THE EFFECT OF THONZYLAMINE HYDROCHLORIDE AND PHENOBARBITAL SODIUM ON CERTAIN PSYCHOLOGICAL FUNCTIONS

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A. INTRODUCTION AND PROBLEM

During the past five years several new chemical agents have been isolated or synthesized which have the physiological result of counteracting the effect of histamine in the body (2). These agents are known as antihistamines. Histamine and the antihistamines play an important role in anaphylaxis, allergy, and possibly, the common cold. An undesirable "side-effect" attributed to the antihistamines is that some of them tend to produce some feeling-state such as drowsiness or depression which may last for several hours after the ingestion of each dose. This feeling-state is a subjective experience. Whether it occurs to an equal degree in all individuals, is actually produced by any or all of the antihistamines, or whether the feeling-state actually influences to any marked degree the efficiency of psychological function has not been experimentally demonstrated.

A commonly used antihistamine is thonzylamine hydrochloride \( (N, N\text{-dimethyl-N'\text{-2-pyrimidyl-N'}-p\text{-methoxybenzyl-ethylenediamine})\). \( ^2 \) This agent is sold without prescription in 25 milligram tablets for the treatment of the common cold. It is employed in the treatment of allergic conditions by physicians in the form of 50 mg. tablets. Because of its wide acceptance and usage it seemed desirable to find what, if any, effect it might have on the efficiency of psychological test performance, particularly on objectively measurable performance.

Since there is little agreement among psychological investigators as to objective tests which might be suitable to demonstrate drug effects we felt...
it necessary to try out a variety of simple tests which might be sensitive indicators of possible changes produced. Since there was no way of foretelling whether thonzylamine would act as a stimulating or as a soporific agent it was necessary to establish with the tests employed the effects of ingested agents which previous investigators had shown to be associated with changes in psychological test scores. It was necessary, also, to make use of a placebo in order to ascertain the variability of test performance when no agent was ingested. In a preliminary trial series of experiments we received an unfortunate but educative demonstration of the effectiveness of suggestion. We told our subjects that we were doing an experiment on the effect of drugs. Certain of the subjects reacted so strongly to the "drug" effect that no credence could be given to any of the test scores.

In all succeeding experiments we made use of subjects who were naive so far as psychological tests were concerned. We "abolished" the word drug from the vocabulary of every member of our experimental team. We told everyone connected with the experiments that we were studying the effects of certain chemical agents which might augment vitamin action. We did give in combination with every ingested dose of any agent, including the placebo, 5 mg. of ascorbic acid (vitamin C) which has never been shown to have any psychological or physiological effect at such a small dosage in the normal individual.

In all of these experiments the agents ingested were given in capsules of the "0" or 700 mg. size. The agent contained in the capsule was "diluted" with lactose where small doses were employed so that all doses were of the same bulk. The placebo capsules contained only lactose. In the preliminary experiment the stimulating agent was dextro-amphetamine (dexametidine) in 5 mg. doses, the soporific was phenobarbital sodium in 15 mg. doses, while the antihistamine thonzylamine was given in 25 mg. doses. As noted above, ascorbic acid doses of 5 mg. were given in a second capsule with each dose. The capsules were made up according to a color code so that they could be identified by the experimenters.8

After several trial investigations a complete preliminary experiment was carried through using the smaller dose combinations with 24 normal subjects (1). The agents were ingested by each subject 5 hours, 3 hours, and one-half hour before the subject started the tests. The design of the experiment randomized the order of the ingestion of the agents by each subject over four successive days. The tests employed were choice speed response, cancellation, speed of tapping, critical flicker fusion (strobotac), a con-

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8All capsules were made available to us by the Nepera Chemical Company.
tinuous problem experiment, reading comprehension, and rating scales of subjective states.

In the analysis of the data obtained it was assumed that persons who had taken dextroamphetamine would tend to give scores differing from those obtained when they took the placebo, which in turn might be expected to reflect only the effects of continued practice on the test in question. It was hoped that it would be possible to locate the effects of the thonzylamine in reference to these standards. The analysis of the data obtained indicated that these assumptions were generally correct but that either the dosages employed had been too small or the variability of the individual subjects too great, for the obtained differences to reach the level of statistical significance for any of the individual tests. There was a clear tendency for the thonzylamine to approximate closely the placebo effects with each test employed. Furthermore an overall measure derived from the tests did show that a statistically significant difference in mean score was obtained when phenobarbital was compared to dextroamphetamine.

