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# Behavioral Responses to Amphetamines in Identical Twins

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Male, monozygotic twins (six pairs) were repeatedly tested before and after d-amphetamine, l-amphetamine, or placebo administration. Drug effects on cognitive, psychomotor, personality, mood, and pain variables were assessed. Members of a twin pair tended to respond similarly on several tests under placebo conditions, indicating genetic determination of the behavioral variables. In addition, cotwins tended to show similar responses to amphetamine as measured by one test of cognitive function, by several mood and personality variables (hostility, autonomic arousal, friendliness, feelings of tension and loss of control), and tended to have similar plasma levels of both amphetamine isomers. Although shared environmental effects cannot be ruled out, the results are consistent with genetic mediation of a variety of behavioral effects of amphetamines.

**Key words: Psychopharmacogenetics, Amphetamines, Psychopharmacology, Behavioral genetics, Twins**

## INTRODUCTION

Substantial individual differences are known to occur in response to psychoactive drug treatment. Two major factors seem to compose the organic basis for such variability: differences in the sensitivity of target tissues to a drug, and differences in the distribution, binding, biotransformation, and excretion actions of the organism on a drug. The role of genotype in the control of exaggerated drug responses was systematically documented by Kalow [9] for a handful of drugs. Since this seminal work in the field of pharmacogenetics, the importance of genetic factors in drug response has been documented in several lines of research. Kalow [10] demonstrated that the development of malignant hyperthermia by certain individuals following inhalation anaesthetics is inherited as an autosomal dominant trait. Vesell and his colleagues [3,18,19] found significantly higher intraclass correlation coefficients among MZ than among DZ twins for metabolic rates of several drugs. Similar

findings were reported by Alexanderson et al [1]. Together, these investigations demonstrate virtually complete genetic determination of metabolic rates for the specific compounds studied, including nortryptilene, halothane, and barbiturates.

While these advances in our understanding of the importance of genotype in the prediction of drug response are of unquestionable importance to the therapeutic application of these compounds, a major area of psychopharmacology has remained essentially outside the field of pharmacogenetics. This area covers the self-administration of substances, where the posible contribution of genotype to the development of drug abuse is just beginning to be explored [4,5,7,8,12,14,15]. Certainly, the reasons why only some individuals who experience a particular drug's effects develop a pattern of abuse, and why the subjective effects of the drug vary widely among individuals, might conceivably include genetic factors predisposing, for example, to a euphoric drug response. While it is likely that genetic factors play a role in the development of abuse for some drugs, such as alcohol, the possible role of genes in the abuse of amphetamines is far less clear. The lack of information regarding the genetic determinants of response to drugs of abuse in particular, and the desire to gain knowledge of the role of genotype in the psychological aspects of response to drugs in general, led us to investigate the effects of amphetamines on a number of psychological variables in monozygotic twins.

## MATERIALS AND METHODS

### Subjects

Male, monozygotic twins were recruited by newspaper, radio, and television advertisements for paid participation in the study. Of those twin pairs responding, six pairs were ultimately chosen for participation in the study[1]. All were 21–28 yr of age, nonsmokers, had no obvious medical problems and were not regular users of drugs. Zygosity was determined by fingerprint and blood-group antigen matching corroborated by life-history data. (A matching group of dizygotic twins was not available for comparative study.) All subjects underwent thorough physical, psychological, psychiatric, and laboratory testing before participation.

### Procedure

**Test and Drug Administrations.** Each subject was seen for three days of testing according to a quasirandom schedule that prevented both members of a twin pair from receiving the same drug on the same day. The three sessions were at least one week apart. On each day, the subject received an i.m. injection of either placebo, 10 mg d-amphetamine sulfate, or 10 mg l-amphetamine sulphate according to the schedule in Table 1. During each testing (drug condition) day, there were three test sessions: a morning predrug baseline; a session 1–4 h after drug or placebo administration; and a 5–6 h postdrug session. Tests of cognitive and psychomotor performance, pain sensitivity, mood, and personality were administered according to the schedule in Table 2. Some tests were given in each test session (i.e. 3 times), others only once or twice.

