*EFFECTS OF ATROPINE ON THE REPEATED ACQUISITION
AND PERFORMANCE OF RESPONSE SEQUENCES
IN HUMANS*

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The present study assessed a 24-hr time course for the acute effects of intramuscular injections of atropine sulfate (0, 1.5, 3.0, and 6.0 mg/70 kg) in healthy adult humans responding under a two-component multiple schedule of repeated acquisition and performance of response sequences. Subjects resided in an inpatient research ward for the duration of the study. In each component of the multiple schedule, subjects completed a different sequence of 10 responses in a predetermined order using three keys of a numeric keypad. In the acquisition component, the subjects' task was to acquire a new sequence each session. Eight sessions were conducted daily: one immediately before administration of the drug and then 0.5, 1.5, 3.0, 5.0, 7.0, 9.0, and 24.0 hr after administration. In the performance component, the response sequence always remained the same. Overall percentage of errors increased and overall response rates decreased in the acquisition and performance components as an orderly function of drug dose. However, these effects were selective in that behavior in the acquisition component generally was affected at lower doses than in the performance component. When behavior was affected in both the acquisition and performance components, the time courses of effects were similar. Drug effects began at 0.5 or 1.5 hr, reached peak effects between 3.0 and 5.0 hr, and returned to placebo levels between 7.0 and 9.0 hr postdrug in both schedule components. None of the drug doses produced reliable effects the day after drug administration (24-hr postdrug) in either schedule component. The present study provides the first within-subject assessment of the magnitude and duration of the effects of an anticholinergic on repeated acquisition and performance baselines and extends to atropine the selective effects on these two baselines demonstrated previously with other compounds in humans and nonhumans.

Key words: repeated acquisition, multiple schedules, response sequences, learning, atropine, anticholinergics, behavioral pharmacology, key press, humans

Repeated acquisition of behavioral chains, a procedure pioneered by Boren (1963) and refined by Thompson (1973), has been effective in studying drug effects on the acquisition of new behavior (i.e., learning) in individual subjects. In this procedure, reinforcement delivery is contingent on the subject emitting a predetermined sequence of responses across several operanda. The "correct" sequence re-

mains the same during an experimental session, but in each session reinforcement delivery is contingent on a new sequence of responses. After sufficient training, the number of errors made in acquiring a new sequence and the rate of responding become stable, thereby providing an effective baseline to study drug effects. This procedure has been used with nonhumans to characterize the effects on the acquisition of new behavior of many different compounds including anticonvulsants, anticholinergics, antipsychotic and antianxiety agents, barbiturates, alcohol, opioids, and stimulants (Bartholomus, Leander, & McMillan, 1978; Moerschbaecher, Thompson, & Winsauer, 1983; Penetar, 1985; Picker & Poling, 1984; Thompson, 1973, 1974). It has been used under both acute and chronic dosing regimens. In humans, repeated acquisition has been used in studies on the effects of barbiturates, benzodiazepines, *d*-amphetamine, alcohol, and cocaine, and also has been used in several nonpharmacological studies (Desjar-

The authors gratefully acknowledge the technical and collaborative contributions to this research by members of the Tri-Services Joint Working Group on Drug Dependent Degradation in Military Performance. The opinions and findings contained in this report are the authors' and should not be construed as an official position of the Joint Working Group. Preparation of this manuscript was supported by Research Grant DA/AA-04545 awarded to the first author. The authors extend their appreciation to Richard Lamb for assistance in organizing the atropine project and to Warren K. Bickel and John R. Hughes for helpful comments on this manuscript. Correspondence and reprint requests should be sent to S. T. Higgins, Human Behavioral Pharmacology Laboratory, Department of Psychiatry, University of Vermont, Burlington, Vermont 05401.

dins, Moerschbaeher, Thompson & Thomas, 1982; Fischman, 1978; Griffiths, Bigelow, Stitzer, & McLeod, 1983; Higgins, Bickel, O'Leary, & Yingling, 1987; Higgins & Stitzer, 1986; Perone & Baron, 1982; Vaughan, 1985; Walker, 1981).