In view of these findings the experiment was redesigned as follows: The comparison was limited to placebo, thonzylamine, and phenobarbital. The dosage was increased to 50 mg. of thonzylamine and 50 mg. of phenobarbital. Dextroamphetamine was omitted since it seemed clear that thonzylamine would be nearer the placebo in effect and any possible stimulation could be gauged by comparing it to the placebo. A three-day placebo-agent-placebo schedule was adopted so that all subjects received placebo on the first and third days. On the second day one-third of the subjects received placebo, one-third phenobarbital and one-third thonzylamine. If P represents a placebo dose, Ph a phenobarbital dose, and T a thonzylamine dose, then the schedule of dosage went as follows: Monday night on retiring — P; Tuesday four hours, two hours, and one-half hour before the tests started — P; Tuesday night before retiring — either P, Ph, or T depending upon the experimental group to which the individual belonged; Wednesday four hours, two hours, and one-half hour before the tests started — P, Ph, or T; Wednesday night before retiring — P; Thursday four hours, two hours, and one-half hour before tests started — P. The dose one-half hour before the test started was given at the laboratory by the manager of the experiment. The doses were made up in appropriately labelled pill boxes so that each box indicated the exact time the capsules in the box should be taken.

In this experiment 72 normal persons (30 men, 42 women) of an average age of 30 years (range 21-41) who were of superior educational achievement (61 college or graduate students, 11 high school graduates)
volunteered their services and were given a small honorarium for their cooperation. All were interviewed by a physician before the experiment started. No one of them had any heart condition, active allergy, chronic or intercurrent disease, or was pregnant at the time. No one was using any antihistamine agent or phenobarbital at the time. On the schedule of dosage given each person the following statement was printed:

We are investigating the effect of certain combinations of chemical agents which may affect psychological test performance. In order to avoid subjective effects such as fatigue, suggestion and the like, the agents used are given in differing amounts. Part of the time the dose is a placebo, that is milk sugar which has no effect. The investigators doing the experiment do not know which agent is being employed at any particular time.

In order that our results may be as clear-cut as possible we wish to avoid including in our study group anyone who is pregnant, has an allergy or a heart condition.

The schedule which we request that you personally follow with respect to time of taking capsules and pills, and for appearing for tests is as follows; etc.

A laboratory was set up in a six-room building in the village where all the subjects were resident. Twenty-four subjects were studied on Tuesday, Wednesday, and Thursday of three successive weeks. Subjects came to the laboratory at 15-minute intervals between 10 A.M. and 5:45 P.M. each day, each subject coming at the same time each day.

On Monday of each week each person was interviewed by a physician, and if no medical indication of unsuitability was found he was introduced to each member of the experimental team. Each experimenter explained the tests which he would administer and had the subject try the procedure until it was clear that he understood fully and completely the task involved. We attempted to avoid any formal practice with any one of the tasks on Mondays. Lastly the subject was carefully instructed by the manager of the experiment about the capsules to be taken and the time of each dose. He was instructed to write on the pill box the actual time, to the minute, that he took each particular dose. The manager answered questions raised by the subjects and was quite clear and frank on every point save that of the identity and the possible effects of the agents. On these points the manager truthfully said he was not acquainted with the contents of any particular capsule or of the effects that the capsule might produce with any particular person but that previous experiments had shown that no one was made sick or perceptibly inconvenienced. The assigning of the particular agent to any individual was made on a completely random basis.
Seven tests and an interview were given each subject on each of three successive days. The tests were given in the same sequence every time. Each test took a fixed number of minutes so that the time relation of test to dose was constant. The same experimenter gave each subject the same tests each day.

B. Description of Tests and Interview

1. Choice Speed Test (CST)

This test consisted of depressing the (+) or (−) key of a Monroe automatic calculating machine which had a speed of 600 number changes a minute. The subject was instructed as follows:

Please note the register on the calculating machine. Notice that when I press the (+) key the numbers on the register increase very rapidly in size and when I press the (−) key they decrease in size. Now I will set the register so it shows all “0’s.” Then I will call off a series of numbers, like 13, 24, 17, 31. As I call the number press the (+) or (−) key which will start the machine going in the direction of the number I have called. Try to get your finger off the key so the machine will stop at the number I call.

