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A VIEWPOINT ON "DRUG ENHANCEMENT"

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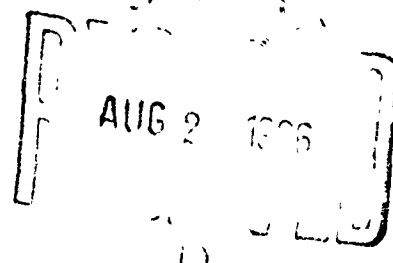
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bodily survival mechanism such as fear, fatigue, reactive inhibition, etc. Thus, an effect which should be considered as "behavioral toxicity" in some situations might be beneficial in certain other situations. It would seem likely that the modern world is quite full of situations in which such criteria apply: namely, that a "basic survival mechanism" may be maladaptive.

Since biological man can be described as the result of the years of natural selection begun in pre-mammalian times, the influence of the last few centuries, or indeed millenia, should be slight. Yet the world, and its requirements for human behavior, have changed a great deal during this tiny fraction of man's tenure. High susceptibility to boredom or reactive inhibition was probably of much value to the primitive hunting and hunted creature, for whom variability of behavior was at a premium. It is frequently of negative value to the age-of-specialization man. The acute stress syndrome was likely of value when the stressor was a hungry carnivore, and the appropriate response was fight or flight. Yet it could be of negative value when the stressor is a final examination or an air attack, and the needed response involves complex perceptual-motor or cognitive performance. The Yerkes-Dodson Principle implies that stress reactions might often be too severe in modern-world situations.

The drug effects involved in these examples can be regarded as temporary, selective interference with one or more such

mechanisms. Thus, a "tranquilizer" interferes with the stress mechanism. A "stimulant," regarded from this viewpoint, does not "hop up" the mental machinery; rather, it interferes with fatigue or boredom mechanisms. There seems to be a widespread opinion that stimulants such as d-amphetamine operate in a manner analogous to making a computer work faster by increasing the input voltage--inspired, in part, from analogy with these drugs' peripheral sympathomimetic effects. Yet the pharmacological mechanisms for these two classes of effects, central and peripheral, cannot be profitably correlated. Essentially, we just don't know how these drugs exert their "CNS-stimulatory" properties.

The selective interference viewpoint is concerned with cognitive effects, and not with effector phenomena such as physical strength, endurance, manual steadiness, etc. where the mediating mechanisms may well be quite different. It represents something of a broadening of Barmack's (1938) earlier view that enhancement can be expected from stimulants such as the amphetamines only when performance has been degraded by fatigue or boredom. The selective interference viewpoint includes other potential sources of degradation, such as stress or anxiety, which may be antagonized by certain "stimulants" as well as by the "ataractic" CNS depressants.

Toward Operationally-Defined Hypotheses

To test the value of the selective interference viewpoint, it is necessary to derive testable predictions, of the form "Performance may be enhanced by drugs in Situation X_1 , but will not be enhanced

in Situation X_2 ." The differences between the two situations would be the presence versus absence of some "survival mechanism" inappropriate to the general situation, X_1 . In the case of fatigue from sleep deprivation, the defining properties are easily derived. When reactive inhibition or stimulus satiation is thought to be involved, the defining properties can be manipulated in terms of inter-trial spacing, variability of stimuli and/or response requirements, etc. When emotional stress is involved, defining properties could involve the presence versus absence of some extrinsic stressor such as electric shock, ego stresses induced by the experimenter, etc.

More difficulty is encountered with the defining properties when the stress is believed to be intrinsic to the task. This problem will be discussed in more detail later, when a framework is suggested for manipulating the defining properties in "task-induced" stress situations.

Evidence

Consider, first, the situations in which cognitive performance enhancement has been observed with the various "CNS stimulants:" caffeine, amphetamines, and other drugs whose effects include psychoanaleptic components.

Shortly after discovery of the "stimulatory" properties of the amphetamines, some investigators (e.g., Sargent & Blackburn, 1936; Molitch & Eccles, 1937; Molitch & Sullivan, 1937) reported

that these drugs increase test intelligence. These results were not confirmed, however, in subsequent studies (e.g., Barnack, 1940; Cutler, Little, & Strauss, 1940; Morris, Macgillivray, & Mathieson, 1955). Other investigators (Andrews, 1940; Golla, Blackburn, & Graham, 1940; Hecht & Sargent, 1941; Flory & Gilbert, 1943; Duker & Duker, 1960; Nash, 1962; and Evans & Smith, 1963) have tested the effects of amphetamines on a wide variety of higher mental functions, including numerous measures of intelligence and reasoning ability, with results ranging in general from no observed effect to a modest facilitation.