### Test Battery

**Cognitive Functioning.** *Oral Arithmetic (OA).* Each S was presented with a card on which addition or subtraction of three- and four-digit numbers was required. Seven problems were presented. Since differences in the difficulty of the sets of seven problems were present, each subject's score (# correct) was transformed to a $z$-score ($X = 10$, $SD = 1$) for the population of all Ss scores on that set.

*Digit Span (DISP).* The Digit Span subscale of the Wechsler Adult Intelligence Scale (WAIS) was given during the first morning baseline session and after drug administration [20]. Each Ss score was calculated as follows: Total (forward + backward) postdrug score − baseline + 10.

[1]The subjects in this study had already participated in an earlier similar study of the response to morphine, conducted several months prior to the study reported here [8,12].

*TABLE 1. Schedule of Drug Administration**

| | Twin | Test day 1 | Test day 2 | Test day 3 |
|---|---|---|---|---|
| Twin pair 1 | 1A | D | PL | L |
| | 1B | L | PL | D |
| Twin pair 2 | 2A | L | D | PL |
| | 2B | PL | D | L |
| Twin pair 3 | 3A | PL | L | D |
| | 3B | D | L | PL |
| Twin pair 4 | 4A | PL | D | L |
| | 4B | D | PL | L |
| Twin pair 5 | 5A | D | L | PL |
| | 5B | L | D | PL |
| Twin pair 6 | 6A | L | PL | D |
| | 6B | PL | L | D |

*Sequence of drug administration for each subject. PL = Placebo, D = 10 mg d-amphetamine, L = 10 mg l-amphetamine. Dr. Donald Jenden, Chairman, Department of Pharmacology, UCLA, and his associates provided the drugs and schedule of administration for the double-blind experiment. All injections were given intramuscularly.

*Digit Symbol Substitution (DSS).* The Digit-Symbol Substitution scale from the WAIS was administered twice daily. Scores were computed as follows: Scaled score (drug session) − scaled score (morning baseline) + 10.

In addition to these direct assessments of cognitive functioning, two self-assessment scales (State Dependent Effects Questionnaire:SDEQ and National Institute of Mental Health:NIMH Mood Scales) and one psychiatric rating scale (Psychiatric Interview Rating Scale:PIRS) also included cognitive assessment. These are described later (see Mood and Personality).

**Psychomotor Performance.** *Pursuit Rotor (PR).* Each S was tested with his dominant hand twice each day on a rotary pursuit task. Each PR test was conducted at two speeds (30 rpm, 60 rpm) with each of two targets (circular and triangular), so that the task had four subtests of distinguishable difficulty. During the morning baseline sesson on the first test day, Ss had practice in all four target-speed conditions. On the other two test days, only the 60 rpm tests were conducted in the morning. Scores analyzed were time on-target during the drug session test.

*Hole-Steadiness (HOST).* Three times daily, each S was tested for his ability to hold an electrified rod in a hole without touching the sides. Ss were tested on eight holes of decreasing size with each hand. Scores reported are for total time on the wall with the dominant hand summed over all eight holes. Since differences in baseline performance were detected, scores were initially computed as follows: Drug − Baseline + 1.0. This eliminated pre-drug biases, but skewness was also present. Consequently, analyses were performed on: log (Drug − Baseline + 1.0).

*Tapping (TAP).* Ss were given 30 s to tap a pencil dot into as many as possible of 100 squares presented as a 10 × 10-cm grid [6]. This test was given twice daily. Scores were computed as follows: Number of squares (drug) − number of squares (baseline) + 10.