A series of 50 numbers was called. Record was made of the digits shown by the register on the machine after each finger withdrawal. Since the speed of the machine provided numbers which represented tenth-of-second response measures, the score was derived by summing up the deviations shown on the register at each stopping of the machine and dividing the sum by 50. A false reaction, where the machine was started in the wrong direction by punching the wrong key or when the number called was already showing on the register due to over- or undershooting on the previous trial, was given the average score of the correctly carried through responses of the series. The final score then was the average number of tenths-of-seconds error in a 50-trial choice reaction test, which took approximately three minutes to finish.

2. Continuous Problem Experiment (CPE)

The subject was seated before a panel of lights and a table of keys which controlled the lights. [This test has been described by King (3), and by Nesberg and Smith (4)]. He was instructed as follows:

Notice that a green light and a red light are lit. Think of the red light as the point and the green light as the head of an arrow. Then the arrow is pointed either up, down, right, or left, which is the direction and name of one of the four groups of switches here on the table.
and which you are to manipulate. Next attend to the white light. The position of the white light indicates which particular switch in the up, down, right, or left group you are to turn. When you turn the proper switch you will see that all the lights change and a new combination of a green, red, and white light appears. Now select the proper switch again by imagining the red light is the point of an arrow and the green light is the head of the arrow and then attend to the white light which shows the proper knob in the group. Work as rapidly as you can for the next three minutes.

The score was the number of correct solutions minus the number of errors (wrong switches turned) during three minutes.

3. Cancellation (Can-A)

This test consisted of 29 lines of printed pied type composed of 50 random appearances of each of the 26 letters. The subject was instructed:

Please cancel out by marking through with this pencil all the B, C, G, and N's. Work as rapidly and accurately as possible. I will say "Stop" at the end of three minutes.

Four different letters were cancelled on Days 1, 2, and 3 respectively. The score used was the number of correctly cancelled letters divided by the total number of letters scanned in three minutes; that is, an accuracy quotient (6).

4. Tapping, Speed (Tap-S) and Tapping, Endurance (Tap-E)

The tapping test was carried through with all subjects in two fashions which we shall refer to as Tapping, Speed (Tap-S') and Tapping, Endurance (Tap-E). In both parts of the test the subject was seated on a metal stool at a table on which there was fastened a 3 x 6 inch aluminum plate divided by a wooden block, .5 x .5 x 3 inches. He was instructed as follows:

With your index finger tap just as rapidly as you can, first one and then the other half of this plate for 10 seconds. Then you will rest 20 seconds, tap again 10 seconds, rest 20 seconds, and finally tap another 10 seconds.

The subject was connected through a high sensitivity relay and the stool so that when he touched the plate he completed the circuit and actuated an electrical counter. (The flow of electrical current was so small that no sensory effects were ever noted.) His score on Tap-S was the sum of the number of taps for the three 10-second intervals.
He then rested a minute and was told, "Now tap in the same way just as rapidly as you can but this time for 60 seconds." The number of taps during this period constituted the Tap-E score.

5. Critical Flicker Fusion, Episcotister and Strobotac (CFF-E and CFF-S)

This test is one in which a determination was made of the point at which a patch of flickering light apparently becomes a steady light, or at which a steady light is first perceived to flicker. The critical point at which flicker becomes steady was expressed in cycles per second (cps). Two methods were used which will be referred to as Critical Flicker Fusion, Episcotister (CFF-E) and Critical Flicker Fusion, Strobotac (CFF-S).

The CFF-E experiment consisted of the viewing of a circular spot of light of about 0.5 inch diameter at a distance of 14.3 inches (visual angle of 2°). This spot was illuminated by a white Mazda (tungsten) lamp. A focused beam of light from the lamp was interrupted by an episcotister (a spinning sector disc) which cut the beam at its focal point producing two pulses of light and two equally long dark intervals for each revolution of the disc. The disc was mounted on the shaft of a motor whose speed would be accurately governed by a General Radio Company Type 1701 AK Variac. The speed of the motor could be read in revolutions per second from a specially calibrated dial. The white matte field which the subject viewed through a stereoscope hood was uniformly illuminated by white light having a brightness of 27.6 millilamberts. The spot of light had an apparent brightness of 2.4 ml. when measured just above apparent fusion. The subject was instructed as follows:

Look into this box. You see a small bright circle of light. Now I will make that spot flicker, and after it starts flickering I will make it appear steady. I want you to observe it closely and call out "Steady" or "Flicker" whenever it seems to change.

Five binocular determinations of the flicker-to-steady and five of the steady-to-flicker were made for each subject. His CFF-E score was the average of these 10 determinations.