In general, it would seem that short-term intellectual performance, where boredom is not a factor, is neither markedly nor consistently enhanced by amphetamines. The accumulated evidence suggests one of two conclusions: Either (1) The "positive" findings of some investigators are artifactual, due to absence of critical controls (allowance for regression and serial effects, use of double-blind techniques, etc.), as is implied by Weiss & Laties in reviewing intellectual performance effects of caffeine and amphetamines (1962, pp. 18-21), or (2) Amphetamines do exert a facilitative influence, but of such small magnitude that statistical significance is often not obtained, being a function of test reliability, number of subjects, and the working of chance. Any real effect of this size could well be due to motivational rather than cognitive mechanisms, as implied by Evans & Smith (1963) in consideration of mood effects of these drugs. (To be discussed subsequently). In either case, the implication is that very

little gain is to be expected in the way of intellectual *capacity* by the use of caffeine or amphetamines as opposed to improved personnel selection.

A strikingly different picture is obtained when we view the effects of stimulants in situations in which cognitive performance might ordinarily suffer from boredom effects. For example, Hollingworth (1912) found improvements in typing and color-naming with caffeine, and both he and Lehmann & Csank (1957) reported improvements in cancellation tests. With amphetamine, improvements in adding and multiplication were observed by Kleemeier & Kleemeier (1947), and in cancellation by Tyler (1947) and by Lehmann & Csank (1957). With methylphenidate, Vondracek & Martanova (1959) obtained improvement at subtraction and repeating of figures. Perhaps the most striking mitigation of boredom effects has been observed in tasks of a vigilance nature, where strong positive effects have been obtained with amphetamines by Mackworth (1950), Payne & Hauty (1954), Payne, Hauty, & Moore (1957), and Kornetsky, Mirsky, Kessler, and Dorff (1959), and with mephentermine and pipraorol by Payne & Moore (1955).

With some exceptions, the foregoing data seem to support a "selective interference" viewpoint. When motivation is normally at a level appropriate to task demands, as it presumably is in the usual mental test situation, drugs elicit scant improvement in performance. When it is degraded, substantial gains can be made.

If we can attribute the degradation to mechanisms such as boredom and fatigue, the interference viewpoint is upheld.

Consider, now, the evidence with regard to "CNS depressants:" sedatives, tranquilizers, opiates, alcohol, or other drugs with varying psycholeptic components. There is a very large body of evidence, which will not be reviewed here, that depressants usually impair task performance in non-disturbed subjects. These results are, in general, unremarkable. Even "tranquilizers," which are sometimes not classed as "depressants," generally exert some depressing effect if the dosage is large enough or the measurement sufficiently sensitive. Of greater theoretical interest is the occasional finding, in particular situations, of performance enhancement.

Of the relatively few instances in which enhancement has been reported for such agents, the majority seem to involve use of the drug to allay interfering emotional responses due to some "stressful" aspect of the task or situation. Thus, Mill, Kornetsky, Flanary & Wikler (1952) found that morphine tends to restore reaction times toward normal levels when they have been lengthened by fear of shock. Holliday & Dille (1958) found, with a pointer-pursuit task, that 800 mg. of meprobamate tended to abolish the disruptive effects of anxiety induced by an automobile horn, air blasts, and electric shock (used as punishment for time off target). Interestingly, improvement from meprobamate over the placebo base was noted only on the interspersed "non-punishment" trials, which were presumably more stressful than those on which punishment actually occurred.

Matlin (1964) found that chronic administration of chlordiazepoxide (10 mg. twice daily for two weeks in the guise of vitamins) improved productivity in 64 "retarded" workers who were believed to have been suffering from tensions, instabilities, and neuroses. Unfortunately no placebo controls were used. Granting that the suggestion effect was reduced by administration in the guise of vitamins, there is still the problem of regression phenomena.