**Pain Sensitivity-Cold Pressor (CP).** Each S was tested twice each day according to procedures described by Wolff et al [22]. The test consisted of immersion of the dominant hand in lukewarm water for 2 min, followed by ice-water immersion (0–1°C). The subject indicated when pain was first experienced and continued to hold his hand in the water until he could not bear it any longer. Two measures were calculated in each session. Pain threshold (latency to declare pain sensation) was analyzed for the drug session only, since no baseline differences were present. Pain sensitivity range (the length of time between the declaration of "pain" and the time that the hand was withdrawn) was used as a measure of pain tolerance that corrects for individual differences in pain sensitivity. A maximum pain sensitivity range of 2 min was employed. Pain sensitivity range in the afternoon (drug) session was

*TABLE 2. Test Battery Administration Schedule*

| Test | Morning predrug baseline | Hours after drug administration | |
|---|---|---|---|
| | | First postdrug | Second postdrug |
| State-Dependent Effects Questionnaire | — | .75 | 5.25 |
| Pursuit Rotor | Yes | 1.00 | — |
| Addiction Research Center Inventory | — | 1.75 | — |
| Oral Arithmetic | — | 1.85 | — |
| Digit Symbol Substitution | Yes | 2.00 | — |
| Tapping | Yes | 2.15 | — |
| Psychiatric Inventory Rating Scale | Yes | 2.25 | 6.00 |
| Hole Steadiness | Yes | 2.50 | 5.50 |
| Pain Sensitivity | Yes | 3.00 | — |
| Digit Span | — | 3.25 | — |
| Written Arithmetic | Yes | 3.50 | — |
| NIMH Mood Scales | Yes | 3.75 | 5.65 |

expressed as a difference from predrug morning baseline. For both the pain threshold and pain tolerance measures, latencies were skewed, requiring log transformation of the scores. The test procedures and details of instructions to subjects have been reported [8].

**Mood and Personality.** *State-Dependent Effects Questionnaire (SDEQ).* This self-report pencil-and-paper test required that Ss check off applicable items from a list of 260 items. It was administered twice daily at 0.75 and 5.25 h postdrug. Scales validated for the following factors were computed: Improved Cognition, Tension, Sensitivity and Autonomic Arousal, Impaired Cognition, Perceptual Sharpness, Relaxation and Well-being, and Increased Control.

*NIMH Mood Scales.* This test was also a self-report measure, similar in format to the SDEQ [16]. Subscales assessing Depression, Hostility, Guilt-Shame, Anxiety, Carefreeness, Fatigue, Friendliness, and Cognitive Loss were employed. The test was administered three times each day. The two drug-session scores were corrected for predrug baseline scores.

*Psychiatric Interview Rating Scale (PIRS).* Three times each day, each S was interviewed by a psychiatrist who evaluated psychological state with this checklist instrument [Liston, unpublished]. Scales for Extraversion, Anxiety, Fatigue, Depression, Obsessive-Compulsivity, Cognitive Dysfunction, Hostility-Aggression, and Suspiciousness were examined after correction for predrug baseline. For a more detailed description of the scales, see Jarvik et al [8].

## Statistical Analyses

Following appropriate transformations of the test data, as indicated for the individual tests, analyses of variance were performed employing a mixed, factorial design treating twin pairs as a "between-subjects" factor. Drug conditions and, where appropriate, test sessions were treated as repeated measures (within subjects) factors [21]. Following significant main effects and interactions, individual comparisons were tested by the "Tukey (a) procedure" [21, Ch 3] using critical values for the studentized range statistic, $q_r$. Where critical values for simple effects were not tabled, the q-prime approximation to the Tukey q statistic was employed, and critical values were calculated as suggested by Kirk [11].

## Amphetamine Assay

Amphetamine was analyzed in plasma by gas chromatography/mass spectrometry, using ($^2H_3$)-amphetamine as an internal standard [3a]. A Hewlett-Packard Model 5980 GCMS system with electron impact ionization was used for selected ion monitoring at m/z 140 and 143 to represent unlabeled compound and internal standard, respectively. The relative ion current was transformed to mole ratio by reference to appropriate standard data.