The CFF-S was determined in the same way and with the same instructions as for CFF-E. In this experiment the spot of light was red-orange in color and had an apparent brightness of 6.2 ml. when measured just above fusion. The surrounding field of view had an apparent brightness of 9.3 ml. and was illuminated by red-orange light reflected from a white matte surface. The spot was illuminated by the lamp of a General Radio Company Type 631-B Strobotac. This instrument is essentially a neon
lamp which is caused to flash by the discharging of a condenser. The rate of discharge of the condenser can be accurately set, varied, and controlled. The rate can be read from a dial which is calibrated in cycles per minute. The light in the CFF-E experiment was on half of each cycle and off the other half, that is the light-dark ratio was 1-1. In the CFF-S the flash of the lamp had a duration of 48 microseconds with, comparatively speaking, a very long dark interval before the next flash. When CFF-S fusion was at 38 cps the L-D ratio was 1-547. In this experiment there were three major differences between CFF-E and CFF-S: (a) color of spot and surround, (b) brightness of spot and surround, and (c) the light-dark ratio. The light-dark ratio was probably the most important difference so far as this investigation was concerned.

6. Interview

On each day of the experiment the subject went to an interviewer after completing the seven tests. He was engaged in conversation for 10 to 15 minutes. The interviewer attempted to get the subject to provide relevant information on three topics: (a) How did each one of the tests seem to go today? (b) How have you felt today in contrast to yesterday? (c) Do you think that the capsules you've taken today have anything to do with the way you feel today? The interviewer had had considerable previous experience in clinical interviewing. He was casual in his conversation and questions, and avoided any suggestion of praise, blame, or kind of answer desired. The interview was recorded in symbols on a coded sheet so that there was no apparent "history taking" and the easy flow of conversation was maintained. The coded record could be translated into an almost verbatim account.

C. Results Obtained With Tests

The means and standard deviations for the tests for the entire group studied and for the three agent subgroups are given in Table 1.

Application of appropriate statistical procedures to the means given in Table 1 indicated that the mean of the placebo group and of the phenobarbital group differ significantly on the second day for the Tap-S, Tap-E, and CFF-E tests when the differences between the groups on the initial day are allowed for. In the case of CST, CPE, Can-A, and CFF-S the

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<tr>
<th>Day</th>
<th>Entire group</th>
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<th>Thionylamine</th>
<th>Phenobarbital</th>
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<th>Thionylamine gain or loss</th>
<th>Phenobarbital gain or loss</th>
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TABLE 1
MEANS, STANDARD DEVIATIONS, GAINS AND LOSSES FOR THE SEVEN TESTS

CAMERON LANDIS AND JOSEPH ZUEIN
means differ, in that the means of the phenobarbital group are lower than those of the placebo group but the difference was not statistically significant. In brief, the phenobarbital group obtained an average score on one of the tests of flicker fusion, and on tapping, speed, and endurance, which was significantly different from the mean of the placebo group. The average score on the phenobarbital group was lower on the choice speed test, the continuous problem experiment, cancellation and strobotac flicker, though not to the point of statistical significance.

The thonzylamine group differed significantly from the phenobarbital group in the same direction and almost as significantly as the placebo group did for the Tap-8, Tap-E, and CFF-E. On the other tests the mean of the thonzylamine group (when corrected for differences in original level) lay between the phenobarbital and the placebo average, but nearer to the placebo figure. Otherwise stated, thonzylamine had no effect on any one of the test performances which we used. When compared to the depressing effect of phenobarbital it showed a convincing lack of effect on any one of these objective measures.

D. Analysis of Information Obtained from Interviews

So that the reader may have some idea of the sort of conversational remarks collected, the following samples are given. Remarks of placebo subjects who thought that the capsules had a possible effect were: "I'm somewhat stimulated. I feel like when I've taken dexedrine. I feel positive it's the pills and not suggestion [2]—the first day they had no effect; the second quite pronounced effects; today I'm just normal [3]." Another subject said, "I feel lazy today [2]—I felt in a daze yesterday, jittery-like [3]."

Sample remarks of the subjects who ingested thonzylamine and who thought it possible that the capsules had had a positive effect were: "I was quite nervous till bedtime yesterday; I don't know why [3]." "I'm jittery today, but it could be loss of sleep [2]." "Yesterday I was very nervous but today I'm quite calm [3]." Sample remarks of subjects who thought that thonzylamine had a negative effect were: "I've felt lazy and sleepy all day; no energy [2]—feel a lot better today [3]." "I feel weak and washed out [2]—yesterday afternoon was a lousy day [3]."

