An Attempt to Establish a Placebo Effect in Rats With Psychopharmacological Agents.

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AN ATTEMPT TO ESTABLISH A PLACEBO EFFECT IN RATS
WITH PSYCHOPHARMACOLOGICAL AGENTS

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Doctor of Philosophy

in
The Department of Psychology

by

Charles J. Black, Jr.
B.S., Texas Technological College, 1952
M.A., Southern Methodist University, 1958
January, 1963
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ABSTRACT

The central purpose of this investigation was to determine the extent to which white rats could acquire the tendency to react to hypodermic injections of neutral saline solutions (placebos) as they normally might react to injections of certain psychopharmacological drugs. The experimental hypothesis of this study was the belief that the above purpose might be achieved by individual groups of subjects for the effects of ethyl alcohol, Dexedrine and lysergic acid diethylamide-25 (LSD-25) respectively. Apparently these psychopharmacological agents have never been studied in this fashion. Furthermore, they have certain easily recognized effects on the behavior of animals, and each in turn represents a certain class of drugs.

The subjects of this experiment were forty albino male Sprague-Dawley rats, weighing between 325 and 400 grams at the beginning of their respective training periods. These animals were not litter mates; four groups of animals, consisting of ten animals each, were separately purchased as the sequential conditions of the experiment permitted their use. Three of these groups were treatment groups and one was a control group.

Of primary importance in the assessment of behavior was the individual response record and anecdotal evidence obtained from the daily fifteen minute performance of each rat.
in a Skinner box. This apparatus, which did not automatically record the response rate of rats, was adjusted to dispense a small food pellet on a fixed ratio of one pellet per two presses of the manipulandum.

Positive results were to be reflected in two ways: (1) similarity of performances from the latter part of a period of daily drug injections through the first of a following period of saline injections. (2) Similarity in performance covering the same periods, but between a treatment group and the control group in the form of smooth monotonic functions based on mean daily performance in the Skinner box.

Training began with the alcohol group first. Each rat of this group was placed on a 24-hour food deprivation schedule prior to beginning the first of three successive stages of training. The first stage of training consisted of rats learning to manipulate the lever in the Skinner box for the food reward. Each rat trained in the box in the same order each day for a fifteen minute period, and training continued in this manner until they had reached an asymptote. Immediately following this the second stage of training began. This period of training lasted exactly fifteen days, and it consisted of the same treatment as the first stage, except that a buzzer was presented with an intraperitoneal injection of 10% ethyl alcohol solution prior to each fifteen minute period. Sixteen days after the start of the second stage of training the third and final stage commenced. Training during
this period was exactly like that of the second stage of training, except that a neutral saline solution was substituted for the drug. The volume of this solution was the same as that which the alcohol had been: 1.522/100g body weight. This ratio remained the rule governing the volume of substances administered to all other subjects of this experiment.

The group of animals that received Dexedrine was the second group of animals to undergo training. The training procedures for this group were exactly the same as that for the alcohol group, except that Dexedrine (1.25mg/kg body weight) was the agent injected during the second stage of training.

Following the Dexedrine group a third treatment group also underwent the same training conditions as that of the alcohol group. Again the only difference in treatment was that of the drug, which in this case was LSD-25 administered at the dosage level of .25mg/kg body weight.

The final group to undergo the training conditions described for the alcohol group was the control group. In this case the animals received a distilled water injection during the second stage of training.

The results of the investigation appeared to be partially successful. The data produced by the alcohol group conformed to expectations based on the experimental hypothesis. That data produced by the other two treatment groups, however, did not favor the idea that a placebo effect could be established under such conditions.
INTRODUCTION

It is neither a new idea nor a novel one to suppose that certain organisms can be induced to perform for inactive substances much as they might normally perform for some given agent or drug. In a recent review of the subject of "placebo effect" Shapiro (1960) has noted that medieval philosophers and physicians resorted to the use of mementos, panaceas, homeopathic mixtures and the like for the treatment of human disease and misery. Pare, a sixteenth century French military surgeon, used a medication of earthworms steeped in turpentine and oil of puppies and lillies which he applied to battlefield wounds of French soldiers (Garrison, 1921).

Paracelsus, also living and practicing medicine in the sixteenth century, was something of a mystic in Europe. He advocated extracting "Mumia" from a patient’s body and inoculating it "into a plant bearing the signature of the disease." He supposed that this procedure would attract the specific influence from the stars because Paracelsus believed that diseases were caused by astral influences acting upon the astral body of man (Garrison, 1921, p. 198). Paracelsus also used "sympathetic powder," a powder held by alchemists to be a sovereign cure for a wound even if the powder were applied merely to blood from the wound, or to the weapon inflicting such a wound (Shapiro, 1960).
Janet (1925, p. 342) has said that certain material symbols (such as magnetized water and cachet of methylene blue) can succeed in modifying subconscious phenomena, provided the formula for such symbols can be varied to suit the subject's age and education. He noted that the essential point of success in such ventures depends on the extent to which such symbols conflict with the patient's knowledge. At testifying to the fact that the specific effects desired through the use of material symbols have not always been successfully achieved is the following account of treatments given Charles II by his physicians:

"A pint of blood was extracted from his right arm, and a half-pint from his left shoulder, followed by an emetic, two physics, and an enema comprising fifteen substances: the royal head was then shaved and a blister raised; then a sneezing powder, more emetics, and bleeding, soothing positions, a plaster of pitch and pigeon dung on his feet, positions containing ten different substances, chiefly herbs, finally 40 drops of extract of human skull, and the application of bezoar stone; after which his majesty died" (Van Dyke, 1947, p. 322). After results such as the above some authorities were moved to angry denial of the worth of such medicinal practices whose efficacy was based on irrational empiricism and superstition. Oliver Wendell Holmes (Shapiro, 1955) described the worth of the pharmacopoeia of his day by saying that it
would be so much the better for mankind and the worse for the fishes if it all could be sunk to the bottom of the sea. However, in spite of the faulty logic and superstition that has surrounded their use, as well as the misunderstandings of scientific men, interest in the effect of placebos has continued up to the present time.

Until very recently the use of a placebo in medical research efforts seems to have been reserved for those instances where it was desired to verify the value of some drug or reagent. The use of a placebo in the so-called "double blind procedure" is an example of this. Probably with the increasingly influential voice of psychiatry and its gradual emergence as a worthy discipline among other medical specialties, however, the effects of placebos themselves have come under closer scrutiny in medicine. For an example Wolf and Pinsky (1954) studied the use of placebos to test the effectiveness of mephenesin, a substance reported to allay subjective anxiety and tension. Using 31 patients of a New York hospital, they found almost the same amount of improvement or the lack of it regardless of whether a patient took a placebo pill or a mephenesin pill. Many of these patients had minor or equivocal complaints such as lightheadedness, drowsiness, and anorexia while taking both mephenesin and placebos. Hillis (1925) conducted a careful study on the power of a placebo to inhibit the cough reflex in human subjects. Using a neutral saline solution as a placebo he
obtained an effect as great as that observed with 0.03 grams of codeine. Another investigator (Diehl, 1933) studied the "toxicity" of placebo administration. He used lactose placebos as a control for a variety of medications taken by mouth in the treatment of the common cold. Diehl found that some subjects who took the placebo developed nausea, faintness and diarrhea.

As a result of the change in interest to placebo and its effects per se, a need for a new definition which goes beyond the older concepts has arisen. The term "placebo" originally arose from its Latin usage meaning "I shall please." The 1957 Dorland Medical Dictionary defines it as: "An inactive substance or preparation, formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substances." Wolf (1959) has advocated defining the placebo effect as, "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties." Wolf says that the fundamental stimulus, which is the mechanism of placebo action, is the meaningful situation. Citing several studies, he then shows that there is abundant experimental evidence indicating that many of the component changes in disease processes including fever, leucocytosis, headache, nausea, etc. are capable of being set in motion by impulses arising in the cerebral cortex. Classic by its unique method of study was the work of Steward Wolf (1950) on Tom, a patient who had a gastric
fistula. This study showed among other things that it was possible to demonstrate that the effects of certain drugs on the gastric function were directly dependent on the emotional state of the subject. For instance when Tom was relaxed, administration of urogastrone caused cessation of gastric function, but when Tom was already provoked the same substance increased gastric activity. Furthermore, an injection of sterile water enhanced gastric blood flow. Wolf concluded that placebo effects which modify the pharmacologic actions of drugs or endow inert agents with potency are not imaginary but may be associated with measurable changes at end organs. Important factors at the time of administration were the state of the end organ, the setting, and the conditioning factors. His concluding remarks contain a caution for the investigator who resorts to the double blind technique without giving attention to the influence of suggestion.

