskal-Wallis tests.

In addition to the perspective represented by univariate analyses, the study will explore the extent to which the combination of several variables could explain the characteristics by using multivariate analyses. Possible confounding effects of ethnic, epidemiologic, psychological, and psychiatric risk factors will be assessed using multivariate analyses. Standard general linear models (GLM) will be used to study interrelations among variables. Specifically, multiple regression analyses can be used when outcomes are continuously measured, and multiple logistic regression analyses can be used when outcomes are dichotomous or categorical in nature.

## STRENGTHS AND WEAKNESSES

The strengths of this proposal are that all the power of the explosive field of molecular genetics can now be brought to bear to provide an under-standing of the risk factors in drug abuse at the most fundamental level available—human genes. In addition, sufficient preliminary data are already available to indicate that many of the most important genes involved have probably already been identified, cloned, and sequenced; the method of determining if these genes play a role in a specific behavior is clear-cut. This determination involves identifying genetic variants at the candidate genes of interest followed by studies of sufficient numbers of subjects and racially matched controls to determine if the alleles of these polymorphisms are present at a significantly different frequency in drug abusers than in controls. These are called association studies.

A further strength of this approach is that it is not necessary to identify the mutations that affect the function of the candidate gene in question. Since such mutations can occur anywhere in the thousands of base pairs 5' and 3' to the gene or in introns, exons, or transcribed portions of the gene, their identification can be very difficult. However, the presence of a phenomenon called linkage disequilibrium allows almost any polymor-phism in the region of the gene to provide some genetic information about the role of that gene in a specific behavioral disorder. Because of the relatively small distances between the polymorphism of interest and the putative real mutation affecting

the function of the gene, the alleles of the polymorphism and the alleles of the real mutation segregate nonran-domly. Thus, any difference in frequency of the real mutation in drug abusers will be at least partially reflected by differences in the frequency of most of the more numerous polymorphisms at or near the candidate gene.

While this approach uses association studies, many investigators in the genetic community still assume that linkage studies are the only reliable method of identifying the genes involved in hereditary disorders. However, this assumption is rapidly changing within the psychiatric community. A major impetus for the change is that despite massive efforts to find genetic linkages for many psychiatric disorders including TS (95 percent of the genome excluded), schizophrenia, manic-depressive disorder, alcoholism, dyslexia, panic attacks, and others, no confirmed linkages have been identified. The perception is growing that this failure is due to the fact that these disorders are polygenic rather than due to single, rare autosomal dominant genes with reduced penetrance. One argument favoring association studies of polygenic disorders over linkage studies followed from a computer simulation that showed the power of linkage analysis deteriorates so severely for a disorder caused by more than 4 to 6 genes that a negative lod score will be obtained immediately over loci that in fact do have an effect on the phenotype (Popping et al. 1993). Thus for complex, multifactorial, polygenic disorders such as drug abuse, association studies provide the most appropriate and powerful tool.

The major problem with association studies is the potentially con-founding variable of racial and ethnic variations in the frequency of the alleles being studied. If the racial and ethnic mix of the test individuals and controls is different, spurious results may be obtained. This problem can be circumvented in three ways: limiting the studies to homogeneous racial and ethnic groups, using large numbers of subjects and controls to avoid spurious results due to chance variations in small sample sizes, and using within-group comparisons. An example of the latter would be to compare gene frequencies within the total group of drug addicts stratified by severity measures such as the number of drugs abused or frequency of use. Such a comparison would lessen the degree to which geographical or socioeconomic differences between the subjects and the controls would confound the results. All of these precautions have been taken in this proposal.

## PUBLIC HEALTH SIGNIFICANCE

In an article entitled "Medicalizing the Drug War," Fishbein (1991) reviewed the numerous studies that have shown that the majority of the violence and crime perpetrated upon society by drug addicts can be traced to a relatively small number of individuals who commit a large number of criminal acts and have a very high recidivism rate. These individuals tend to have a history of ADHD and aggressive, undersocialized conduct disorder dating back to early childhood. These observations, as well as numerous twin and adoption studies (Bohman et al. 1982; Cadoret and Stewart 1991; Cloninger and Gottesman 1987; Cloninger et al. 1982; Crowe 1972, 1974; Hutchings and Mednick 1975; Zur Nieden 1951), indicate that genetic factors play a significant role in the behavior of such individuals. Since genetic factors are not expected to be specific to drug abuse, identification of these factors will simultaneously identify genetic factors involved in other behavioral difficulties such as ADHD and conduct disorder. If such behavior can be understood and treated, then researchers will have come a long way toward alleviating major burdens in society.

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