The subjects who had ingested phenobarbital and felt a positive effect made the following remarks: "I feel very good. I don't know whether

*The figure inserted at the end of the remark indicates in which of the three days of the experiment the remark was made.
it's the pills or not but if it is I want a load of them [2]." "It's a question of more energy today; also I'm calmer [2]—yesterday the pills made me feel good [3]." The phenobarbital subjects who experienced a negative effect (sleepy) made remarks such as the following: "I feel terribly sleepy today [2]—I feel fine. I'm not sleepy today [3]." "I've felt woozy since 1:15, I always have my ups and downs but not quite like this [2]." "I was sleepy all day yesterday; maybe it was the pills. Today I'm all right [3]."

Typical of the remarks of subjects who denied any change in feeling state after ingestion of either agent was the following made by a phenobarbital subject on the third day: "I've felt no different any day. Maybe I always had placebos."

It seemed to us that the fairest way to evaluate these subjective reports was to read each report through without knowledge of the agent and to try to see if any evidence could be interpreted as indicative of either "No difference," "Positive feeling-state," or "Negative feeling-state." This was done independently by two of the investigators. Most of the evaluations agreed but such disagreements as occurred between the two were reviewed and an agreement reached. Where no clear-cut opinion had been expressed by the subject we classed as a negative feeling-state any mention of one or more of the following regardless of agent ingested or day of occurrence; sleepy, tired, more relaxed, queasy, dopey, dizzy, heavy head, fuzzy mind. We classed as a positive feeling-state; peppy, feels like benzedrine or dexamphetamine, gay, nervous, jittery, energetic, feel fine, best yet.

After we had made these evaluations of feeling-states we again reviewed the interviews to ascertain the alleged source of each evaluation of "Negative," "Positive," or "No effect." The evaluations were based on reports where the subject said he was (a) sure that the capsules were responsible for his feeling-state, (b) thought that the pills might be ("maybe") responsible, (c) and other remarks which he made which the experimenters felt indicated positive or negative feeling-states but which were not specifically related to the capsules by the subject. This review is presented in Table 2.

In Table 2 we have put together all subject-day interviews when placebo had been ingested, namely 168, in contrast to 24 each for thonzylamine and phenobarbital. Consideration of this table leads to several interesting conclusions.

1. In 141 instances out of 168 (84 per cent) normal subjects who received a placebo reported a "normal" feeling-state. In the remaining 27 instances (16 per cent) if the state was unusual it was twice as apt to be negative as positive, that is more apt to be drowsy than energetic.
<table>
<thead>
<tr>
<th></th>
<th>Entire group</th>
<th>Negative Feeling-State</th>
<th>Positive Feeling-State</th>
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<td></td>
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2. Some difficulty is inherent in any attempt to characterize in a simple fashion the feeling-state which the subject conveyed to the interviewer. We have given samples of the remarks and of the adjectival characterizations employed. When phenobarbital had been ingested, the reports we have classified as negative feeling-state would ordinarily be called "sleepiness" or "drowsiness" while the positive state would be called "calm" or "relief of tension." The reports we have classified as either negative or positive feeling-state after the ingestion of thonzylamine are not so clear-cut so far as a conventional classification is concerned. Subjects who ingested thonzylamine were sure, or thought it probable, that they had taken an agent which induced their subjective state statistically significantly (probability less than .01) more often than when they had ingested a placebo. Although thonzylamine and phenobarbital did not differ significantly in the degree to which they induced negative feeling-states, it will be noted that more of those who had ingested thonzylamine (59 per cent) were sure or thought it possible that the capsules had resulted in their feeling-state than was the case with those who had ingested phenobarbital (46 per cent). This discrepancy seems to be due to the fact that fully one-third (6 out of 17) of those who felt some effect after ingesting phenobarbital failed to connect the capsules with their feeling-state, while in the case of those who ingested thonzylamine only one individual out of the 14 failed to attribute their feeling to capsules.

3. Thonzylamine and phenobarbital produced a positive feeling-state twice as frequently as did the placebo (8 per cent compared to 4 per cent). In brief, the thonzylamine and phenobarbital were associated with a subjectively discriminated feeling-state which might be either positive or negative, beyond the level of statistical significance (probability less than .05).

4. Although the subjective feeling-state was significantly more often negative than positive for both the thonzylamine and phenobarbital, only phenobarbital produced significantly changed scores (as noted above) in three of the seven objective tests employed.