This caution seems especially wise regarding the use of new therapeutic agents where an investigator may not have sufficiently curbed his enthusiasm before their assessment. For an example, the application of this caution to the recent work with carbon dioxide (Meduna, 1950) and acetylcholine (Phillips & Hutchinson, 1954) in the treatment of the psychoneuroses might have eliminated some of the need for more extensive research on these substances. Nevertheless, Hawkings and Tibbetts (1956b) produced contrary evidence for the case of carbon dioxide therapy, and Hawkings and Tibbetts (1956a) and
Pare (1956) also found negative results for the use of acetylcholine therapy. Tibbetts and Hawkings (1956) have inferred that suggestibility, family attitude and other "domestic influences" are the probable mechanisms causing placebos to be effective, and these same factors could also be responsible for the spuriously positive conclusions on the effectiveness of carbon dioxide and acetylcholine therapy.

Lasagna, Mosteller, von Felsinger and Beecher (1954) viewed the importance of personality factors in drug research. They conducted studies on human subjects whom they thought were extra-sensitive to the placebo effect, and they summarized the pertinent personality factors thought to be found in the "reactor type." Trouton (1957), in an examination of the psychological mechanism of placebo reactions, felt that there were well defined groups of placebo reactors and non-reactors. He noted, however, that although there are numerous instances of the surprising efficacy of placebos in a wide variety of conditions, little had yet been done toward providing an explanation of the occurrence of placebo reaction in terms of psychology. He then states his own preference of considering the explanation in terms of learning, with the diminution of responses to the situation of repetition being related to lack of reinforcement. Kurland (1957, 1960) has been more frank in his explanations and has concluded that the placebo effect can best be interpreted as a conditional response where the placebo itself has become a
conditioned stimulus.

The matter of "rector type" is a side issue at this point; but, to conclude first that there are certain "reactor types" of personalities and then later suppose that the placebo effect is a conditioned response seems at once to be both precipitant and contradictory reasoning. Pavlov (1957, pp. 313-342), however, has called attention to differences in "natural type of nervous system" which he believed one must take into account before settling down to a description of action which is supposedly also a partial product of an animal's daily training experience. Modern Russian accounts of animal behavior in experimental conditioning frequently pay note to a consideration of the animal's "natural nervous type" (Ivanov-Smolensky, 1954, pp. 83-96; Vaksleiger, Bozatureva, & Nasledkov, 1958; Voznesenskii, 1960). Of course, credence paid to constitutional type has been the central point of some important views in the psychology of the individual (Kretschmer, 1921; Sheldon, 1944). Additionally, other well known theorists (Murray & Kluckholm, 1953; Murphy, 1947; Freud, 1935) have chosen to place a heavy emphasis upon the psychobiological nature of human behavior. Of relatively recent times Mardones (1951) has reported information on the relationship between deficiency of B vitamins and alcohol intake in rats. After five generations of separate inbreeding, he was able to segregate two populations of animals significantly different in alcohol intake behavior.
It thus appears that any account of animal behavior and drugs might do well to consider the subject of individual differences.

But, returning to the main line of thought, the bridge between views and studies on placebo effect and those on conditioning has not been long in coming since the remarks made by Kurland (op. cit.). Very recently Herrnstein (1962) has shown that scopolamine hydrobromide, when injected into rats performing in a Skinner box, will disrupt their learned behavior in a predictable manner. Physiological saline was found to mimic to some extent the effect of the drug when the two substances are alternately administered in a series of injections. The author believed this placebo effect could be considered as an instance of simple Pavlovian conditioning.

Although Herrnstein's study was one designed so as to produce the maximal probability of developing a placebo effect, it differs somewhat from the traditional studies of this nature. It differs first in making primary use of a response measure that only indirectly identifies Pavlovian conditioning, namely instrumental responding in a Skinner box. Secondly, the schedule of training with drugs and saline was one employing them in alternation, so that in effect the drug (or the saline solution) was administered on a variable schedule. Previous kindred studies with other drugs and chemical substances have resorted to more direct assessment of the reflex responses; and, most usually the schedule of administering
the drug was a constant or regular one (cf. Gantt, 1958).

The history of attempts at conditioning the effects of different chemical substances under conditions resembling the classical laboratory set up of Pavlov is rather lengthy. Many different kinds of drugs and reagents have been carefully studied, although English translations of such work is not to be easily found. However, Pavlov himself has reported studies of conditioned reflex activity where chemical agents were the unconditional stimuli (Pavlov, 1957, p. 403). Using small quantities of dilute acid he evoked secretions of saliva from a dog by introducing the acid in the dog's mouth several times a day. After several days of pairing such activity with mechanical stimulation of the skin of the animal's foreleg the flow of saliva could be obtained by the mechanical stimulation alone. Previous to this investigation Podkopayev (1914), one of Pavlov's oldest co-workers, combined a repeated hypodermic injection of apomorphine with the sound of an organ pipe. He finally transformed this auditory stimulus into a conditioned signal of a nauseous and vomitive reaction, which at first had only been obtained by him with the help of apomorphine. Krilov (1927) further advanced this kind of experiment by giving daily injections of morphine to experimental dogs. After 5 or 6 days he noticed that the injection preliminaries began to produce a reaction identical with that produced by the injected morphine, i.e., a profuse secretion of saliva, nausea and vomiting. In view of these
and other related Russian studies Ivanov-Smolensky (1954) indicates that much detailed attention became devoted to the pathological changes of the higher nervous activity resulting from repeated experimental intoxication and infection.

A more recent source of English translations of the Russian literature has been provided by Horsley Gantt who interpreted the volume by Bykov (1957). In this work are to be found many reports of classical conditioning with such drugs as morphine, nitroglycerin, ephedrine, hydrochloric acid and chologogs. Gantt has been particularly active in not only interpreting the Russian literature but in conducting research with drugs. A part of his interest stems from having worked with Pavlov and his colleagues at the Institute of Experimental Medicine in Petrograd during the early part of his life. Upon his return to this country Gantt became actively engaged in conditioning studies and some of the theoretical problems that this work engendered. In 1927 Kleitman and Crisler, two of Gantt's earlier co-workers in this country, confirmed a previous investigation (Collins and Tatum, 1925) by demonstrating rather conclusively that a conditioned salivary reflex could be produced where dogs were given daily subcutaneous injections of morphine. Kleitman (1927), however, found that repeated subcutaneous injections of pilocarpine did not result in the development of a conditioned salivary reflex in the dog. A subsequent investigation by Crisler (1930) was concluded with the finding that
daily doses of atropine injected subcutaneously in dogs did not produce conditioned salivary reflex behavior. In an investigation (Gantt, 1937) where the CS was a buzzer, the attempt to condition adrenalin-produced hyperglycemia using rabbits and dogs was unsuccessful. Katzenelbogen, Loucks and Gantt (1939) were also unsuccessful when they tried to condition gastric secretion produced in response to injections of histamin in dogs. More recently Gantt (1953) produced results suggesting that it was not possible to condition the effects of acetylcholine on heart rate. Another investigation (Reiss, 1958), however, was successful when the attempt was made to condition the overt behavioral effects of insulin injected into the peritoneum of rats.

Mackenzie and Gantt (1950) concluded in a brief abstract of their work that the criterion as to whether a reaction can be conditioned depends not upon the reaction but upon the method of its production. Using saline injection as a CS and atropine as a US, these investigators reported that a marked heart rate acceleration could not be conditioned owing to atropine being a peripheral nervous system excitant. This viewpoint was elaborated further in a later comment (Gliedman, Gantt & Teitelbaum, 1957) to the effect that conditioning can be obtained for the effect of drugs whose action is on the central nervous system. However, drugs which produce a response through peripheral action on nerve endings (e.g., salivation in response to pilocarpine, hyperglycemia in
response to adrenalin, gastric secretion in response to histamine, and cardiac acceleration in response to atropine) do not result in the establishment of conditioning. This supposedly accounts for the successful results in the case of morphine and salivation, since morphine acts on the central nervous system of dogs to produce nausea of which salivation is a component.