## RESULTS

### Cognitive Functioning

**Oral Arithmetic.** Oral arithmetic performance was significantly impaired by both amphetamine isomers ($P < .05$), with a tendency toward a drug × twin pair interaction ($P = .06$). Five of six twin pairs (10/12 individuals) showed impaired performance after d-amphetamine administration. The differences for l-amphetamine were less pronounced, with 3/6 twin pairs (8/12 individuals) showing impairment. Pairs 3 and 6 were especially impaired by d-amphetamine, while no single twin pair was significantly impaired by l-amphetamine. Within any drug condition there were no significant differences between members of a twin pair or between twin pairs.

The two other direct measures of cognitive functioning, Digit Span and Digit Symbol Substitution, yielded no significant differences as a result of amphetamine administration.

Psychiatrist's rating of Cognitive Dysfunction (PIRS) revealed significant differences beween, but not within, twin pairs ($P < .02$). Pairs 4, 5, and 6 showed the least, and pairs 1 and 2 the most, cognitive dysfunction. These differences did not change as a function of drug condition or time of day (baseline, 2 or 6 h postdrug).

On three self-rating scales of cognitive functioning (SDEQ Improved Cognition, SDEQ Impaired Cognition, and NIMH Cognitive Loss), no significant differences were found among pairs, drug conditions, or time of day.

### Psychomotor Performance

There were no tendencies toward a drug effect on the Pursuit Rotor test. However, striking differences between twin pairs were found in Pursuit Rotor performance. At high speed with both the circular (easy) and triangular (difficult) target, twin pairs differed significantly ($P < .001$). As can be seen in Table 3, the major deviation was that of pair

*TABLE 3. Pursuit Rotor Time on Target in Seconds Most Difficult Condition*

| | Drug condition[b] | | |
|---|---|---|---|
| Twin (subject)[a] | Placebo | d-Amphetamine | l-Amphetamine |
| 1A | 3.84 | 3.11 | 6.45 |
| 1B | 6.22 | 5.61 | 5.22 |
| 2A | 19.75 | 15.51 | 17.52 |
| 2B | 13.81 | 15.58 | 19.40 |
| 3A | 12.44 | 15.42 | 15.27 |
| 3B | 17.64 | 15.42 | 14.11 |
| 4A | 15.72 | 15.59 | 15.82 |
| 4B | 10.63 | 18.04 | 16.54 |
| 5A | 18.97 | 14.52 | 15.12 |
| 5B | 17.94 | 12.16 | 22.40 |
| 6A | 17.37 | 16.04 | 16.23 |
| 6B | 15.99 | 17.63 | 14.65 |

[a]Twin pairs differ significantly ($P < .001$), with pair 1 significantly worse ($P < .01$) than any other pair.

[b]Test was performed 1 h after the administration of drug or placebo with the triangular (difficult) target at 60 rpm.

1. At the slower speed the pattern of differences was the same, but scores were generally so high that statistical significance was not reached.

In the test of Hole Steadiness, twin pairs differed significantly ($P < .05$). Although there was no significant main effect of drug treatment, there was a tendency for a drug × test session interaction ($P = .06$). Both d- and l-isomers tended to suppress the improvement in performance which occurred in the placebo condition 5.5 h postdrug administration.

For the Tapping test, no significant differences emerged.

## Pain Sensitivity

Pain threshold did not differ for different twin pairs and was not affected by amphetamine. Twin pairs differed significantly in the change in pain sensitivity range ($P < .005$) at 3 h postdrug. Over all drug conditions, pairs 3 and 5 showed decreased pain sensitivity range (consistent with increased pain tolerance), while pair 2 had increased range (decreased tolerance), and the other three pairs no change in tolerance.