In view of these relationships we retabulated all scores obtained on each of the seven tests to see whether either agent when it produced either a positive or negative feeling-state gave any reflection in a gain or loss on the test performance. There were 30 subjects whose interviews indicated no effect on the second day, 33 who were negative, and 9 who were positive. Table 3 gives the comparisons of the mean gain or loss in the second day score.

In considering Table 3 it should be remembered that the choice speed
test (CST) was one where a decreasing score meant a more efficient performance. This being true then the only failures to gain with practice on Day 2 compared to Day 1 on the part of the no-effect group was on Can-A and for the negative group on CFF-E. The means of the positive group show a gain for every test. In brief, there is only one instance where a negative feeling-state was reflected in the scores when an agent had been taken, namely CFF-E. In order to see whether the thonzylamine and phenobarbital had comparable effects on performance when they induced comparable feeling-states the tabulation given in Table 4 was made.

Again recalling that a minus entry for CST represents a gain in efficiency, examination of the figures in Table 4 may be summarized as follows:

1. There is no regularity in gain or loss in mean score on CST, CPE,

<table>
<thead>
<tr>
<th>TABLE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN GAIN OR LOSS IN TEST SCORE AS RELATED TO FEELING-STATE AND AGENT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Thonzylamine</th>
<th>Phenobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-effect</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>No.</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>CST</td>
<td>-1</td>
<td>.04</td>
</tr>
<tr>
<td>CPE</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Can-A</td>
<td>.05</td>
<td>-0.1</td>
</tr>
<tr>
<td>Tay-S</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Tay-E</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>CFF-E</td>
<td>.2</td>
<td>-.4</td>
</tr>
<tr>
<td>CFF-S</td>
<td>.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Can-A, or CFF-S when the negative or positive feeling-state experienced was associated with placebo, thonzylamine, and phenobarbital. Otherwise stated, four of seven tests fail to indicate in a regular fashion that the feeling-state attributed to the agent ingested and the gain or failure to gain on the tests on the second day are associated.
2. The negative feeling-state associated with ingestion of thonzylamine was never associated with an average loss in score on any test. Negative feeling-state associated with phenobarbital was associated with average loss in scores on speed and endurance on the tapping test and episcotister flicker (Tap-$S$, Tap-$E$, CFF-$E$). These differences were not sufficiently large to be statistically significant.

3. The positive feeling-state which was reported by two subjects who had ingested phenobarbital was associated with loss in scores on Tap-$S$, Tap-$E$, and CFF-$S$. The two subjects who reported the positive state following thonzylamine showed a marked gain on these same tests. Because of the limited number of instances in which a positive state was reported there can be no particular significance determined but the contrary tendency of effect by the two agents is most suggestive.

4. It was shown earlier that Tap-$S$, Tap-$E$, and CFF-$E$ were sensitive indicators of the effects of phenobarbital. It is now apparent that these same tests are differentially sensitive to the feeling-states associated with the ingestion of thonzylamine and phenobarbital. It is also apparent that the negative feeling-state induced by thonzylamine and that induced by phenobarbital are not equally associated with an interference of efficiency on objective test performance. Ingestion of phenobarbital may give rise to a report of no effect, negative or positive feeling-state; in any of these the efficiency as indicated by the three sensitive tests is reduced. Ingestion of thonzylamine may give rise to a report of no effect, positive or negative feeling-state, but in no one of the seven tests employed were the scores effectively reduced.

E. Discussion

The tests which we used are commonly held to be associated with differing physical and mental operations, hence there is no presumptive reason why either thonzylamine or phenobarbital should affect all tests equally or in the same way. Sollmann (5) notes that the barbiturates, including phenobarbital, have "marked variations of the central response with different individuals, including delayed effects, extreme depression, excitement, even mania."

The dosage of phenobarbital employed in this experiment, 200 mg. with 150 mg. of the total ingested during the 4½ hours before the tests started, gave rise to no extreme reactions although the subjective feeling-state induced did vary from subject to subject. The same was true for thonzylamine.

In the choice of tests employed we were guided by a double objective. We desired sensitive tests, i.e., tests which would give a definite change
in score when either phenobarbital or thonzylamine had been ingested in contrast to the change when placebo had been ingested. Second, we hoped to find tests which were representative of a variety of psychological functions so that we might have some indication of whether the agent affected one sort of function rather than another.