Uhr, Platz, Fox & Miller (1964) observed that a single 1600 mg. dose of meprobamate significantly improved performance on the Michigan Continuous Attention Task, which was administered under stressful conditions (shock trials interspersed with non-shock trials). The interpretation is obscured, in that improvement occurred under non-shock as well as shock conditions, with the shock x drug interaction being nonsignificant. The authors suggest that a punishment-anticipation effect may have been responsible for the drug's effect on the non-shock trials. (Compare with Holliday & Dille, above.) This conclusion is strengthened by previous findings by Townsend (1957) and by Kelly *et al* (1958) of no significant effects for meprobamate on somewhat similar monitoring tasks performed in the absence of shock stress.

While such perceptual-motor enhancement by CNS depressants is of significance, it is even more noteworthy that enhancement of cognitive performance has occasionally been elicited by such drugs.

Ritter, Sells, & Nebane (1958) studied the effects of 400 mg. meprobamate, as opposed to 2 mg. nipradrol, 10 mg. methylphenidate,

placebo, or no capsule, upon a variety of anxiety and performance indices. They obtained an F-ratio significant at $p < .01$ on the Wechsler digit-symbol substitution test, with all three drug groups markedly excelling the placebo group. They remark, however, that interpretation is impossible because the no capsule group *also* markedly excelled the placebo group. Interpretation of the results of this powerful ($N=225$) study is subject to the further finding that reported comfort was significantly lower in the no capsule group than in any other. Thus, the placebo effect was negative for performance but positive for comfort. One might infer accordingly that increased anxiety facilitated performance, but this conclusion is at variance with the facilitative effect reported for meprobamate.

Burnstein & Dorfman (1959) obtained a reliable 17% reduction in learning time in a complex memory task with 1200 mg. meprobamate. The authors indicate that a relatively high level of anxiety or emotionality was involved in this situation, due to the high degree of inter-item competition.

Korman, Knopf & Austin (1960) found that serial learning under shock stress conditions was slightly but significantly enhanced by a mild (30 ml.) dose of ethyl alcohol. The results are interpreted as forming an exception to "the dictum of Jellinek & McFarland (1940) that alcohol has a depressing effect on all psychological functions yet measured." Of additional significance, and in accord with the authors' hypothesis, the control (non-stress) groups showed poorer performance under alcohol. Dimascio (1963) also investigated competitive

paired-associate learning (CPAL) under various CNS depressants: phenyltoloxamine, 100 and 200 mg., secobarbital, 50 and 100 mg., and meprobanate, 200 and 400 mg. The college student subjects, who served as their own controls (placebo), required significantly fewer learning trials to reach criterion under the higher doses of meprobanate and phenyltoloxamine, and tended ($p=.10$) to make fewer errors in the process. Paradoxically, the lower dose of phenyltoloxamine significantly increased the number of trials to criterion. The "anxiety" or "stress" factor again enters the picture in the form of Taylor MAS scores. These appeared to have no bearing on CPAL under placebo, whereas under 200 mg. meprobanate the subjects with the higher MAS scores significantly ($p<.05$) excelled those with lower MAS scores, both in rapidity of learning and in freedom from errors during the learning process. There was a similar tendency ($p=.10$) under 50 mg. secobarbital or 200 mg. phenyltoloxamine for subjects with the higher TMAS scores to learn the lists with fewer errors than were made by those with lower TMAS scores.

Hughes, Forney, & Gates (1963) used delayed auditory feedback as a stressor in evaluating effects on a variety of performance tests of alcohol, benzquinamide, or a mixture of the two. They found that the tranquilizer significantly improved performance at reverse reading and "subtraction plus seven." Alcohol quite generally depressed performance. Synergism between the two agents was not evident. Their tranquilizer data support the viewpoint of enhancement through selective interference: their alcohol data do not, and also tend to contradict

Korman *et al* (1960). The difference here may have resulted because (1) different types of stressors were involved, or (2) Hughes *et al* used 45 ml. alcohol per 150 lb. of body weight, whereas Korman *et al* used a standard 30 ml. dosage. Certainly, if alcohol is ever to enhance performance, one would expect the dosage level to be critical.