Another effective use of the repeated-acquisition procedure has been to contrast drug effects on the acquisition of new behavior (transitional behavior) versus the performance of previously acquired behavior (steady-state behavior) (Thompson & Moerschbaeher, 1979). Using such a baseline, important differences in the behavioral effects of drugs across acquisition and performance conditions have been identified. Acute administration of benzodiazepines, barbiturates, alcohol, and stimulants to nonhumans, for example, increases overall error levels in the acquisition condition at doses that do not significantly affect errors in the performance condition (e.g., Barthalmus *et al.*, 1978; Thompson, 1975; Thompson & Moerschbaeher, 1979). More recently, such selectivity has also been demonstrated with diazepam and alcohol in humans using this procedure (Desjardins *et al.*, 1982; Higgins *et al.*, 1987).

Another difference between acquisition and performance conditions is that tolerance to the behavioral effects of drug develops more slowly in the acquisition condition than in the performance condition (Thompson, 1974, 1977), although this has yet to be demonstrated in humans. Such differential effects across acquisition and performance conditions are an important demonstration of the influence environmental variables exert in modulating the behavioral effects of drugs. The greater degree of stimulus control (inferred from error rates) established prior to drug administration in the performance compared to the acquisition component has been proposed most often as the behavioral mechanism controlling the differential effects obtained (Thompson & Moerschbaeher, 1979). Reinforcement and response rates also differ in the two conditions, however; this may contribute to the differential effects observed.

One class of compounds that has not been investigated using a repeated acquisition and performance baseline in humans or nonhumans is the anticholinergics (e.g., atropine, scopolamine), which block the action of acetylcholine at muscarinic receptor sites (Weiner, 1985). There has been renewed interest in the

behavioral effects of these compounds, due in part to the putative role of the cholinergic system in learning and remembering and in pathological conditions such as Alzheimer's syndrome (e.g., Bartus, Dean, Beer, & Lippa, 1982; Deutsch, 1971; Drachman, 1977; Perry, 1980). Numerous reports have been published on the effects of anticholinergics in humans using traditional learning and memory tasks (e.g., Dunne & Hartley, 1986; Ghoneim & Mewaldt, 1975, 1977; Wesnes & Revell, 1984; Wesnes & Warburton, 1983). Of particular relevance to the present study, several of these studies have reported that anticholinergics disrupt acquisition of new behavior (i.e., learning word lists) but not the performance of previously acquired behavior (e.g., Ghoneim & Mewaldt, 1975, 1977). Another study reported anecdotally that anticholinergics affected the ability of subjects to repeat even brief sentences or number sequences, but they could correctly answer questions on topics of common knowledge (Ketchum, Sidell, Crowell, Aghajanian, & Hayes, 1973).

Several studies in nonhumans have demonstrated that anticholinergics disrupt accuracy in the repeated-acquisition procedure, but performance components were not investigated (Howard & Pollard, 1983; Levy, Elmsore, & Hursh, 1984; Peele & Baron, 1988; Penetar, 1985). In one of these studies with monkeys (Penetar, 1985), atropine increased errors above control levels even during the latter part of acquisition sessions when subjects had achieved a relatively high level of proficiency on the sequence, suggesting that behavior under acquisition and performance conditions may be equisensitive to the drug's disruptive effects. On the other hand, when the effects of scopolamine were examined with pigeons responding under fixed-interval schedules with and without time-correlated stimulus changes added (i.e., "clock" stimuli), effects were greater in the latter condition (Laties & Weiss, 1966). That is, scopolamine's effects appeared to be modulated by the greater degree of stimulus control in the schedule with clock stimuli added. Laties and Weiss' (1966) findings suggest that the effects of anticholinergics are likely to be greater in the acquisition than in the performance component due to the relatively greater degree of stimulus control in the latter condition. In the present study, a multiple schedule of repeated acquisition and performance of response sequences was used to char-

acterize the acute effects of atropine in normal adult humans. Atropine is a prototype of the anticholinergic compounds (Weiner, 1985).

METHOD

Subjects

Subjects were 7 healthy male volunteers (5 white and 2 black) who were screened medically and who signed informed consent statements prior to participating in the study. Their mean age was 26 years ($SD = 3.7$), mean body weight at the start of the study was 72.4 kg ($SD = 19.6$), mean educational level was 11 years ($SD = 1.9$). Subjects resided in the inpatient research ward of the Addiction Research Center for the duration of the study. In general, 2 subjects participated in the protocol over the same time period.