It is rather surprising to find so few of the above-mentioned studies reporting the use of the so-called psychopharmacological agents. The term "psychopharmacological" in this country was first suggested by Himwich (1955) who noted that this term appeared to be descriptively designative of those drugs and medicines which modify the human mind by affecting "its morphological substrate, the brain" (Himwich, 1960, p. 41). This authority believes that such a designation embraces a broad spectrum of drugs which includes psychomimetic agents of comparatively early origin (e.g., marijuana, peyote, hallucinatory mushrooms, etc.) as well as the anti-depressant and tranquilizing agents which have more recently come into prominence.

The satisfactory efforts cited above with the use of morphine on dogs leads one to suppose that it might be possible to achieve similar results with other kinds of psychopharmacological agents. Apparently, however, work in this more limited area has not been very extensive. The principle reason for undertaking the present investigation was to
determine the extent to which certain well known drugs, i.e., ethyl alcohol, Dexedrine and lysergic acid diethylaminitic-25 (LSD-25), lend themselves to establishment of a placebo effect. The above examples of psychopharmacological agents have apparently never been studied in this fashion. Furthermore, they have certain dramatic effects on the behavior of animals, and each in turn represents a certain class of drugs. Ethyl alcohol is representative of a class of drugs usually considered as depressants. Dexedrine is a trade name for the dextrorotatory isomer of amphetamine sulfate which is a powerful central nervous system excitant. LSD-25 is considered to be a psychomimetic drug because small quantities of it will produce behavioral effects in humans that "mimics" certain mental disorders.

Stated more explicitly, therefore, the central purpose of the present investigation was to determine the extent to which white rats could acquire the tendency to react to hypodermic injections of neutral saline solutions as they normally might react to injections of certain psychopharmacological drugs. The experimental hypothesis of this study was the belief that the above purpose might be achieved by individual groups of subjects for the effects of ethyl alcohol, Dexedrine and LSD-25 respectively. The effect on rat behavior in the particular of these drugs is relatively well known: ethyl alcohol (Arvola, Sammalisto, & Wallgren, 1958; Wallgren, Arvola, & Sammalisto, 1960), Dexedrine (Stone,
Calhoun, & Klopfenstein, 1958), and LSD-25 (Rothlin, 1957; Cook & Weidley, 1957). It was supposed by the investigator that if the above hypothesis could be affirmed, manifestations of these effects in some degree could be observed when a saline solution was administered. It was further assumed that if such positive results were found, evidence would be had that a placebo effect had been produced. In this case it was assumed that positive results would be reflected in both objective and subjective response measures. It was assumed that positive results in objective measures would appear in the form of smooth, monotonic functions based on the mean daily performance of subjects in a Skinner box as they passed from a period of drug injections to a period of saline injections. It was assumed that positive results in subjective measures would appear during the initial period of saline injection wherein the rats would reproduce in some degree the overt behavioral symptoms manifested in previous training in response to drug injection.
METHOD

Apparatus

For objective measurement of an animal's performance a Skinner box permitting assessment of performance in terms of response rate was used. The apparatus was constructed to dispense food pellets as a reward when a lever was depressed. The mechanism was not completely automatic making it necessary to keep response records by hand. The Skinner box was located in a room two rooms removed from that housing the subjects of the experiment. This arrangement permitted semi-insulation of sounds generated by a buzzer located near the Skinner box.

Subjects

Forty white male Sprague-Dawley rats weighing between 325 and 400 grams at the beginning of their respective training periods were the subjects for this experiment. These animals were not litter mates; four groups of animals, consisting of 10 animals each, were supplied by the Holtzman laboratories in Houston, Texas as the sequential conditions of the experiment permitted their use.

Materials

The agents used in this experiment were psychopharmacological drugs. The kinds and dosage levels of these drugs
are shown in Table 1. The ethyl alcohol was a standard USP 95% ethyl alcohol. The Dexedrine (dextro-amphetamine sulfate, SK&F) was obtained from the Smith Kline & French Laboratories in Philadelphia, Pennsylvania. The lysergic acid diethylamid-25 (LSD-25) was obtained from Sandoz Pharmaceuticals in Hanover, New Jersey.

The drugs mentioned above were administered in 5cc. luer lock syringes using 1/2 inch by size number 25 intravenous needles. This equipment was kept semi-sterile by a sequence of tap-water rinses and rinses in a solution of Zephiran Chloride (benzalkonium chloride) immediately after each day's use.

Each animal was maintained on a daily ration of 12 to 15g. of Laboratory Chow manufactured by the Purina Laboratories. The food reward dispensed by the Skinner box was a small pellet 4mm x 3.3mm x 45mg. in size and manufactured by the P. J. Noyes Company of Lancaster, New Hampshire.

**Design**

The plan of this study was one employing 4 groups of male albino rats, with 10 animals to a group. Three of these groups were treatment groups and one was a control group. Of primary importance in the assessment of behavior was the individual response record and anecdotal evidence obtained from the daily performance of each rat in the Skinner box. Each animal of the experiment daily underwent experimental conditions where he was intently observed for 15
TABLE 1

KINDS AND CONCENTRATIONS OF THE VARIOUS AGENTS GIVEN TO TREATMENT AND CONTROL GROUPS

<table>
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<th>Agent</th>
<th>Concentration</th>
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<td>Lysergic acid diethylamide-25</td>
<td>.25 mg/kg body weight in a vehicle of 0.9% saline solution. Administered at rate of 1.5 cc/100g body weight.</td>
</tr>
<tr>
<td>Dexedrine</td>
<td>1.25 mg/kg body weight in a vehicle of 0.9% saline solution. Administered at rate of 1.5 cc/100g body weight.</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>10% (w/v) of 95% alcohol solution in distilled water. Administered at rate of 1.5 cc/100g body weight.</td>
</tr>
<tr>
<td>Saline solution</td>
<td>0.9% standard neutral saline solution. Administered at rate of 1.5 cc/100g body weight.</td>
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minutes each day, and, to a less intent degree, for subsequent periods after this time interval. As a result of the extensive time required for such observation, the separate treatment and control groups were purchased as needed and trained sequentially rather than concurrently.

A summary of the design and procedure of training animals is shown in Table 2. From this table it can be seen that each of the 4 groups of rats underwent 3 stages of training: stage I, pretraining in the Skinner box, stage II, continued training in the Skinner box accompanied by drug injections, and stage III, continued training in the Skinner box accompanied by saline injections. A glance at the table shows that in this case pretraining experience consisted only of learning to manipulate the lever in the Skinner box for a food reward. All animals during this period learned to perform in the Skinner box until they had reached an asymptote in their rate of responding. The period of drug injection, stage II, followed immediately after the pretraining experience. During the drug-injection period a given rat was first exposed to the noise of a buzzer and then injected with a drug solution prior to being placed in the Skinner box for 15 minutes. At the start of stage III all conditions continued as before except that a neutral saline solution was substituted for the drug. This constituted the last and final stage of training.

The design of this experiment was such that it provided
<table>
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<th>Stage II</th>
<th>Stage III</th>
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<td>Alcohol Group:</td>
<td>Each rat trained 15 minutes a day to an asymptote. The food reward schedule was FR-2.</td>
<td>Training continued, but a buzzer was presented with alcohol injection prior to each 15 minute period.</td>
<td>Training continued as before, except that a saline solution was substituted for the drug.</td>
</tr>
<tr>
<td>Dexedrine Group:</td>
<td>(Training same as that for the alcohol group.)</td>
<td>(Training same as that for above group, except drug was Dexedrine.)</td>
<td>(Training same as that for the above group.)</td>
</tr>
<tr>
<td>LSD-25 Group:</td>
<td>(Training same as that for the alcohol group.)</td>
<td>(Training same as that for the above group, except drug was LSD-25.)</td>
<td>(Training same as that for the above group.)</td>
</tr>
<tr>
<td>Control Group:</td>
<td>(Training same as that for the alcohol group.)</td>
<td>(Training same as that for the above group, except agent was a distilled water solution.)</td>
<td>(Training same as that for the above group.)</td>
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two principal control measures for assessing whether the test hypothesis was confirmed or not: (1) In one instance a given treatment group served as its own control when comparison of its stage II performance with its stage III performance was made. (2) In the other instance each treatment group's stage III performance was compared to that of the control group's.