Evans & Smith (1963) measured performance in normal subjects, at a variety of mental tasks, with either 10 mg. d-amphetamine sulfate, or 16 mg. morphine sulfate, or both, versus lactose placebo. The tasks, derived from Guilford's "structure of intellect" model, comprised various tests classified according to the type of mental operation demanded, i.e., Evaluation, Convergent Production, Divergent Production, Memory, and Cognition. Among the many drug effects found, it is most interesting that morphine enhanced the scores of all three tests in the Evaluation category. The authors interpret this finding as follows:

"Guilford has stated that tests in the Evaluation category measure the ability of subjects to make a judgment as to which is the correct response of a limited number of possible alternatives. It may be that tasks of this type require a 'focusing' or the concentration of attention on task relevant cues will be benefited by the decrease in excitement and distractibility produced by morphine. (Calloway & Stone, 1960)"

It would appear from these findings that the "depressant" group operates in a manner quite analogous to the "stimulant" group: performance may at times be enhanced, but only when it would otherwise be degraded below some "normal optimum." In the case of "stimulants," such degradation would presumably have resulted from fatigue or boredom; in the case of the "depressants," the degradation

would have resulted from emotional stress. Note that all of the "depressants" cited above have staractic, as well as psycholeptic, properties.

In the studies cited, the "stress" involved was presumably due to the introduction of some extraneous "stressor" into the task situation: electric shock or delayed auditory feedback. The Evans & Smith data cannot, however, be interpreted in this manner. The only possibility for a "selective interference" interpretation is to assume that the stress was inherent in the tasks themselves. This introduces a whole new class of phenomena which might fruitfully be explored for drug enhancement via "stimulants" and/or "depressants." Certain task parameters--e.g., high input pacing in the presence of certain perceptual and/or decision-making demands--appear to induce a type of stress in the human operator. Many operational tasks involve these parameters. The occurrence of a "dropoff" phenomenon, a sharp performance decrement when input rate exceeds a critical value, has been demonstrated in the laboratory by various investigators, e.g., Alluisi, Muller, & Fitts (1957), and Jeantheau (1959).

Results such as the foregoing are susceptible to at least two alternative interpretations:

(1) The decrement is caused by "emotional" factors which interfere with the optimal functioning of the human data-processing machine, or,

(2) The decrement is merely a function of input queuing, due to channel-capacity limitations in the organism, which results in the loss of inputs during short-term storage while awaiting processing.

The latter interpretation, which is derived from the single-channel hypotheses set forth by Hick & Welford (1956), Broadbent (1957), and Welford (1960), does not exclude the former possibility as a contributing factor.

To the extent that the first (emotional) factor operates to produce a decrement, performance can be restored by any agent which reduces the undesirable emotional response to the task, but does not interfere with the operator's normal ability to perform the storage and processing functions involved. Consequently, those stimulants possessing mood-active components might improve performance in such situations, and the degree of improvement might in some cases be greater than with the "attractive" depressants.

One class of stimulants with apparent mood effects is the amphetamine group. There is some reason to believe that this mood effect is of a nature that might block, selectively, the emotional component of task-induced stress. If we consider the emotional stress factor to be something akin to fear, then a mood effect in the opposite direction is to be sought. In this respect, the effects of these drugs are ambiguous, but the bulk of findings with the amphetamines does give some support to an anti-fear postulate:

Voluntary expressions of increased confidence, such as the feeling "that it is relatively easy to perform a task," were obtained by Bahnsen, Jacobsen & Thesleff (1938). Decreases in clinical reports of anxiety were obtained by Schilder (1938) and

by Korey (1944). A decrease in rated anxiety of a "threatened" group was reported by Lanzetta, Wendt, Langham, & Haefner (1956). Hurst (1962) reported that d-amphetamine produces increased risk-taking in an experimental, uncertain-outcome situation, where high stresses of a monetary nature are involved. Smith & Beecher (1964) found that amphetamine increases self-ratings of performance by students taking calculus tests.

On the negative side, Smith & Beecher (1960b) found that amphetamine induces pessimism with regard to swimming speed in a standard course traversed by trained athletes. This may have been due to a direct effect on time estimation, which tends to be increased by amphetamines (cf. Frankenhauser, 1958; Goldstone, Boardman & Lhamon, 1958). Hauty & Payne (1957) found no significant effect upon level of aspiration scores on the Air Force SAM task. The dosages, however, were rather small (5 mg. d-amphetamine).