Apparatus

A Corona® microprocessor and monochrome video monitor controlled experimental sessions and recorded data. The Corona® keypad located on the right-hand side of the keyboard functioned as the response console, and the video monitor displayed experimental stimuli.

Drug

Atropine sulfate was administered intramuscularly (deltoid) in 1 mL of volume. Doses were 0 (saline), 1.5, 3.0, and 6.0 mg per 70 kg of body weight. Subjects and staff were blind to drug dose but were informed that atropine or placebo would be administered. A minimum of 72 hr elapsed between injections. Subjects were exposed twice to each dose condition. To evaluate the safety of the doses, Subjects 908 and 919 were exposed to each dose condition in an ascending and then a descending dose order; the other 5 subjects were exposed to the drug in two randomized blocks.

Procedure

Multiple schedule. Subjects performed under a multiple schedule of repeated acquisition and performance of 10-response sequences (Desjardins et al., 1982; Higgins et al., 1987). In each schedule component, subjects completed a different 10-response sequence using Keys 1, 2, and 3 of the numeric keypad. As is illustrated in Figure 1, reinforcement delivery was contingent on depressing the keys in a

Illustrative Response Sequence

Video Screen #'s: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9

Correct Response Keys: 3, 1, 2, 3, 2, 1, 3, 2, 1, 3

Fig. 1. The steps involved in moving through a typical 10-response sequence used in this study. The 0-9 sequence that appeared sequentially in the center of the video screen is presented above the corresponding 10 correct responses on the numeric keypad. Subjects were instructed to depress Key 1, 2, or 3 as each number appeared sequentially in the center of the video screen. Correct responses advanced the number to the next step in the sequence. Incorrect responses initiated a 2-s timeout; completion of the timeout period returned the subject to the step in the 10-response sequence at which the error was made. Each completed sequence added one point to a running total and returned the number in the center of the video screen to zero for the start of the next trial (from Higgins et al., 1987, p. 2).

predetermined order in the presence of the numbers 0-9, which appeared sequentially in the center of the video screen. In the illustrative sequence presented in Figure 1, for example, reinforcement delivery is contingent on depressing the keys in an order of 3, 1, 2, 3, 2, 1, 3, 2, 1, 3 in the presence of the screen numbers 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9, respectively. That is, as each number appears in the center of the video screen in the 0-9 sequence, it is necessary to depress the correct key in order to advance to the next step in the sequence.

Incorrect responses initiated a 2-s timeout during which the color of the screen was gray and responses had no programmed consequences; completion of the timeout period returned the subject to the step in the 10-response sequence where the error was made. Each completed sequence added one point to a running total shown at the top of the screen and returned the number in the center of the screen to 0 for the start of the next sequence.

In the performance component of the multiple schedule, the 10-response sequence remained the same throughout the experiment. The performance sequence for all subjects was to depress the keys in an order of 2, 1, 3, 1, 3, 2, 1, 3, 2, 1 in correspondence with the video screen numbers 0–9, respectively. The performance component was paired with a yellow screen and the word “Performance” was printed in the center of the screen. In the acquisition component, a new 10-response sequence had to be acquired each session. Sequences in the acquisition component were selected via the following criteria: (a) The performance sequence was never used in the acquisition component. (b) The first three links in a sequence were never in a 1, 2, 3 order. (c) No two consecutive responses were the same within a sequence. (d) Position repetitions did not occur in any of the 10 positions in two consecutive acquisition sequences; for example, if the second link in a sequence was the 2 key, the 1 or 3 key would have to serve as the second link in the next sequence. (e) Subjects were not exposed to any sequence more than once. The acquisition component was paired with a black screen and the word “Learning” was printed in the center of the screen.

The components of the multiple schedule alternated after 20 sequences were completed. Sessions always began in the performance component. Sessions ended after 40 sequences were completed (20 acquisition and 20 performance) or 5 min had elapsed, whichever occurred first. On drug days, subjects completed sessions immediately prior to and 0.5, 1.5, 3.0, 5.0, 7.0, 9.0, and 24 hr after drug administration. Points obtained by successfully completing a response sequence served as programmed reinforcers and were redeemable at 0.5 cents per point. Subjects also received a standard base rate of \$15.00 per day. The present experiment was conducted as a com-

ponent of a larger multidisciplinary study, which required that subjects participate in other procedures (vital signs, electroencephalograph recording, self-report procedures, “psychomotor” testing) between observations on the repeated-acquisition procedure.