## Mood and Personality

Several aspects of mood and personality showed differences among twin pairs, were altered by drug treatment, or showed drug effects specific to twin pair. Hostility was assessed by self-report (NIMH) and psychiatrist's rating (PIRS). By self-report there were significant twin pair ($P < .05$), drug ($P < .001$), drug × twin pair ($P < .001$), and test session × twin pair ($P < .001$) differences. l-Amphetamine significantly reduced hostility ($P < .01$), although this effect was confined to pairs 5 and 6. Pair 6 had significantly reduced hostility under both d- and l-amphetamine ($P_s < .01$), but the meaningfulness of this finding is questionable, for pair 6 also had high morning baseline hostility scores on the placebo day, resulting in a similar "reduction" by placebo treatment ($P < .01$). Pair 3 reported more hostility after d-amphetamine treatment ($P < .01$).

Examination of the PIRS corroborates the high placebo-day morning baseline hostility scores for pair 6. Correcting for baseline differences, a tendency toward twin pair differences was found ($P = .07$). The effect of drug treatment was significant ($P < .05$), with l-amphetamine attenuating the reduction in hostility over time in every twin pair. The significant twin pair × drug interaction ($P < .05$) consists entirely of the differences due to pair 6. In the PIRS, as well, pair 3 was one of the only two pairs to show increased hostility after d-amphetamine treatment.

Feelings of self-control were assessed directly by one scale on the SDEQ (Increased Control) and indirectly by another (Tension, Jitteriness, Loss of Control). d-Amphetamine significantly ($P < .05$) increased feelings of control; this was evidenced in pairs 3, 4, 5, and 6 and was a larger effect at 5.25 h than at 0.75 h postdrug. Examination of the Tension/Loss of Control scale of the SDEQ revealed significant drug × twin pair and drug × test session interactions ($P < .02$ and .01, respectively). Both drug isomers tended to increase tension, although the effects varied over twin pairs. Pair 2 reported increased tension after l-amphetamine and decreased tension after d-amphetamine ($P < .01$); for pair 4 the opposite pattern was evidenced ($P < .01$). Pair 2 was the most responsive (increased tension) to l-amphetamine and pair 4 the most responsive to d-amphetamine. Pairs 1, 5, and 6 showed increased tension under both drugs, while pair 3 showed no change with either drug on this test.

On the Sensitivity and Autonomic Arousal scale of the SDEQ, there was a significant drug × twin pair interaction ($P < .02$). Here only pair 4 reported the increased arousal

after d-amphetamine ($P < .05$), while all other pairs reported increased arousal after l-amphetamine. The relative consistency between this result and that for the Tension/Loss of control scale suggests that feelings of autonomic arousal are related to the perception of self-control.

For psychiatrist's ratings (PIRS) of obsessive-compulsive behavior, a significant difference was found ($P < .001$) between twin pairs due primarily to very high ratings for pair 3 on all test sessions of drug days.

Friendliness, assessed by self-report on the NIMH scale, declined from predrug baseline scores as testing progressed. Significant drug ($P < .01$), drug × twin pair ($P = .05$) and twin pair × test session ($P < .02$) effects were found. d-Amphetamine significantly elevated friendliness, most strikingly in pairs 3 and 6 ($P < .05$) but also in pair 1, while l-amphetamine tended to reduce friendliness.

Depression, assessed by psychiatrist rating (PIRS), differed significantly between twin pairs ($P < .05$), while self-reported depression (NIMH) did not. Item analysis of the two scales revealed that the two items contributing most to PIRS ratings were "slow speech" and "monotone," both of which are behavioral characteristics rather than mood items per se.

In the SDEQ scales for Perceptual Sharpness and Relaxation, the NIMH scales for Guilt-Shame, Anxiety, Carefreeness, and Fatigue, and the PIRS ratings of Extraversion, Anxiety, Fatigue, and Suspiciousness, no significant differences were found.

