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## *Research Articles*

# Method for Evaluating Behavioral Effects of Central Depressants

By MARVIN COHEN* and JOHN W. NELSON

**A new method for the evaluation of central nervous system depression is presented. It is based on the scoring of behavioral responses to subhypnotic doses of central depressants. The application of the method to the study of two different types of depressants, pentobarbital and chlorpromazine, both alone and in combination, is shown. The time-response scoring method appears to be useful as a screening method and as a tool for more theoretical studies when appropriate modifications are made for different types of pharmacological agents.**

The problem of drug interaction and its evaluation is a fundamental one in the field of general pharmacology. Studies in this area, such as those of Bliss (1), Gaddum (2), Berger and Lynes (3), and Gruber (4) have led to an accumulation of considerable information. Such data, however, have largely been obtained by means of toxicity studies (1) or by the measurement of sleeping times in cases where central depressants have been employed (2–4). Gruber (4) has commented on studies of this type by stating that the data obtained in this way, being only relative values, cannot be measured and compared with any degree of accuracy. More quantitative studies, using animals given subhypnotic doses of depressants, have been performed by such workers as Swinyard (5), Lim

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TABLE I.—CRITERIA USED TO EVALUATE DEPRESSANT ACTIVITY

| Degree of Depression | Numerical Equivalent | Description |
|---|---|---|
| LOSS OF SPONTANEOUS MOTION | | |
| No loss | 0 | Behavior of animal indistinguishable from normal — exploratory and cleansing activities. |
| Slight loss | 0.5[a] | Animal motionless (standing or lying) with head in or above plane of body. Readily responds to external stimulus by seeking source of disturbance. |
| Moderate loss | 1 | Animal motionless (standing or lying) with head below plane of body or touching floor of cage. |
| Marked loss | 2 | Partial loss of righting reflex—animal takes longer than 1 sec. to regain correct posture when placed on its back. |
| Loss of righting reflex | 3 | Failure to regain normal posture when animal is placed on its back. |
| RESPONSE TO STIMULI | | |
| Response to air stimulus | 0 | Animal shows startle response (stiffening of body, widening of eyes, rapid movement of vibrissae) or defensive response (rises on hindlegs and faces source of air blast). |
| Response to pain stimulus | 1 | Animal responds to air blast by moving head away from direction of air, moving only a few muscles, or not moving at all. Application of pain stimulus causes animal to attack source of pain within 5 sec. |
| Sluggish response to stimuli | 2 | No satisfactory response to air stimulus. Application of pain stimulus causes aimless movements without attack within 5 sec. |
| No response (loss of righting reflex) | 3 | No response to air or pain stimuli. |
| DEGREE OF ATAXIA | | |
| No ataxia | 0 | Animal brings hindlegs up to bar within 1 sec. |
| Slight ataxia | 1 | Hindlegs are lifted after a lapse of 1–5 sec. If legs are lifted immediately, they repeatedly slip off bar. |
| Moderate ataxia | 2 | Hindlegs not lifted within 5 sec.; animal hangs by forepaws. |
| Marked ataxia | 3 | Animal unable to hang by forepaws. |
| Loss of righting reflex | 4[b] | Animal unable to hang by forepaws in addition to maximum response to other tests. |

[a] It was found that both a normal and a slightly sedated animal could exhibit slight loss of spontaneous motion. In addition, this response was relatively fleeting and often could not be detected on successive observations. For these reasons, a value of 0.5 was given so that it would contribute less to the total response.

[b] Degree of ataxia was given a maximum value of 4 because it was found to be the response component that gave the most dramatic changes in behavior and thus contributed more to the total response.

(6), and Kinnard and Carr (7). In this type of study, certain criteria and/or numerical values were established both for different levels of sedation and different aspects of behavior. A survey of the literature revealed that the above method had not been applied to combinations of central depressants. In addition, many of the criteria used seemed to be too subjective for a detailed study. It was felt that the development of a more objective method would contribute additional information to the study of central depressants at dose levels that permitted a clearer interpretation of drug-induced responses.

## EXPERIMENTAL

Chlorpromazine and pentobarbital were chosen for this study for several reasons. Preliminary studies with pentobarbital showed it to be a central depressant that produced sharply delineated responses with increasing subhypnotic doses. For this reason, pentobarbital was used as a "standard" for establishing the behavioral criteria described below. Pentobarbital is also a classical example of a cortical depressant, particularly in the doses employed in this study.

Chlorpromazine was used because it can be considered as a typical example of the class of drugs known as tranquilizers. It is believed to act predominantly on subcortical regions of the brain rather than on the cortex (8). Chlorpromazine was found to have a longer duration of action than pentobarbital, particularly in higher doses; in addition, chlorpromazine brought about a different pattern of response than did pentobarbital.