Training. Subjects were trained in the performance sequence (40 training trials) prior to beginning training on the multiple schedule. Subjects were exposed to at least 30 practice sessions under the multiple schedule before initiating drug testing. On drug-testing days, subjects always completed 20 trials in the performance component only prior to beginning the series of tests under the multiple schedule. These 20 trials were considered a “warm-up” session and were not included in data analyses.

Subject instructions. Before each session on the multiple schedule, the following instructions appeared on the video screen:

This task involves you pressing the three keys labeled 1, 2, and 3 in a particular sequence. Press only one key at a time with your preferred hand. Every time you complete a sequence of 10 correct responses, the top counter advances. Your goal is to advance the counter as quickly as possible.

In the center of the screen, one of 10 numbers is presented. The number 0 will be presented at the beginning of the sequence. When you make your first correct response, the number in the center will change from 0 to 1. When you make your second correct response, the number will change from 1 to 2, and so on until the sequence of 10 correct responses is completed.

If you make an error, the number in the center will be erased for 2 seconds and the screen will become gray. Do not respond on the keys when the number is not shown. The yellow screen indicates a performance condition in which the sequence is the same from session to session. The black screen indicates a learning condition in which the sequence is different from session to session. The yellow and black screens will alternate within a session.

Press one of the keys when you are ready to begin.

Data Analysis

Data from each component of the multiple schedule were analyzed separately. Errors were defined as responses on any key other than the one designated as correct at a particular step in a sequence and were analyzed as overall percentage of errors by dividing the total num-

ber of errors in a component by the total number of responses in that component and multiplying by 100. Additionally, a within-session analysis of errors was conducted for the acquisition component by estimating quarter-life (Gollub, 1964). Subjects had a maximum of 20 trials to acquire a new sequence each time they did the task. We calculated the percentage of trials elapsed in making 25% of the total number of errors per session (Higgins et al., 1987). Quarter-life values less than 25% indicate that cumulative errors across trials were negatively accelerated (i.e., sequence was being acquired), whereas values of 25% and greater represent a constant error pattern and positive acceleration, respectively (i.e., sequence was not being acquired). Quarter-life was not calculated for the performance component because of the relatively low number of errors in that component, which can obscure interpretation of results in a quarter-life analysis. Overall response rates in each component were analyzed as responses per second by dividing the total number of responses in each component by the total number of seconds in each component. The 2-s timeouts that followed errors were excluded in calculations of response rate.

Atropine was considered to have produced an effect when drug values (mean of two observations) exceeded the range of placebo values. During Subject 966's first exposure to the 6.0-mg dose, he was deemed by the nursing staff to be unable to perform the task due to side effects from the drug at the 1.5- and 3.0-hr postdrug observations; with Subject 962, the session timed out prior to alternating to the acquisition component at 1.5, 3.0, and 5.0 hr postdrug during his first exposure to the 6.0-mg dose. In those instances, data were available only from the second observation with the 6.0-mg dose. Additionally, placebo data were available from only one observation for Subject 1002.

RESULTS

Overall Percentage of Errors

Effects of atropine on overall percentage of errors are shown across a 24-hr time course in Figure 2. During no-drug conditions (i.e., predrug and placebo sessions), subjects generally exhibited relatively low levels of errors in both schedule components, although, as ex-

pected, for all subjects errors were greater in the acquisition than in the performance component. During the predrug observations, for example, the group means for percentage of errors in the acquisition and performance components were 7.5 and 1.4%, respectively. Values for individual subjects ranged from 2.9 to 15.3% and 0 to 7.8% in the acquisition and performance components, respectively, at the same observation time.

In the acquisition component, administration of the 3.0- and 6.0-mg doses of atropine increased overall percentage of errors well above placebo levels in 5 (908, 919, 937, 966, 1002) of the 7 subjects. The 3.0-mg dose produced only a small effect on errors in Subject 962, and for Subject 1050 only the 6.0-mg dose increased errors. The 1.5-mg dose increased errors in Subjects 937 and 962 but not in the other subjects. Onset of drug effects in the acquisition component was discernible at 0.5 or 1.5 hr postdrug, and peak effects generally were observed between 3.0 and 5.0 hr postdrug. The duration of these effects was dose dependent, with the 3.0- and 6.0-mg doses exerting discernible effects for as long as 7.0 to 9.0 hr postdrug, whereas the effects of the 1.5-mg dose were of a briefer duration. None of the drug doses produced a reliable carryover effect on percentage of errors the day after drug administration (24 hr postdrug), although errors were slightly increased above placebo levels in Subjects 919 and 966 at the 6.0-mg dose and Subject 908 at the 1.5-mg dose.