In apparent contradiction to the "anti-stress" notion are the studies of self-ratings on mood factors, which have often revealed increases in anxiety from amphetamines (Nowlis & Nowlis, 1956; Smith & Beecher, 1960a; Ross, Krugman, Lysterly & Clyde, 1962). This may, however, be a semantic problem: Increases in "jitteriness," etc., caused by direct or indirect CNS activation may parallel cerebral effects involving increases in boldness and self-confidence, as inferred from other adjectives checked by these same subjects.

To the extent that the second factor (simple queuing effect) contributes to the observed decrement, no substantial drug enhancements would be predicted from the selective interference viewpoint. To offset this "queuing" loss would require something like a lowering of disjunctive reaction time, or an increase in short-term storage capacity. Of the two families of stimulants most studied, the amphetamines and the xanthine derivatives, little promise has been shown either for reducing disjunctive RT under normal conditions (cf. Adler, Burkhardt, Ivy, & Atkinson, 1950; Kornetsky, 1958), or for increasing short-term storage capacity (cf. Brengelmann, 1958a, 1958b).

A study directly relevant to this question is that of Kenyon & Pronko (1960), who observed the effects of a capsule containing 10 mg. d-amphetamine sulfate (versus placebo capsule, versus no capsule) upon performance in a task containing both intrinsic and extrinsic stressor elements. The task required the subjects to read aloud and follow a series of simple statements that directed them to make dial and switch adjustments on a panel before them. A reading pacer provided the intrinsic stressor: extrinsic stressors were delayed auditory feedback and threat of shock. No significant differences in task time or number of panel operations were observed among the three treatment conditions. Noteworthy, also, is that a similar study by Pronko & Kenyon (1959) failed to show any consistent differences in performance at this task as a function of 200 mg.

meprobamate versus placebo versus no capsule. Yet "stress" was evidently present, since pulse rates averaging over 120 per minute were obtained under all treatment conditions, and performance at this task is normally degraded by the extrinsic stressor (*ibid.*). It is important to note, however, that the performance measures were obtained at time intervals averaging 15 to 25 minutes after ingestion of the d-amphetamine or placebo capsules (personal communication from G. Y. Kenyon). This may not have been a sufficiently long interval to register maximum effects from the drugs.

In order to avoid contamination of stress effects with vigilance phenomena it might be desirable to employ a task of very short duration, as was done by Kenyon & Pronko. An alternative would be to sample behavior at various points in time, in a task of moderate duration. Separate analyses over various time intervals should permit separate assessment of drug effects upon phases of the experiment in which fatigue/boredom decrements occur in control groups. A factorial design, permitting orthogonal manipulation of drug and stress variables, should permit clear interpretation, in terms of the stress variable, of any drug effects upon performance. In terms of the drug variable it would be desirable to employ at least three drugs:

1. A "pure" psychoanaleptic, such as picrodrol or methylphenidate, which exerts an alerting function but has little effect on mood.

2. A "pure" ataractic such as chlordiazepoxide (Librium), which apparently has an anxiety-reducing property at dosages which have little psycholeptic or analeptic effect.

3. D-amphetamine, which has been postulated to have an ataractic as well as a psychoanaleptic component.

These three drugs, when compared with a no-drug condition, should yield telling comparisons as the stressfulness of the task is manipulated. This research strategy should yield evidence concerning the relative roles of input queuing and emotionality in the various "dropoff" phenomena observed in tasks having high levels of input pacing.

Such an experiment has just been completed by Furst & Weidner (1964), involving the administration of d-amphetamine sulfate (10 mg.), methylphenidate HCl (10 mg.), chlordiazepoxide (10 mg.), and no drug to separate treatment groups. All drugs were administered in disguised form, and separate "placebo effects" were obtained by comparing the effects of the drugs with and without prior administration of blank capsules. The task involved was the paced sequential memory task of Lloyd, Reid & Feallock (1960), and extrinsic stress was manipulated by varying the payoff condition: fixed pay (\$10.00), vs. payment based upon performance (\$5.00 to \$15.00, graduated). This incentive variation seems to have effectively increased the stressfulness of the situation, since the variable payoff groups rated themselves 46% more anxious ($p < .001$) than the fixed payoff groups on a Nowlis ACL administered immediately preceding the "payoff session."