**Procedure**

When training began the group of animals that was to receive ethyl alcohol was the first to start. Prior to the beginning of their training each of these animals was placed on a 24-hour food deprivation schedule. Free access to a plentiful supply of water was maintained. Animals of this group began with the pretraining period as defined above. In this and in all other cases the schedule of reinforcement in the Skinner box was a fixed ratio of one reward for each two presses of the Skinner box lever (FR-2). This schedule of reward was chosen because it is mastered by rats relatively fast, and because a fairly uniform rate of responding ensues. In this experiment each animal was trained individually and in the same consecutive order each day. A given day of pretraining with the ethyl alcohol group proceeded with an animal being taken from his home quarters and placed in the Skinner box to train for 15 minutes. The total number of responses the animal attained each 5 minutes while in the Skinner box was recorded. Each of the 10 animals of
this group received pretraining under these conditions until they had established an asymptote in performance. The total time of training all animals each day in the Skinner box was 2 hours and 30 minutes. Training continued in this manner 6 days a week for a total of 12 days of training.

After all animals had established asymptotes under pretraining conditions, stage II training under the same reinforcement schedule commenced immediately. In this case the training consisted of pairing the sound of the buzzer with injections of ethyl alcohol. The procedure and order of training during this period was the same as that during pretraining, except that for the first time the buzzer and the drug were introduced. Using rat number one as an example, the sequence of training was as follows: Upon entering the laboratory the first day of stage II training, the weight of each animal of the alcohol group was recorded. Based on the weight of rat number one, the first of 10 syringes was filled with the capacity of ethyl alcohol solution as per the requirement shown in Table 1. Because alcohol is relatively volatile, fresh solutions of 10% alcohol of sufficient volume for about 2 animals were mixed as the training sequence of the 10 animals called for it. Thus, each day of training led to about 5 separate solutions being prepared. After filling the syringe animal number one was removed from the home cage and carried with the syringe to the experiment room, with the door to the room housing the
animals being closed behind. Once in the experiment room with the Skinner box the door to this room was also closed, there being another laboratory between that housing the animals and that where the Skinner box was located. Next, the buzzer was turned on simultaneously with the start of a stop watch. This watch timed the duration of the buzzer. After the buzzer had been on for exactly 30 seconds, an intraperitoneal injection of the alcohol solution was begun. The uniform procedure in this case was to hold the animal in the left hand while injecting the solution with the right hand. The total time required to administer the injection was 30 to 40 seconds, depending on the amount of struggle and resistance the animal demonstrated. The buzzer remained on for about 1-1/2 minutes after the injection had begun. Altogether the buzzer was presented for exactly 2 minutes. Immediately after the injection was completed the animal was placed in the Skinner box and its door was immediately closed. Simultaneously with the closing of the Skinner box door an electric timing device and a second stop watch were started. The electric timing device measured time to the nearest 1/100th of a second, and was for the purpose of measuring the time lapse before lever-pressing activity began. The second stop watch was used for the purpose of timing the animal's 15 minute period in the Skinner box. Using this stop watch the total number of responses occurring in each 5 minute period, and in the total 15 minute
period could be recorded. Generally the effects of the drugs used in this experiment (including that of alcohol) began to be noticeable in an animal's behavior within 1-1/2 to 2 minutes after injection. Thus, the buzzer-drug relationship was forward in sequence, if not actually contiguous, in all instances of the experiment. When the animal's 15 minute period in the Skinner box had expired, he was removed and returned to his home cage. On being placed in the cage he was given his small, 12 to 15g. daily food ration of laboratory chow. This, together with the amount of pellets he earned in the Skinner box, constituted his total food supply for the 24 hour period.

All animals of the alcohol group were trained during stage II in the manner described above for animal number 1. The sequence of training the animals was the same each day. The period of training for the 10 animals lasted a total of 2 hours and 30 minutes each day, and it continued for exactly 15 consecutive days. During this 15 day period, periodic checks of each animal's weight were made in order to adjust the dosage of alcohol injection in case of weight variation. The record of an animal's weight together with his drug dosage is shown in the Appendix.

When stage II training had been completed, stage III training under the same food reinforcement schedule began. This period of training began immediately the next day after the last day of stage II. The procedure during stage III
training was exactly the same as that for the preceding stage II training, except that after the buzzer was presented during a given day of training, the ethyl alcohol did not follow. In the place of ethyl alcohol a neutral isotonic saline solution of the same volume was substituted. Other than this there was no difference in treatment conditions between the stage II and stage III training. Stage III training continued until all animals were once again performing at the asymptotic level reached during pretraining. Their training ended on June 6th.

The first day of stage I training with group of animals that received Dexedrine began May 16. Thus, for a period of several days the alcohol and Dexedrine group trained on the same day. During this period of overlap in training the order of training and time of commencing on any given day for the alcohol group was not disturbed. Animals of the Dexedrine group during this period were routinely trained after the alcohol group on such a given day. The purpose of this overlap in training was merely to speed up the experiment and shorten the total length of time required to complete it.

Animals of the Dexedrine group were placed on a 24-hour food deprivation schedule shortly before this time. All training procedures with these animals were exactly the same as those under which animals of the alcohol group performed, except for the drug condition. Instead of alcohol, members...
of this second group of treatment animals received Dexedrine at the strength shown in Table 1. A total of 84mg. of Dexedrine was mixed in 600cc. of a 0.9% saline solution (the vehicle in which Dexedrine will form a true solution). This formed a 0.7mg./5cc. solution, a solution which provided sufficient strength to meet the requirements shown in Table 1 and still be contained in a 5cc. syringe. The same size syringe used with the alcohol group. When ready for use, the amount of solution for a given animal was measured out, and the necessary amount of the 0.9% saline vehicle was then added to meet the volume requirement of 1.5cc./100g. body weight. All animals of this group were periodically weighed to adjust the dosage of Dexedrine injection in case of weight variation. The record of their weight and drug dosage is shown in the Appendix.

The last day of training in stage III for the Dexedrine group was June 27. The first day of stage I training for the LSD group was June 13. Thus, for a period of time the Dexedrine and LSD group trained on the same day. The time and order of the Dexedrine's training, however, continued as before this period of overlap. Animals of the LSD group were routinely trained before the Dexedrine group during this period on a given day. During this given day the LSD group trained in the space of time previously allotted to the alcohol animals, but no longer used by this latter group since it had completed all training stages.
All training procedures with the LSD animals were exactly the same as those for the alcohol and Dexedrine groups save that of the drug used. This third treatment group received LSD-25 at the strength shown in Table 1. A total of 100mg. of LSD-25 was mixed in 1000cc. of a 0.9% saline solution. This formed a 0.5mg./5cc. solution, a solution which provided sufficient strength to meet the requirements shown in Table 1 and still be contained in a 5cc. syringe. When ready for use the amount for a given animal was measured out into the syringe and the necessary amount of the 0.9% saline vehicle was then added to meet the volume requirement of 1.5cc./100g. of body weight. All animals of this group were periodically weighed and the record of their weight and drug dosage is shown in the Appendix.

The last day of training in stage III for the LSD group was July 20. The first day of stage I training for the control group was July 5. Again there was overlap in training between groups as described previously for other groups. In this case the control group’s space of training on any given day of this overlap was that which had been previously allotted to the Dexedrine group.

All training procedures for the control group were exactly like those of the treatment group except no drugs were used. In the place of a drug, distilled water injections at the rate of 1.5cc./100g. body weight were used during stage II, and a 0.9% saline solution of the same volume
was used during stage III. Thus, stage III treatment for the control group was exactly like that of the 3 treatment groups. Also, like the 3 treatment groups, the control group was exposed to a change of quality in the injection from stage II to stage III.
RESULTS

Visual inspection of the graphic records contained in Figure 1 shows that with the exception of the alcohol group, the direction of performance during the initial portion of stage III was not that predicted on the basis of experimental hypothesis. Anecdotal evidence taken from performance of animals in the Dexedrine and LSD-25 group does not confirm the notion that training with drugs under the prescribed conditions of stage II led to a significant tendency to perform similarly for saline injections during stage III. Furthermore, these two groups did not perform like that of the control group. The alcohol group, however, is an exception. Data from the performance of animals in this group leads to the supposition that they did demonstrate a tendency to behave in a manner like that predicted by the experimental hypothesis.