Overall percentage of errors in the performance component was reliably increased above placebo levels by the 6.0-mg dose in all subjects. The 3.0-mg dose produced small increases in percentage of errors in Subjects 966 and 1002 but not in the 5 other subjects. The 1.5-mg dose increased errors only in Subjects 962 and 1002. Drug effects generally followed the same time course as described above for the acquisition component. None of the drug doses produced a reliable carryover effect on percentage of errors in the performance component at 24 hr postdrug, although Subject 1002 showed a small increase following the 6.0-mg dose.

Within-Session Errors

To assess the effects of atropine on within-session error decline, a 24-hr time course of effects on quarter-life is shown in Figure 3.

Fig. 2. Individual-subject data for the effects of atropine on overall percentage of errors as a function of time postdrug. For each subject, effects in the acquisition and performance components are aligned. Shaded areas represent the range of placebo values. Data points generally represent means of two observations per dose condition. Note that the ordinate scale in the acquisition component for Subject 1002 differs from the others. Doses are mg/70 kg.

In the no-drug conditions, subjects typically acquired the sequence within several trials. At the predrug observation, for example, the mean quarter-life for subjects as a group was 3.8%, indicating that 25% of the total errors in the acquisition component occurred in the first trial. For individual subjects, predrug quarter-life values ranged from 1.9 to 6.6% during predrug observations.

Administration of atropine increased quarter-life as an orderly function of dose in all 7 subjects studied. Quarter-life remained below 25% (negatively accelerated) under all conditions for all subjects. Thus, although drug-produced disruption was clearly evident in these subjects, some degree of acquisition still occurred. Note, however, that the 6.0-mg dose increased quarter-life to 24% at 3 hr postdrug in Subject 1002, suggesting that acquisition was almost totally eliminated at that time. The time course of effects on quarter-life generally

was the same as occurred with overall percentage of errors.

Overall Response Rate

Effects of atropine on overall response rates are shown for individual subjects in Figure 4. In the no-drug conditions, subjects exhibited relatively moderate and high rates of responding in the acquisition and performance components, respectively. Group means for overall response rates at the predrug observation, for example, were 1.6 and 2.7 responses per second in the acquisition and performance components, respectively. Values for individual subjects at that same observation time ranged from 1.0 to 2.2 and 2.4 to 3.2 responses per second in the acquisition and performance components, respectively.

In the acquisition component, the 3.0- and 6.0-mg doses reliably decreased overall response rates below placebo levels in 6 (908,

Fig. 3. Individual-subject data for the effects of atropine on quarter-life (in percentage) as a function of time postdrug. Shaded areas represent the range of placebo values. Data points generally represent means of two observations per dose. Doses are mg/70 kg.

919, 937, 962, 966, 1002) of the 7 subjects studied. Subjects 937 and 962 also exhibited slight rate decreases in the acquisition component following administration of the 1.5-mg dose. Subject 1050 exhibited decreases in response rate following only the 6.0-mg dose. Effects in the acquisition component began between 0.5 and 1.5 hr postdrug, peaked between 3.0 and 5.0 hr postdrug, and typically returned to placebo levels between 7.0 and 9.0 hr postdrug. None of the drug doses produced a carry-over effect on overall response rates at 24 hr postdrug that was reliable across subjects.

The 6.0-mg dose also decreased overall response rates in the performance component in all subjects. The time course for the effects of this dose generally was the same as that described above for the 6.0-mg dose in the acquisition component. The 3.0-mg dose also decreased overall response rates in the performance component in Subjects 908, 937, and 966, but the magnitude of the effects was smaller and the duration shorter than effects observed in the acquisition component. Subject 1002's rates were quite variable following the 3.0-mg dose, and he appeared to exhibit a small decrease following the 1.5-mg dose. Subject 962's rates remained below placebo levels at 24 hr after receiving the 6.0-mg dose.