The choice speed test (CST) is largely a reaction-time indicator although some degree of attention and decision are involved. CST was more acceptable to the subjects than the conventional choice reaction-time experiment of reacting to two lights of different color by pressing the appropriate key connected with a chronograph. The test as we used it was done by most subjects as a kind of game in which the object was to catch the right number on the dial as often as possible. The test indicated some day-to-day practice effect in that the average score decreased (.136, .128, .123) on the three successive days while the standard deviation remained relatively constant. The phenobarbital group failed to show as much practice gain on the second day as did the placebo or thonzylamine group. The failure was not associated with feeling-state since the most marked mean failure on this test was shown by the nine subjects who reported a positive feeling-state on the second day (Table 3). In general this test indicated tendencies, but was not particularly satisfactory as an indicator of either drug effects or feeling-state.

The continuous problem experiment (CPE) was originally devised but not used, by the Army Air Forces in World War II. King (3) used the test before and after psychosurgery with mental patients. He stated: “We desired to observe by this task . . . the patient’s ability to bear in mind principles once learned in face of a minor stress situation—confusing spacial relationship and timed performance—for a prolonged period of time. . . . Contrary trends were observed in the operatee and control groups which generally showed ‘better’ performance . . . on the part of the control group.”

In the present experiment a very rapidly accelerating day-to-day learning function was obtained (57.5, 67.2, 75.8). In reviewing the gains or losses in score made by individual subjects on Day 2 it was found that no thonzylamine subject failed to gain on Day 2 while two placebo subjects and four phenobarbital subjects failed to gain. In spite of this, the average gain of the thonzylamine and phenobarbital group was the same, while the positive or negative feeling-state was reflected by no regular trend in the mean score of the subgroups. This test was the least indicative of drug effect or feeling-state of the seven which were employed. The lack of discriminating power was in all probability due to the rapidity of the practice effect which
obscured all other indications including whatever differential sensitivity the agents may have had on the ability to benefit from practice.

The cancellation test (Can-A) has been employed in a wide variety of psychological experiments. Various investigators have held that this test measures or indicates functions such as attention, discrimination, rate of perception, concentration, and fatigue. We tried a variety of different methods of scoring this test in the search for a score which would be most differential between the placebo and phenobarbital group. No method tried had any particular advantage, hence, we used the accuracy score (number of letters surveyed in 3 mins., divided by the number of correct responses), which seemed the simplest representative score. In Table 1 the mean gains of the thonzylamine and phenobarbital groups were shown to be inferior to the gain of the placebo group. In Table 4 it was shown that the negative state as reported by the placebo group actually is accompanied by a loss in mean score (gain in efficiency), while similar reports by the thonzylamine and phenobarbital groups are not accompanied by a loss. In general, cancellation is a better indicator of feeling-state than of drug effect but in this experiment it was not a sensitive indicator of either.

The tapping test is one of the simplest tests used in psychological investigations and one which has frequently been found to reflect more or less significantly a state of impaired psychological efficiency. As here used it may be regarded as an indicator of the ability to produce short bursts of speed (Tap-S), and to maintain a high psychomotor output at a maximum rate for a one-minute period (Tap-E). This function is not subject to any considerable practice effect in adults. As Table 1 shows the Tap-S average score was 140, 145, 148, and Tap-E 276, 282, and 290 for Days 1, 2 and 3 respectively.

On Day 2 the mean of the thonzylamine group increased seven points on both Tap-S and Tap-E while the phenobarbital group lost two and one points. The second day score of the phenobarbital group, when corrected for initial level on Day 1, was significantly different from either that of the placebo or the thonzylamine group. In Table 3 it will be seen that both tapping scores show smaller gains when the feeling-state was reported as negative and larger gains when it was reported as positive. Table 4 shows that the loss in score when a negative state prevailed comes for the most part from the phenobarbital group, while the gains when a positive state prevailed come from the thonzylamine group. Tapping is a sensitive test of the depressing effect of phenobarbital, but it remains unaffected under thonzylamine. As an indicator of feeling-state it is not discriminative for either the
negative or positive feeling-state produced by phenobarbital or thonzylamine.