## Pharmacokinetic Analysis

Analysis of variance of fitted pharmacokinetic parameters did not show any statistically significant twin effect, although similar analyses of individual time points show significantly less within-pair than between-pair variation at two of six time points for both d- and l-amphetamine (Table 4). The overall probability using Fisher's $\chi^2$ for pooling independent tests was .002 for d-amphetamine and .006 or l-amphetamine, indicating a significant twin effect for plasma concentrations of both isomers.

*TABLE 4. Plasma Concentration of Amphetamine*

| | | d-Amphetamine[b] | | | l-Amphetamine[c] | | |
|---|---|---|---|---|---|---|---|
| Time[a] | Pairs | DF | F | P | DF | F | P |
| 50 | Between | 5 | 0.261 | 0.93 | 5 | 1.203 | 0.43 |
| | Within | 6 | | | 6 | | |
| 95 | Between | 4 | 0.832 | 0.59 | 5 | 0.468 | 0.81 |
| | Within | 5 | | | 6 | | |
| 185 | Between | 5 | 18.879 | <0.01 | 4 | 2.995 | 0.16 |
| | Within | 6 | | | 5 | | |
| 365 | Between | 4 | 2.619 | 0.19 | 5 | 10.348 | 0.01 |
| | Within | 5 | | | 6 | | |
| 725 | Between | 5 | 12.671 | <0.01 | 5 | 10.482 | 0.01 |
| | Within | 6 | | | 6 | | |
| 1325 | Between | 3 | 5.071 | 0.11 | 5 | 2.673 | 0.15 |
| | Within | 4 | | | 6 | | |

[a]Minutes postdrug administration.
[b]$P = .002$ by Fisher's $\chi^2$ test for pooling independent tests.
[c]$P = .006$ by Fisher's $\chi^2$ test for pooling independent tests.

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## DISCUSSION

Significant similarities between monozygotic twins were found in this investigation for four different sorts of variables: cognitive, pain sensitivity, psychomotor, and mood and personality variables. Since we could only examine a few subjects, we were statistically limited to the detection of very large drug effects (see below). However, even given this limitation, significant drug effects were detected for several variables differentiating twin pairs (significant drug × twin pairs interactions). These included cognitive dysfunction induced by amphetamine (Oral Arithmetic), and several mood and personality factors as measured by rating scales (hostility, autonomic arousal, feelings of tension and loss of self-control, and friendliness). These results suggest that a wide spectrum of the effects of the amphetamines may be under some degree of genetic control, a suggestion consistent with the small literature on genetic determination of responses to amphetamines in experimental animals [2]. However, since a matched dizygotic twin group was not studied for comparison, possible effects of a shared environment cannot be ruled out.

Although several variables showed differential sensitivity of the twin pairs to the amphetamines, no twin pair or pairs seemed to be generally more sensitive than other pairs. However, there were significant between-pair differential responses to the two amphetamine isomers for these variables; in some cases opposite between-pair effects of the isomers were observed. Moreover, in each of these instances intrapair effects of the two isomers were concordant. This suggests that some behavioral responses to the d- and l-isomers may vary considerably among individuals and that this variability may be genetically determined. Furthermore, while no significant interactions between blood level of amphetamine and behavioral parameters emerged, significant between-pair versus within-pair differences in plasma concentration of both isomers were detected. These findings may shed some light on the controversy in the literature concerning the relative potencies and differential neurophysiological and behavioral effects of d- and l-amphetamine [13,17,23]. It would seem likely, therefore, that different responses to amphetamines are mediated by different sets of genes. Although rigorous evidence for this assertion is lacking, it is, again, consistent with the limited animal literature [2].

A recent study of the response to morphine [8,12] employing these twin pairs and others, found greater within-pair than between-pair similarity in pain tolerance, as did the present study. Moreover, twin pairs were completely concordant for nausea or vomiting after morphine administration. Although the drug and drug × twin pair effects were not significant in the amphetamine study, it is of some interest to examine the relationship betwen pain tolerance and pain threshold as it emerged in the present study. Generally, it seemed that the decreased tolerance of pairs 3 and 5 was due to large ($> .1$ log unit for pair 5) decreases in the placebo conditions. Indeed, the tolerance of pair 5 was increased under the d-amphetamine condition. All three pairs in whom pain thresholds increased with d-amphetamine also showed increased pain tolerance under this condition. For l-amphetamine, no systematic relationship between threshold and tolerance measures emerged.