Looking at the evidence from the view of the first of the two principal controls provided in this investigation, performance at the lever by the alcohol group as a whole during the first day of stage III was remarkably like that of the previous 10 days of stage II. The similarity is in the continuation of the monotonic change shown in Figure 1. The mean rate of response for the 10 animals during the 15 minute daily training periods formed an upward-directed trend
PERFORMANCE RECORDS OF THE FOUR GROUPS OF RATS DURING THE 3 STAGES OF TRAINING.
EACH FUNCTION REPRESENTS THE MEAN RESPONSE RATE OF TEN RATS
DURING DAILY 15-MINUTE PERIODS.
during the last 10 days of drug training. The first day of saline injection led to results that are directly in line so that a relatively smooth continuation of this trend appears up to the second day of stage III. When the same data are broken down into the 3 different 5 minute periods, the trends are not so smooth and clear, but are nevertheless present.

The injection of ethyl alcohol in a naive rat at the dosage level shown in Table 1 produces a characteristic reaction occurring most usually about 3 minutes after the hypodermic needle is inserted in the peritoneum. In this experiment the first day of injection led to a reaction consisting of an initial slowing in rate of response, followed eventually by a complete stop during which the rat remained still for a few moments before finally losing its balance and rolling over on to the floor as intoxication mounted. Altogether this period usually lasted about 10 minutes. As the number of days of training progressed the symptoms of intoxication became less apparent after each injection. By the 15th and last day of alcohol injection there was little to really mark it by save the animal's ready disposition to have the drug injected into him. All rats without exception seemed to enjoy the experience afforded by the drug, and only rarely offered resistance to its injection except in the case of a malfunctioning syringe or a poorly inserted needle. Thus, because of this gradual adaptation to the drug and its effects over the 15 days of daily injection, the dramatic
quality of behavior demonstrated the first day by the animals was not to be expected as evidence of positive results on the 16th day, which was the first day of stage III.

The kind of behavior disposing one to believe positive effects were to some extent achieved with the alcohol group is not limited to the similarity of monotonic increase in lever-pressing behavior from the last day of stage II through the first day of stage III. Further evidence seems provided in the abrupt depression in response rate which is recorded for the second day of stage III. Looking at the anecdotal records for each animal during that day, only rat numbers 1 and 2 failed to show some tendencies to be distracted at some time during the 15 minute period. Rat numbers 1 and 2 produced a greater number of responses this second day than they had the first, and they were relatively persistent in lever-pressing activity. The remaining 8 rats, however, showed varying degrees of distraction from lever-pressing activity. Some, such as numbers 3, 4, 5, 6, and 8, delayed responding for 45 seconds and more after the buzzer had ceased. In some instances, as in the case of rat numbers 5 and 9, a lapse without responding occurred which lasted longer than 60 seconds. In both instances these lapses began shortly after the buzzer ceased. During these lapses the animals behaved as if they were searching the box for something. At these times they either stood motionless as if waiting for something, or they moved about the box occasionally stopping to stand on
their rear legs to sniff at the walls.

The fact that this depression in response activity occurred the second day of stage III instead of the first is a compelling provocation for assuming that the first day of stage III represents a placebo effect. Common experience with human alcoholics as well as the article by Thimann and Gauthier (1959) lend themselves to the argument that the results of the second day of stage III represents a consequence of being withdrawn from alcohol. But, in reality all members of this group had been withdrawn from the drug on the first day of stage III, not the second. Of course, there were individual differences in the amount of distraction shown on the second day; and, 6 of the animals showed a decrease on the first day, although such decrements were quite small relative to that of the second day. However, a careful inspection of the alcohol group's performance in Figure 2 shows that on the first day of stage III the animals as a group tended to show decrements only during the second 5 minute period. On the following day, however, they showed decrements during each of the 3 periods; and, more importantly, the first 5 minute period witnessed greater depression than the second.

Looking at the evidence from the view of the second of the two principal controls provided in this investigation, performance at the Skinner box lever by the alcohol group is the only one of the three treatment group performances which
approaches in similarity that of the control group. The similarity between the two is the degree of linearity maintained by both groups when their mean daily performance rates are compared during the period extending from the 5th day of stage II through the 1st day of stage III. Both groups during this period produced results that form a monotonically increasing function as shown in Figure 1. When a comparison of the two groups' performances based on the averages of the 5 minute periods during these same days is made, there appears to be much less similarity. There are no cros-overs at all of the 3 functions representing the control group; however, many occur with those of the alcohol group.

The conclusions about results from the alcohol group are probably best made with reservedness, so far as they pertain to any positive effects this group may have demonstrated. While it seems doubtful to suppose that the depression exhibited by the animals on the second day of stage III can be attributed to artifact, it, nevertheless, was not a property attending the performance of every animal that day. Furthermore, as has already been indicated, those animals that did exhibit this depression in rate of response tended to vary considerably among themselves in terms of degree.

The results of the Dexedrine group's performance as illustrated in Figures 1 and 3 are obviously far removed from that which one would expect had a placebo effect been established. The effect of Dexedrine injection on rats performing
Fig. 2. The Alcohol Group. Three Separate Functions Each Representing the Mean Response Rate of Ten Rats During 5-Minute Intervals.
in the Skinner box for a food reward was that of depressing their drive for a food reward. It is by now rather commonly known that the dextrorotatory isomer of amphetamine sulfate, in addition to being a powerful stimulant, also has marked appetite-depressing properties (Leake, 1958). This property of the drug was so obviously at work during the 15 days of stage II, although a glance at the group's functions shown in Figure 3 reveals that such a property did not manifest itself until the last two 5 minute periods each day. Had the training conditions of stage II been such that they lent themselves to development of a placebo effect, the functions shown in Figure 3 would have continued to reveal food aversion during the initial day or days of stage III. That this was not the case can be detected by noting that an immediate and abrupt increase in response rate began as soon as saline injections commenced.

The subjective observations recorded for members of the Dexedrine group also do not provide bases for supposing that a placebo effect was established. Previous research (Hamilton, 1960) has concluded that there is very little tendency for animals to develop adaptation properties to frequently administered doses of Dexedrine. Testament to continued strength of its effectiveness during the 15 days it was administered to the animals is the record of the animals' weight loss shown in the Appendix. Here it can be seen that their weight losses were steady and persistent.
Fig. 3. The Dextroplane Group. Three Separate Functions Each Representing the Mean Response Rate of Ten male Rats During 5-Minute Intervals.
Fig. 4. The LSD-25 Group. Three Separate Functions Each Representing the Mean Response Rate of Ten Rats During 5-Minute Intervals.
If the last day of Dexedrine administration was about as effective as on the first day, one would expect to see the behavioral manifestations of such an injection showing up on the first day of stage III if the hypothesis of this experiment were upheld with this group. This was not the result. The behavioral symptoms manifested by subjects on the first through the last day of drug injection were not present on the first or any other day of the saline injection. For the most part the symptoms of drug injection during stage II were those of delay and inattention to lever-pressing activity, although some of the animals demonstrated activity of one kind or another during these delays. As a whole this group appeared to be more resistive to being injected with Dexedrine than was the group which received alcohol.

The third treatment group, the group that received LSD-25, produced results that as a whole are incongruous with the idea that their training conditions led to the establishment of a placebo effect. With the exception of the performance by rat numbers 3, 5, and 6 of this group all animals performed at a more rapid pace at the lever on the first day of saline injection than they had the day before, which was the last day of LSD-25 injection. The exceptional rats mentioned above do not appear to have given evidence of a placebo effect, but there may be room for question.