Critical flicker fusion is one of the most delicate indicators of functional efficiency of the retina and/or the central nervous system which is available. It is varied by many conditions inherent in the organism such as metabolic level, state of light or dark adaptation, or fatigue. It is varied by many conditions attendant on the stimulus such as brightness, color, or light-dark ratio of stimulating light, as well as by the same variables in the immediate surround of the flicker test patch. We attempted to hold as many of these variables constant as was possible under the conditions of this experiment. As Table 1 shows, the CFF-E and CFF-S means of the entire groups were remarkably constant from day to day, 38.0, 38.2, and 38.2 cps and 36.6, 37.3, and 37.3 cps respectively. The standard deviation for each of the six means is relatively small. Since each group started with a somewhat different mean it was necessary to make the appropriate statistical corrections for the differences in means on Day 1 in order to be sure that the changes shown by the group means on Day 2 were significant. When these corrections were made, the differences between the phenobarbital and either the thonzylamine or placebo were statistically significant at the .01 level for CFF-E. The differences for the CFF-S were not statistically significant, though the tendency for change was in the same direction as that of CFF-E. A review of the literature indicated that the color employed in the flicker experiment had never been shown to be differentially affected by the action of drugs or chemicals, while several investigations have shown that the variation of the light-dark ratio does give differential effects with respect to physical pathology or psychological functions. For this reason we are inclined to attribute the difference in results which we obtained to the difference in the light-dark ratio. Table 3 shows that CFF-E reflected the negative feeling-state markedly while CFF-S tends to do so. Table 4 indicates that all agents were associated with a lowered threshold when a negative state was reported. When a positive state was reported an elevation in threshold occurred for the placebo and thonzylamine groups but not for the phenobarbital group. This relationship is shown by both CFF-E and CFF-S, though the former shows it more clearly, but neither of these differences is sufficiently large to be statistically significant. Critical flicker fusion (CFF-E) proved to be a sensitive indicator of negative feeling-state either when that state was associated with placebo or phenobarbital but not when it was associated with thonzylamine. This we regard as evidence of the fundamental difference in physiological basis of negative feeling-state produced by phenobarbital in
contrast to that produced by thonzylamine. The CFF-S results were in the same direction but not statistically significant.

F. Summary

The effect of the ingestion of four doses of 50 mg. each of thonzylamine (an antihistamine agent) and phenobarbital (a soporific agent) have been studied in groups of 24 normal adults and contrasted to the effect of similarly administered placebos in a group of 24 normal adults. All 72 persons received placebos on the first and third days while the agents being investigated were given on the second day. Special precautions were taken to obviate insofar as possible variations which might be attributed to suggestion and motivation. The tests employed were choice speed test, continuous problem experiment, cancellation, tapping speed and endurance, and critical flicker fusion point determined in two ways. Subjects were interviewed at the end of each experimental period in order to determine their impression of their feeling-state on that day.

1. Tapping, both speed and endurance, and the flicker fusion point with an equal light-dark interval proved to be sensitive indicators of a decreased efficiency at a statistically significant level, on the ingestion of this dosage of phenobarbital no matter what the subjective feeling-state of the individual may have been.

2. The other four tests indicated a tendency for phenobarbital to decrease test efficiency in contrast to the placebo but the change did not achieve the level of statistical significance.

3. No statistically significant changes were produced in average scores between placebo and thonzylamine with any of the seven tests. In every test the thonzylamine average was nearer the average of the placebo than it was to the average of the phenobarbital after appropriate corrections for differences in initial level had been made.

4. The interviews gave evidence that the subjects experienced either a negative feeling-state (tired, sleepy, relaxed, lazy) or a positive feeling-state (jittery, peppy, energetic) significantly more frequently when they had ingested phenobarbital or thonzylamine than when they had taken the placebo. A greater degree of subjective certainty that the capsules ingested were responsible for the feeling-state was associated with thonzylamine than with phenobarbital.

5. That the subjective feeling-state is an unreliable indicator of objective performance was best shown by the finding that only the flicker fusion point (CFF-E) was apparently related to a negative feeling-state. This test was
a sensitive objective indicator and this relationship held no matter whether the negative feeling-state was associated with phenobarbital, thonzylamine, or placebo.

6. Further evidence of the untrustworthy nature of the subjective feeling-state following the ingestion of these agents was provided by the finding that the feeling-state associated with thonzylamine was not reflected by a uniform change in direction of scores on any of these tests, whereas the feeling-state associated with phenobarbital was related in the case of the sensitive tests, tapping, and flicker.

7. Although thonzylamine taken under conditions where the subject had no clue to the agent he had ingested resulted in a statistically significant frequency of occurrence of some feeling-state the ingestion of this agent did not interfere with the efficiency of psychological test performance on these seven tests.

REFERENCES


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