In the morphine studies, as well as the experiment reported here, twins tended to be more similar in observer-rated than in self-rated mood and personality variables. Genetic differences were also found in cognitive dysfunction scores assigned by a psychiatrist, but not self-reported. Members of a twin pair, however, did tend to respond similarly to d-amphetamine on an objective measure of cognitive impairment (oral arithmetic). Two other measures of cognitive ability (DISP, DSS) did not reveal concordant twin × drug

responses, possibly because they are more directly related to short-term memory capacity than to arithmetic skills. This difference may result from the tendency of even a trained observer (psychiatrist) to rate twins more alike than unrelated persons despite the fact that twin partners were not tested on the same day and were usually seen only after the lapse of at least one week. An alternative possibility is that the scales employed for self-report were less sensitive to postulated genetic bases for response similarity than the observer rated scales (PIRS). Finally, and in our opinion the most likely explanation, the small variability present in the self-report measures precluded the detection of genetic differences. We noted a similar tendency in the pursuit rotor task: Under the two easier test conditions, no genetic difference was detectable because performance was generally good. In contrast, the two difficult test conditions allowed detection of significant twin pair similarities.

In general, twin partners resembled each other more than did members of artificial pairs of unrelated individuals constructed from the participants according to the method previously described [12] on most of the tests employed. That twins may be similar in their responses to drugs of known abuse potential raises the intriguing question whether genes could influence some cluster of responses to amphetamines important to the development of patterns of abuse. Our limited study could have detected such a cluster of correlated responses only if it had been extremely obvious. Nonetheless, the observation of several significant twin effects and drug $\times$ twin interactions in so small and homogeneous a sample suggests that future studies which include dizygotic twins as controls may be designed to identify genetic components of amphetamine responses, which could ultimately lead to our understanding of the role that genotype plays in abuse of psychoactive agents.

Our ability to detect significant twin effects or twin $\times$ drug interactions could have been enhanced in many instances had we been able to examine a few more monozygotic twin pairs. The power of the statistical tests we employed varied widely from variable to variable, probably due jointly to error intrinsic to measurement of specific variables and the degree of genetic determination of twin's responses. The power of this method in general is perhaps most usefully expressed by estimates of the number of MZ twin pairs that would be necessary to detect between-pair differences of the same magnitude we report here, assuming that the error per experimental unit would remain the same. For a few variables (e.g., Oral Arithmetic, Hostility-Aggression rated by psychiatrist), the addition of even a single twin pair to our study would have revealed a statistically significant ($P < .05$) drug $\times$ twin pair interaction or twin pair main effect, respectively. For some additional variables, 12 twin pairs would have sufficed. If 20 twin pairs had been tested, many variables (e.g., Hole-Steadiness, Relaxation, and Increased Control scales of the SDEQ) would have yielded statistically reliable drug $\times$ twin pair interactions. Thus, to the extent that our procedures and variables are representative of this approach, it would seem to be desirable to test 20 MZ twin pairs in experiments of this sort in order to achieve greater statistical power.

Using monozygotic twins provides an efficient approach to the screening of effects which may measure differences between drugs, and also to the screening of drugs for detection of genetic differences. Positive results require further investigation. For example, family studies focussing on Mendelian segregation patterns constitute a step toward confirmation of the genetic contribution.

Demonstration of relatively small variability in drug response between members of monozygotic twin pairs in this preliminary investigation leads us to believe that there is a

potential wealth of information regarding the genetics of behavioral drug responses. Such genetic information may offer insight into psychological factors influencing the development of patterns of drug abuse.

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