The subjective reports of animal behavior that bears on the possibility of positive results provide better evidence
In this case than that of the response rates. When LSD-25 is injected into a rat at the dosage level shown in Table 2, the following behavioral changes come about fairly soon: urination and defecation, crouching on the floor of cage as if a vestibular disturbance of some sort were occurring, piloerection, and erection of the ears in a characteristic manner. These symptoms follow fairly uniformly in all animals and can be easily observed without undue effort. Previous investigations (Black, 1962; Hamilton, 1960) have found there are few tendencies for animals to develop strong resistances or adaptation to LSD-25. The effect of LSD-25 at the start of a 15 day daily period of injection, for an example, should leave a group of animals almost as susceptible to its effects by the last day as they were the first day. This present investigation did not produce contrary results in this respect. This being the case, one would expect to see at least some degree of these behavioral effects being demonstrated on the first day of stage III. This apparently was not the case. The last day of stage II witnessed meticulous observation of rat behavior; on this day and each previous day prior to it in stage II, the number of pellets defecated by each rat as a result of LSD-25 injection was recorded. The mean number of pellets defecated the last day of stage II for the 10 animals of the LSD-25 group was 5.2. During this same day all 10 animals defecated without exception and the number ranged from 10 to 3 pellets. The
first day of stage III witnessed no defecations with the exception of a single animal, rat number 6, which defecated 3 pellets. This rat is one of the three mentioned above that proved exceptional to the extent of performing at about the same response rate at the lever on the first day of stage III as they had on the last day of stage II. The other two animals, rat numbers 3 and 5, although they resembled rat number 6 in response rate, did not defecate and really did not show convincing evidence of the LSD-25 symptoms. Besides the defecation of rat number 6, no convincing evidence of other LSD-25 symptoms appeared.

The conclusion of the results for this LSD-25 group is that most likely a placebo effect was not produced. While it may be possible that rat number 6 was an exception, in view of not finding similar results with any other animal it may be that his behavior is based on artifact or happenstance. The importance of individual differences should not, however, be overlooked or discounted in studies such as this.

The last group to be trained in this investigation was the control group. It was anticipated that this group would so become accustomed to daily injections of neutral solutions that on the first day of stage III, they would continue to perform as they had during the previous days of stage II. Results tend to confirm this generally. Reference to the mean daily performances of this group shown in Figures 1 and 5 reveals that the rate of change in bar-pressing activity
Fig. 5. The Control Group. Three Separate Functions Each Representing the Mean Response Rate of Ten Rats During 5-Minute Intervals.
was relatively uniform from the last 10 days of stage II through the initial days of stage III. Apparently, the advent of stage III with its training conditions did not produce a significant signal for change in response rate, so far as such conditions affected the animals of the control group. Reference to the records of this same period made by the experimenter as he observed the animals performing provides no contrary information to that already stated about the control group. These same records do, however, show that with little exception the members of this group were much more resistive to the introperitoneal injections than were members of treatment group to their respective injections. This comparison holds true even when the LSD-25 group is considered, which was unexpected since LSD-25 is a toxic drug and usually produces painful stimulation upon being injected into living tissue. The only occasion the experimenter was seriously bit by any animal occurred during the handling of a control rat. The particular animals used in this experiment were normally unusually docile. During injections, however, the members of the control group proved exceptional in this respect.
DISCUSSION

The results of this investigation provide some confirming evidence that certain psychopharmacological agents do lend themselves to the production of placebo effects defined in the manner of Wolf (1959). The confirming data appear to be provided exclusively by those subjects that underwent experimental conditions where ethyl alcohol was the psychopharmacological agent. Those results derived from the treatment of animals with LSD and Dexedrine did not yield such generous information; however, this cannot confidently be construed to mean that the behavioral effects produced by these two agents on rats are not subject to being simulated by placebos. Such an assumption would seem to be as ill-advised as that of concluding with complete finality that the behavioral effects produced by ethyl alcohol absolutely lends itself to the establishment of a placebo effect. The apparent novel achievement of success with ethyl alcohol in this investigation merely adds further credence to the hypothesis that a placebo effect for its behavioral manifestations can be established. Further research under the same and perhaps under slightly variant circumstances are called for in order to readily conclude that placebos for ethyl alcohol can be had.

The aim of this investigation was entirely an exploratory one. This experiment was an empirical examination
conducted with certain psychopharmacological agents to
determine their potentialities for lending themselves to the
establishment of a placebo effect. No thought was given to
designing the experiment as a crucial test of certain theo­
retical points of view on how placebo effects become estab­
lished. The assumption that the effects achieved with ethyl
alcohol in this experiment provide evidence that a placebo
effect can be achieved with this agent constitutes an un­
critical bias on the part of the investigator. The definition
of "placebo effect" offered by Wolf (1959) is an acceptable
one at this point, so far as the results of this research are
concerned. As such, the results with ethyl alcohol have been
interpreted as positive evidence.

One point which has an important bearing on how results
of an experiment such as this are interpreted has to do with
the objective response measures employed. Rate of response
as an index of assessment in this type research can bear
critical examination. Bar-pressing activity in a Skinner box
is usually considered a sensitive response measure and many
investigators have resorted to its use in the assessment of
drug influence on animal behavior (Dews, 1956; Miller, 1957;
Sidman, 1955). Usually such use is related to an animal per­
forming continuously over a 24-hour a day period. If, how­
ever, records are made of only brief periods of activity,
response rate as an index leaves something to be desired by
way of assessment. Furthermore, the entire spectrum of
behavioral change in all its subtleties consequent to drug injection is not adequately observed, and those intervals when an animal does not respond at all to the Skinner box manipulandum is a testament to this. Miller (1957) has included Skinner box performance as only one of several ways by which the influence of drugs on animal behavior can be observed. The degree to which positive results of a given study depend on the amount or kinds of drug behavior that is assessed will to some extent determine the need to sample the range of techniques for observation. Furthermore, some indices afford more specific control and precision of measurement with certain drug effects than other indices do. Arvola, et al. (1953), for an example, have proposed the use of a "tilting plane" for the assessment of intoxicated behavior of rats after they have been given ethyl alcohol. Such an apparatus permits an observer to measure the angle to which the plane can be turned before an intoxicated rat falls off. This measure directly assesses motor coordination, a property of animal behavior that is greatly modified by ethyl alcohol. Hunt (1956) has reported a technique for assessing locomotor activity in a confined area using a grid pattern drawn on the floor of the area. Maher and McIntire (1960) used a similar technique in the form of a box with plexiglas sides and top to which strips of tape were attached that clearly divided the box into quadrants. These two techniques are well-suited to measure something like CER (conditioned emotional response),
and the dramatic quality of the effects produced by LSD-25 injection is remarkably like that of CER behavior.

Since the present investigation was primarily an exploratory one, several drugs were used to enhance the likelihood of gaining success. Because of this, rate of response in a Skinner box was chosen as the response measure since it could uniformly be applied to assess the behavior of all three treatment and control groups. Of all the objective response measures available, therefore, rate of response probably offered as much precision and control for such divergent effects as any other, with the exception of one point. The one point has to do with the intermittent use of this measure in assessment of drug effects to which the organism shows a tendency to adapt. Adaptation in this case can be defined in non-rigorous operational terms. Such behavior was inferred to have occurred when animals that had initially dropped from a previously attained asymptotic level, began to perform at an increasing rate of response each succeeding day in the Skinner box after receiving a drug injection. Such was the case with the group that received ethyl alcohol. Re-examination of Figure 1 showing this group's mean daily performance will reveal the gradual upward-directed trend that is broken only by the "depression effect" during stage III. The point to be made here is that, obviously, if a group's performance has already begun an upward trend in daily activity such as this, then its withdrawal from the drug will not
be nearly so obvious as that of a group which had not already begun such a trend. This, of course, assumes that the drug is of a quality which leads to increased activity once it is withdrawn from the animals. The saving grace of the alcohol group in this case was the "depression effect" noted on the second day of stage III. Nevertheless, one is led to wonder what the results would have been with, say, the Dexedrine group had the daily dosage been weaker. Would they not have shown an adaptation effect; and, if so, would the response measure have lent itself to the production of a trend that would have been deceiving by its continuous and smooth appearance from drug to placebo periods of administration? Obviously, this chance possibility leaves something to be desired in the way of precision and control with the kind of objective response measure used in this investigation.

One alternative which would provide a solution to this problem for future research with the Skinner box and drug behavior is that of reducing the number of subjects used and then assessing an animal’s activity for a 24-hour period. It would also be prudent to give thought to the use of a technique recently explored by Stone, et al. (1960). These investigators studied the effects of Dexedrine on rats using a Skinner box where interresponse interval was the response measure. Interresponse interval is the time between bar-pressing activity; in this case, responses were recorded on a revolving kymograph. This modification would obviously be
very sensitive to continuous activity that included times
when bar-pressing was completely inhibited by drug injections.