The paced sequential memory test was given twice. The first form, under no payoff, was given 40 to 65 minutes after drug ingestion, and the second, for fixed vs. variable payoff, 95 to 145 minutes after ingestion. The results were analyzed by 12-minute intervals. Superior performance was manifested by the d-amphetamine groups relative to the other drug groups throughout all periods of both sessions. The other two drug conditions varied inconsequentially from no drug. The superiority of d-amphetamine declined as the testing progressed. It was reliably superior to no drug at $p < .02$ during the first half of the first session, and at $p < .05$ during the second half of the first session. This superiority faded into insignificance during the second session except for the second 12-minute quarter. Placebo effects were generally insignificant except during the first quarter of the second session, when a significant ($p < .05$) negative placebo effect appeared. There was no significant main effect for the incentive ("stress") variable, nor did this interact significantly with drug condition. There was, however, a non-significant trend for d-amphetamine and chlordiazepoxide scores to be higher (by 9% and 10%) under "high stress" as opposed to "low stress," whereas the no drug scores were 7% lower under "high stress."

The appearance of a significant enhancement effect from d-amphetamine during the first 12 minutes of testing supports the postulate of an "anti-stress" component. This improvement can scarcely be attributed to fatigue or boredom mitigation since it tended to fade out during the later stages of testing. The tendency

for d-amphetamine and chlordiazepoxide groups to perform relatively better under greater stress also supports this viewpoint: virtually all of d-amphetamine's overall margin of superiority derives from the data taken under "high stress."

One interesting aspect of these findings is the unusually short latency (40-52 minutes) registered for the maximum enhancement effect of d-amphetamine. Although this may have been due to the "stress" effect being greatest early in the test session, as suggested, it makes an interesting contrast with the results of Eysenck *et al* (1957) and Smith & Beecher (1959), who obtained maximum increases in pursuit performance and athletic performance, respectively, at considerably greater latencies after administration of amphetamines. Franks & Trouton (1958) obtained significant effects of d-amphetamine on eye-blink conditioning at a two-hour latency, but not at a 45-minute latency. A possible interpretation is, in accord with the "two component" hypothesis, that the earlier-peaking mood-related effect is responsible for the anti-stress results, and that the later-peaking psychoanaleptic effect is responsible for enhancement of motor performance. This interpretation gains some support from the results of Frankenhaeuser & Post (1963), who measured objective and subjective effects of d-amphetamine (15 mg.) or pentobarbital (200 mg.) at successive 30-minute intervals over a two-hour period following ingestion. Psychoanaleptic effects would, presumably, be reflected by self-ratings on "sleepy," "tired," and "alert," and also by objectively measured reaction speed. The anti-stress component

might be expected to appear in self-ratings of "relaxed," "tense," and "happy," and also in the discrepancy between "objective reaction speed" and "subjective reaction speed" (the "optimism" effect).

Examination of these effects reveals that the "psychoanaleptic" measures, "sleepy," "tired," and "alert," showed progressive changes in the expected directions until 90 minutes after ingestion of the d-amphetamine, with virtually no changes between 90 minutes and 120 minutes after ingestion. Objectively measured reaction speed continued to increase up to the termination of the experiment, 120 minutes post-ingestion. Of the (here presumed) anti-stress measures, "tense" decreased and "happy" increased during the first 90 minutes, and showed little change thereafter. However, ratings of "relaxed," while increasing markedly up to 60 minutes post-ingestion, showed a marked decrease between 90 minutes and 120 minutes. "Subjective reaction speed" reached a pronounced peak at 90 minutes, where it reached 139% of the corresponding placebo value, but decreased to about 117% of the placebo value at 120 minutes. Since objectively measured speed was still increasing during this last interval, this comparison shows a marked decline in the "optimism" effect between 90 minutes and 120 minutes post-ingestion.

Thus, one is left with alternative possible interpretations for the greater superiority of the d-amphetamine groups during the earlier stages of testing. If this was not a measurement artifact, then either (1) it was due to an early peaking of stress effects and therefore of corresponding drug anti-stress effects, (2) it was due to an

unexpectedly early peaking of the relevant drug effects, or (3) some combination of these causes may have been operating.

Currently, further research is underway which should help resolve this issue. It involves the same basic design, but incorporates additional incentive effect introduced upon initial exposure to the task, and further drug variations including a combination of 10 mg. d-amphetamine with either 10 mg. of chlordiazepoxide or 50 mg. of secobarbital, a mood-active barbiturate. This should yield further evidence concerning the role of "anti-stress" components in the situational enhancement of cognitive performance.

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