DISCUSSION

These results demonstrate that the acute administration of atropine produces orderly, dose-dependent increases in overall percentage

of errors and decreases in overall response rates in humans responding under a multiple schedule of repeated acquisition and performance. Although behavior in both schedule components was affected by the drug, behavior in the acquisition component generally was more sensitive to atropine's effects than was behavior in the performance component. Such selective effects extend to atropine results previously obtained with alcohol and diazepam in humans and with a wide variety of compounds in nonhumans using repeated acquisition and performance baselines (Desjardins et al., 1982; Higgins et al., 1987; Thompson & Moerschbaecher, 1979). Moreover, the present results suggest that Laties and Weiss' (1966) earlier demonstration of environmental modulation of the behavioral effects of scopolamine in pigeons has generality to other anticholinergics and, more important, to human behavior maintained under complex reinforcement contingencies. It is important to note that although attention is often directed at the discrepancies between human and nonhuman operant behavior in laboratory settings, there has also been a great deal of generality demonstrated that should not be overlooked (e.g., Griffiths, Bigelow, & Henningfield, 1980; Higgins & Morris, 1984; Higgins et al., 1987).

As was mentioned previously, anticholinergics have been reported to produce selective effects in traditional human learning and memory paradigms (e.g., Dunne & Hartley, 1986; Ghoneim & Mewaldt, 1975, 1977). A single dose of scopolamine (0.08 mg/kg), for

Fig. 4. Individual-subject data for the effects of atropine on overall response rate as a function of time postdrug. For each subject, effects in the acquisition and performance components are aligned. Shaded areas represent the range of placebo values. Data points generally represent means of two observations per dose condition. Doses are mg/70 kg.

example, decreased the number of words subjects could list correctly from a series read to them *after* receiving drug, but did not affect the number they could list from a series read to them *prior* to drug administration (Ghoneim & Mewaldt, 1975, 1977). It was concluded by these investigators that scopolamine affects acquisition but not "retrieval." Such results seem to be consistent with the selective effects atropine produced across the acquisition and performance conditions in the present study. However, it was not the case in the present study that atropine disrupted acquisition and not performance. Rather, behavior in both conditions was affected by the drug, but at different doses or to a different degree. Differences in effects on repeated acquisition and performance in drug studies with nonhumans are also generally dose dependent (cf. Desjardins *et al.*, 1982; see Thompson & Moersch-

baeher, 1979). Thus, Ghoneim and Mewaldt's (1975, 1977) conclusion that scopolamine affects acquisition but not retrieval seems to be premature, especially because they tested only a single drug dose. Their observation concerning scopolamine's selective behavioral effects, on the other hand, appears to have generality both to other anticholinergics and to other experimental arrangements.

Why acquisition and performance baselines are differentially affected by drug administration is unclear. As was mentioned previously, the degree of discriminative control exerted by exteroceptive stimuli is one factor that is known to modulate the behavioral effects of drugs; behavior that is under relatively weak control is more affected by a drug than is behavior under greater stimulus control (e.g., Laties & Weiss, 1966; Thompson, 1978). Based on the higher rates of errors in acquisition versus per-

formance baselines, it has been inferred that the degree of stimulus control is greater in the latter component, thereby making the performance baseline more resistant to drug-produced changes (Thompson & Moerschbaecher, 1979). However, overall response and reinforcement rates also differ across the acquisition and performance components. Certainly we know that rates of responding and reinforcement delivery can be important determinants of the behavioral effects of pharmacological and nonpharmacological events in other procedures, and they could contribute to the differential effects observed in the repeated acquisition and performance arrangement (Bickel, Higgins, Kirby, & Johnson, 1988; Dews & Wenger, 1977; Nevin, 1988). The relative contributions of these different variables have yet to be assessed directly in the repeated-acquisition and performance arrangement. The present study was not designed to investigate this matter and thus offers no apparent insights concerning the role of these variables in the effects observed. An experimental analysis of the degree to which different levels of stimulus control, response rates, and reinforcement rates contribute to the differential drug effects observed in this procedure, however, will extend our basic understanding of the behavioral effects of drugs and will also enhance our overall understanding of the environmental determinants of resistance to behavioral change.