Besides the greater precision and more focused attention
that future research with this subject matter ought to have,
there are interesting speculations and viewpoints about the
meanings that can be sifted from the present investigation,
particularly that with ethyl alcohol. Ethyl alcohol and its
effects on human and animal behavior have been the subjects
of ever increasing research. Since the work of Masserman and
Yum (1946) researchers have been intrigued with how previous
experience of an organism can be related to its disposition
for ethyl alcohol. Efforts designed to explore this variable
and its influence on alcohol intake have included forced alco-
hol consumption (Richter, 1953), specific nutritional defi-
ciencies (Williams, Pelton & Rogers, 1955; Mirone, 1957),
drugs such as propyl thiouracil (Zarrow & Rosenberg, 1953),
and conflict behavior (Conger, 1951). Of all these, the
strongest case appears to have been made by Conger, whose
studies on the influence of alcohol on anxiety reduction are
by now very well known (Conger, 1951, 1955, 1956). This in-
vestigator showed that alcohol reduces the avoidance response
of rats placed in approach-avoidant conflict. Although con-
cern over the difference in recency or sequency of learning
of the approach and avoidance habits has recently been ex-
pressed by Miller (1956, p. 329) and Weiss (1958), this basic
paradigm has been generally accepted.
There seems to be little reason for arguing against the idea that preference for alcohol can be related to tension and anxiety. This general idea seems to meet with good reasoning and common knowledge (Horton, 1943; Ullman, 1952). The results achieved in the present investigation with ethyl alcohol, however, provide one with some provocative ideas on the subject of acquired alcohol preference. Without proposing alternatives to the idea that approach-avoidance conflict is the necessary condition relating to maintaining alcohol drive, there is yet a conceivable way of utilizing this theoretical viewpoint while still supposing that addiction can be initiated by some other mode. Hypothetically, if one could induce rats to acquire a drive for alcohol by introducing it to them as they played a passive role in this experience, it is conceivable that they could maintain a preference for it merely in order to avoid the prospect of its discontinuance. It appears plausible to suppose that once an organism is addicted to alcohol, the prospect of interrupting the addiction provides sufficient "anxiety" to motivate it to avoid the interruption, if it is free to do so. Nichols and Davis (1959) have thought it probable that the development of drug-seeking behavior in morphine addicted subjects results primarily from their desire to escape the withdrawal symptoms, and not from some inherent rewarding properties of morphine. Conger (1956) has suggested that conflict itself is tension-producing, although he primarily had reference to conflict-situations caused by conditions other than the prospect of
being withdrawn from alcohol.

The question of whether the drive toward addiction can be started when the organism plays a passive role (as in the present study where rats were injected) is purely an academic one, and may have little relevance to human addiction. The point on the role played by a need to avoid withdrawal symptoms, however, is not so unrelated. It is well known that the non-periodic heavy drinker requires excessive amounts of alcohol to stave off physiological withdrawal symptoms. Thimann and Gauthier (1959) have described the medical precautions that a physician must take with such an addict, who upon being withdrawn under controlled conditions may require sedatives in order to protect his life and health. Even though we have such practical knowledge from human care and treatment, we apparently do not know from experimental research the extent to which the use of alcohol itself may set off the repetitive pattern of drinking that may become a significant factor in alcohol addiction.

Apparently we do have some indication from the results of this research that the mere semblance of ethyl alcohol is enough to set off behavior which in some respects resembles that of what ethyl alcohol itself produces. The role that such a function may play in addiction may or may not be significant; however, the findings of this study regarding ethyl alcohol may have more to do with the role that placebos in
general can have in future drug treatment programs. The history of successful results with other agents (e.g., morphine, scopolamine hydrobromide) together with the present findings leads one to suppose that similar results can be found using other psychopharmacological agents. Positive results with agents of this type serve as a motive for supposing that mentally disordered patients might be maintained on the basis of relatively infrequent dosages of such medication. Nowadays certain types of mentally disordered people can be maintained only on high dosage rates of certain drugs, and often there are unavoidable toxic accumulations and side-effects resulting from such use. If the same essential results could be achieved with a program of treatment that included both placebos and drugs, the cost of treating patients would be lessened, and the dangers to the patient's health mentioned above could be reduced. The view that positive results with such drugs can only be achieved with those that are "meaningful" to the individual may be true. Several authorities support this contention or cite its importance (Franks, 1958; Gliedman, Gantt, and Teitelbaum, 1957; Pavlov, 1957, p. 142; Wolf, 1959). But according to Himwich's definition (Himwich, 1960) psychopharmacological drugs do affect the central nervous system, especially that portion having to do with "meanings." This would seem to provide all the more reason for supposing that the effects of such agents could be simulated with placebos.
On final point on the note about the use of placebos with human subjects. Kast and Loesch (1959) tested the efficacy of meprobamate and the antispasmodic agent trihexethyl iodide by presenting to patients suffering from anxiety and gastrointestinal difficulties a variation of attitudes of the doctor. The results indicated that the "medical environment" exerted a deep effect on the efficacy of even a potent drug. Altschule and Giancola (1960) found that blood glutathione level and eosinophil counts in 9 schizophrenics were reduced for several weeks following placebo injections. Three of the 9 showed laboratory and clinical improvement. Hankoff, Engelhardt and Freedman (1960) studied the placebo response in 103 chronic schizophrenic patients and found a positive response in 42 cases and a negative one in 20. Some people, after viewing results such as the above, have been quite chary of using placebos, although they do not doubt the existence of their effects (Tuteur, 1958). Other critics question the ethic in using a placebo with patients requiring active treatment (Cabot, 1906; Handfield-Jones, 1953). This questioning attitude is generated on the assumption that the placebo is a lie, and in the long run the lie is found out.

The problem of ethics raised by these latter critics is related to professional standards of conduct, and it is a thorny issue not to be dealt with extensively here. Several authorities, however, have suggested or implied that the use of placebos in the history of treatment of mental problems
is not at all new, and as such it belongs in the armamentarium of every doctor who works with patients (Borgatta, 1959; Conn, 1959; Gliedman, Gantt & Teitelbaum, 1957). The use of a placebo, like hypnosis and waking suggestion, utilizes the faith of the patient in his doctor. It would seem questionable to discount this kind of faith as a lie if its presence is really conducive to better health. It may be that to some extent the success of all therapeutic treatments is dependent on something like a positive attitude by the patient. Everyone is familiar with the attempts to account for the death of the primitive savage who is "voodooed" or otherwise superstitiously assaulted (May, 1950, p. 69). Most such accounts eventually mention the "faith" such victims had in the power of the voodooer. This may represent the most extreme case of how one's health can be affected by his attitude.

Further argument against considering the placebo as a "lie" has to do with what a placebo can represent to a person. If there is any reasonableness at all to the idea that certain functional mental disturbances can be basically considered as a problem which patients have in using certain semantics (Johnson, 1946; Korzybski, 1941), then basically the only practical techniques for dealing with such disturbances are through the use of meaningful situations. Apparently, of necessity these would have to be more or less unilateral situations designed to influence the patient in one direction.
only, namely: better mental health. If such situations happen to be like those of Pavlovian conditioning where a subject is given certain signals followed by, say, an aversive stimulus (cf. Bandura, 1961), why should he want to question the validity of the signal so long as his experience with it has made him a better adjusted and happier person?

The question about the above logic which still evokes thoughtful consideration about ethical practices has to do with the subject of just what constitutes "better mental health," and who are the people to decide its nature. Usually, where placebos are used with patients in manners so that they are not made to appear ridiculous, it is not the patient but the practitioners and experimenters who are most concerned over the subject of whether a placebo is a deception and therefore a problem for ethical considerations. Of course, since placebos are apt to be given for therapy under medical supervision, the ethics regarding their use are likely to be principally the concern of psychiatrists. Nevertheless, Leonard Krasner (1962), writing in the American Psychologist on the subject of ethical implications, has included placebos among two broad categories of influencing, persuasive and manipulatory techniques with which psychologists work. He cites several authorities who, having recognized the necessity for instituting certain attitudinal conditions in patients, are nevertheless aware of inherent dangers from the growing power of man to control human behavior. Krasner concludes
his treatise by noting that in particular, the 1953 formal statement of ethical standards for psychologists is a good first step on this subject, but it is not enough. The control of behavior "may be horribly misused unless the psychologist is constantly alert to what is taking place in society and unless he is active in investigating and controlling the social uses of behavior control." (Krasner, 1962, p. 203)
SUMMARY

An experiment was designed to study the hypothesis that the effects of ethyl alcohol, Dexedrine and lysergic acid diethylamide-25 on rats could be simulated with solutions of neutral isotonic saline. Past research with certain other psychopharmacological drugs, such as morphine and scopolamine hydrobromide, has indicated that such an experiment might be successful. If such were the case, then it was to be assumed that a placebo effect, according to the definition offered by Wolf (1959), had been established.

The design of the experiment employed forty albino male rats. These animals, which were not litter mates, comprised four equal-sized groups: three treatment groups and one control group.

All animals were assessed individually in terms of 15 minute daily response records from Skinner box performance, and in terms of subjective impressions of reactions to drug and placebo injections. The Skinner box, which did not automatically record animal activity, was adjusted to dispense a small food pellet on a fixed ratio of one pellet per two presses of the Skinner box lever.

After being placed on a 24-hour food deprivation schedule, and with the exception of the particular drug used, each
of the treatment groups separately underwent the following training sequences:

1. Pretraining in the Skinner box until each animal had reached an asymptote.

2. Continued training as above in the Skinner box for 15 days where prior to beginning each day of training, a buzzer and an intraperitoneal injection of a drug were presented.

3. Continued training in the Skinner box as above except that a neutral saline solution was substituted for the drug.

The control group underwent the same training conditions as that of the treatment groups, except that in the second sequence, all animals received distilled water injections instead of a drug.

The results of the investigation appeared to be partially successful. The data produced by the group that received ethyl alcohol conformed to expectations based on the experimental hypothesis. Results from the other two groups, however, did not support the idea that a placebo effect could be established under such conditions.
REFERENCES


Crisler, G. Salivation is unnecessary for the establishment of the salivary conditioned reflex induced by morphine. *Amer. J. Physiol.*, 1930, 94, 553-556.


Hankoff, Leon D., Engelhardt, David M., & Freedman, N.


patho-physiology of the higher nervous activity.


## Alcohol Group: Weight and Drug Dosage

<table>
<thead>
<tr>
<th>RAT</th>
<th>1st Day of Training</th>
<th>1st Day of Injection</th>
<th>Dosage From May 15 Through May 19</th>
<th>Dosage From May 20 Through May 25</th>
<th>Dosage From May 26 Through May 29</th>
<th>Dosage From May 30 Through to End</th>
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<td>375 g. 5.66 cc.</td>
<td>380 g. 5.70 cc.</td>
</tr>
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<td>1st Day of Injection June 5</td>
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<td>Dosage From June 8 Through June 9</td>
<td>Dosage From June 10 Through June 11</td>
<td></td>
</tr>
<tr>
<td>-----</td>
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<td>1</td>
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<td>.47mg/5.70 cc.</td>
<td>370 g.</td>
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<tr>
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<tr>
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<td>380</td>
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<td>370</td>
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<td>380</td>
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<td>385</td>
<td>410</td>
<td>.51mg/6.15</td>
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<td>.51mg/6.15</td>
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<td>.50mg/6.00</td>
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<td>385</td>
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<td>370</td>
<td>.46mg/5.55</td>
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Dexedrine Group: Weight and Drug Dosage Cont'd.

<table>
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<th>RAT</th>
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<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>370 •46mg/5.55</td>
<td>370 •46mg/5.55</td>
<td>365 •46mg/5.55</td>
</tr>
<tr>
<td>3</td>
<td>400 •50mg/6.00</td>
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<td>385 •48mg/5.78</td>
</tr>
<tr>
<td>4</td>
<td>340 •43mg/5.10</td>
<td>330 •41mg/4.95</td>
<td>340 •43mg/5.10</td>
</tr>
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<td>380 •47mg/5.70</td>
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<td>375 •47mg/5.63</td>
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<td>365 •46mg/4.48</td>
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<td>8</td>
<td>405 •51mg/6.08</td>
<td>410 •51mg/6.15</td>
<td>395 •50mg/6.00</td>
</tr>
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<td>400 •50mg/6.00</td>
<td>390 •49mg/5.85</td>
<td>385 •48mg/5.78</td>
</tr>
<tr>
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<td>355 •44mg/5.33</td>
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# LSD-25 Group: Weight and Drug Dosage

<table>
<thead>
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<th>RAT</th>
<th>1st Day of Training</th>
<th>1st Day of Injection</th>
<th>Dosage From June 28 Through July 3</th>
<th>Dosage From July 4 Through July 7</th>
<th>Dosage From July 8 Through July 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>315 g.</td>
<td>320 g.</td>
<td>0.8mg/4.80 cc.</td>
<td>305 g.</td>
<td>0.8mg/4.57 cc.</td>
</tr>
<tr>
<td>2</td>
<td>330</td>
<td>325</td>
<td>0.8mg/4.80</td>
<td>295</td>
<td>0.7mg/4.43</td>
</tr>
<tr>
<td>3</td>
<td>315</td>
<td>340</td>
<td>0.8mg/5.10</td>
<td>320</td>
<td>0.8mg/4.80</td>
</tr>
<tr>
<td>4</td>
<td>315</td>
<td>320</td>
<td>0.8mg/4.80</td>
<td>300</td>
<td>0.7mg/4.50</td>
</tr>
<tr>
<td>5</td>
<td>315</td>
<td>320</td>
<td>0.8mg/4.80</td>
<td>295</td>
<td>0.7mg/4.43</td>
</tr>
<tr>
<td>6</td>
<td>320</td>
<td>330</td>
<td>0.8mg/4.95</td>
<td>310</td>
<td>0.8mg/4.65</td>
</tr>
<tr>
<td>7</td>
<td>320</td>
<td>345</td>
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<td>0.8mg/4.80</td>
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<tr>
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<td>0.8mg/4.65</td>
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<tr>
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<td>320</td>
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LSD-25 Group: Weight and Drug Dosage Cont'd.

<table>
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<tr>
<th>RAT</th>
<th>July 12</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>285 g.</td>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
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<td>315</td>
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</tr>
<tr>
<td>4</td>
<td>300</td>
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</tr>
<tr>
<td>5</td>
<td>280</td>
<td>0.07mg/4.20</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>0.07mg/4.50</td>
</tr>
<tr>
<td>7</td>
<td>315</td>
<td>0.08mg/4.73</td>
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<tr>
<td>8</td>
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<td>0.07mg/4.28</td>
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<tr>
<td>9</td>
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<td>0.07mg/4.50</td>
</tr>
<tr>
<td>10</td>
<td>295</td>
<td>0.07mg/4.43</td>
</tr>
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</table>
### Control Group: Weight and Drug Dosage

<table>
<thead>
<tr>
<th>RAT</th>
<th>1st Day of Training (July 5)</th>
<th>1st Day of Injection (July 20)</th>
<th>Dosage From July 20 Through July 25</th>
<th>July 26 &amp; 27</th>
<th>Dosage From August 1 Through End</th>
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</thead>
<tbody>
<tr>
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<td>4.95 cc</td>
<td>330 g.</td>
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<td>310</td>
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<td>310</td>
<td>4.65 320 4.80.</td>
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<tr>
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</table>
VITA

Charles Jackson Black, Jr. was born in Dallas, Texas on April 14, 1929. He is the youngest of three children by Charles J. and Beula Bell Black. He was graduated from Sunset High School in Dallas in 1946, after which he enrolled at Texas Technological College in Lubbock, Texas. After receiving the degree of Bachelor of Science from that institution in 1952, he entered the armed services and served two years in the Army Engineers. Upon being discharged and returned home he enrolled part-time at Southern Methodist University, from which he received the Master of Arts in 1958. In 1958 he enrolled in the graduate school of Louisiana State University, and became a candidate for the degree of Doctor of Philosophy. Professional experience in psychology includes work at Timberlawn sanitarium in Dallas, East Louisiana State Hospital at Jackson, and a two year stint in the intern program at Southwestern Medical School, also of Dallas. Professional affiliations include membership in the American Psychological Association and the Southwestern Psychological Association. Presently he is a Clinical Psychologist at Terrell State Hospital, Terrell, Texas, and he is an instructor in the Department of Psychology, Arlington State College, Arlington, Texas.
EXAMINATION AND THESIS REPORT

Candidate:  Charles J. Black, Jr.

Major Field:  Psychology

Title of Thesis:  An Attempt to Establish a Placebo Effect in Rats with Psychopharmacological Agents.

Approved:

[Signatures]

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination:

January 17, 1963