In addition to affecting overall percentage of errors in the present study, atropine also disrupted the typical pattern of within-session error decline, as illustrated by the increases in quarter-life values. These effects on quarter-life are important in that they document that the increases observed in overall percentage errors represented disruptions in acquiring the sequence and not unsystematic increases in error rates. Note, however, that within-session error patterns remained negatively accelerated (quarter-life <25%) even when the high dose was administered. This demonstrates that although acquisition was adversely affected by the drug, subjects were able to exhibit some level of acquisition under all of the doses of atropine studied. The 6.0-mg dose increased quarter-life to 24% in 1 subject, however, suggesting that this dose of atropine is capable of preventing acquisition. Interestingly, the ef-

fects of atropine on quarter-life observed in the present study are quite comparable to the effects reported previously for alcohol (0, 22, 45, 67 g) and diazepam (0, 10, 20, 40 mg) on the same repeated-acquisition baseline using normal volunteers (Higgins et al., 1987). In that study, quarter-life always remained below 25% except for 1 subject in whom a 40-mg dose of diazepam increased it to 40%. It may be the case that the doses of these compounds that are necessary to prevent reliably the acquisition of response sequences in normal humans would also produce so many other toxic effects (e.g., sedation, ataxia, nausea) that they would be both practically and ethically impossible to study on this baseline. Interestingly, then, although behavior in the acquisition component is more readily affected by the drug than is behavior in the performance component, a great deal of resiliency is nevertheless evident in the acquisition baseline.

The time course of atropine's effects observed in the present study is quite consistent with prior findings on the acute effects of this compound in humans and nonhumans. Ketchum et al. (1973), for example, tested the acute effects of atropine (0 to 12.25 mg/70 kg) on performance in a simple arithmetic test with Army enlisted men. Drug effects were observable by 1 hr, were at maximum levels by 5 hr, and had largely dissipated by 12 hr postdrug. Similarly, Levy et al. (1984) studied the time course of 0.2 mg/kg atropine on repeated acquisition in monkeys and found that effects were detectable by 0.5 hr, reached a peak by 4.5 hr, and had dissipated by 16.5 hr postdrug. In this latter study, effects on errors were reported to last longer than effects on response rate, but we did not observe any difference in time course for these two measures in the present study. Another important aspect of the Levy et al. (1984) study involved a comparison of the effects of atropine and methylatropine. Atropine readily penetrates the blood-brain barrier, whereas methylatropine does not. By studying both compounds, inferences can be made concerning whether effects are peripherally or centrally mediated. Levy et al. (1984) found that both compounds decreased response rates, whereas only atropine affected accuracy of responding. Based on that information, the investigators suggested that atropine's effects on rate and accuracy of responding may be

peripherally and centrally mediated, respectively. No attempt was made in the present study to determine the locus of atropine's activity, but this is a worthwhile issue for future investigation in humans.

Environmental factors that influence the development of tolerance under a chronic dosing regimen sometimes also influence recovery following acute dosing (Beirness & Vogel-Sprott, 1984; Haubenreisser & Vogel-Sprott, 1987; Mann & Vogel-Sprott, 1981). Because tolerance has been shown to develop more slowly in the acquisition versus performance component during chronic dosing regimens (Thompson, 1974, 1977), it was of interest to us to assess whether the time course following acute drug dosing might also differ across these two conditions. To date, we have found no convincing evidence for such differences. In an earlier study on the acute effects of alcohol and diazepam, the time course of effects appeared similar across acquisition and performance, although because time course was assessed in only 2 subjects with alcohol and 1 subject with diazepam, no firm conclusions were reached on this matter (Higgins *et al.*, 1987). In the present study, the effects of the 3.0-mg dose on response rate were of shorter duration in the performance versus the acquisition component in 3 subjects, but similar results were not observed in the other subjects. The 6.0-mg dose produced reliable behavioral effects in both schedule components in all subjects, and these effects generally followed a similar time course.

Overall, the present results provide a rigorous within-subject characterization of the magnitude and time course of the acute effects of varying doses of atropine on complex operant behavior, provide another very clear demonstration of the modulating influence exerted by environmental factors over the behavioral effects of anticholinergic compounds, and replicate, extend, and, most important, integrate previous findings from both humans and nonhumans and from both operant and nonoperant experimental paradigms on the behavioral effects of anticholinergic compounds.

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Received October 23, 1987

Final acceptance September 13, 1988