In this study, ampuls containing 25 mg./ml. of chlorpromazine HCl[1] were used as the source of this drug. The commercial solution was diluted 1:20 with saline prior to administration. Pentobarbital was obtained from ampuls containing 60 mg./ml. of pentobarbital sodium.[2] This solution was diluted

[1] Marketed as Thorazine by Smith Kline and French Laboratories.

[2] Marketed as Veterinary Nembutal by Abbott Laboratories.

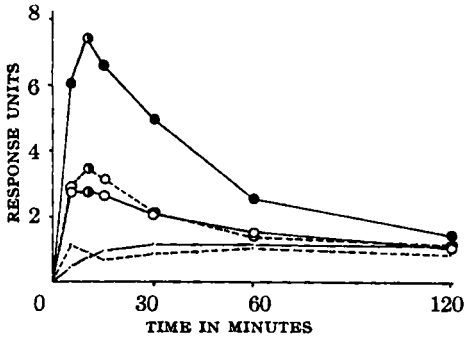


Fig. 1.—Time-response curves for pentobarbital. Key: ----, control; —·—, 5 mg./Kg. pentobarbital; O—O, 10 mg./Kg. pentobarbital; O--O, 15 mg./Kg. pentobarbital; ●—●, 17.5 mg./Kg. pentobarbital; ◑, significant difference of the maximum response from control ($P = 0.05$).

1:10 prior to administration. All drugs were administered by the intraperitoneal route. The animals used were albino male rats of the Wistar strain. They ranged in age from 3 to 5 months and in weight from 150 to 250 Gm. Environmental temperature was generally within the 20–25° range.

The method used to determine levels of central depression was called the *time-response scoring method.* It was based on the assumption that the observed behavior of experimental animals could be translated into numerical values which, when plotted on suitable coordinates, could give a meaningful description of the activity of a drug or drug combination. The time-response scoring method was used to measure depression through the observation of three components of animal behavior under the influence of depressant drugs and under control conditions. These components were loss of spontaneous motion, responses to external stimuli, and degree of ataxia. These three categories were further subdivided into 14 subcategories, each of which had distinct behavioral characteristics. These subcategories, together with their numerical equivalents and descriptions, are shown in Table I.

During experimental runs, the animals (in groups of 4, 8, or 12) were kept in individual cages. Loss of spontaneous motion was determined by direct observation. Response to stimuli was determined by presenting the animal with one or both of two stimuli, depending on its level of depression. The first stimulus was a blast of 4 ml. of air delivered from a 5-ml. syringe through a 25-gauge 0.5-inch hypodermic needle and directed at the animal's face. The second stimulus was the application of pain by pressing the tip of the animal's tail with a finger. Degree of ataxia was measured by the use of a wooden horizontal bar suspended about 4 ft. above the floor. The bar had a roughened surface and an edge for grasping; its dimensions were 8 × 1.25 × 0.5 inches (length-height-width). The animals forepaws were placed on the bar and the animal was allowed to drop from a horizontal position without having its hindlegs touch the bar. The ability of the animal to bring its hindlegs up to the level of its forepaws was used as an indication of ataxia. For a more detailed explanation of this procedure, see Table I.

The experimental design used to evaluate depression produced by chlorpromazine, pentobarbital, and combinations of the two was as follows. After transferring the animals from their home cages to the experimental cages, the animals were allowed approximately 20 minutes to become adapted to their new environment. During this time, their behavior was observed and noted. At the end of this period, the drug or drug combination being studied was administered. Observations were then made at intervals of 5, 10, 15, 30, 60, and 120 minutes after injection. The observation time did not extend beyond 120 minutes because no drug or drug combination used reached a peak of activity after this time.

When sufficient data had been obtained (an average of 12 experimental runs, with a range of 6 to 17 for each point on a graph), they were converted into numerical values and treated in three ways. (*a*) The values obtained for each response component (loss of spontaneous motion, response to stimuli, degree of ataxia) at each time period were summed. These latter values were plotted against time to produce a time-response curve (Figs. 1, 4, 6, and 7). (*b*) The values of each response components were plotted separately against time to determine the contribution of each component to the total response seen (Figs. 2, 3, and 5). (*c*) The maximum response to each drug and drug combination was determined, and this was plotted against dose to give a series of dose-response curves (Figs. 8 and 9). Interpretation of results was made from these graphs.

## RESULTS

Figure 1 illustrates the total response time-response curves obtained for pentobarbital in doses of 5, 10, 15 and 17.5 mg./Kg. Figures 2 and 3 illustrate the response component time-response curves for these doses of pentobarbital. Figure 4 illustrates the total response time-response curves obtained for chlorpromazine in doses of 1 and 5 mg./Kg. Figure 5 illustrates the response component time-response curves for these doses of chlorpromazine. Figures 6 and 7 illustrate the total response time-response curves for combinations of pentobarbital with 1 and 5 mg./Kg. chlorpromazine,

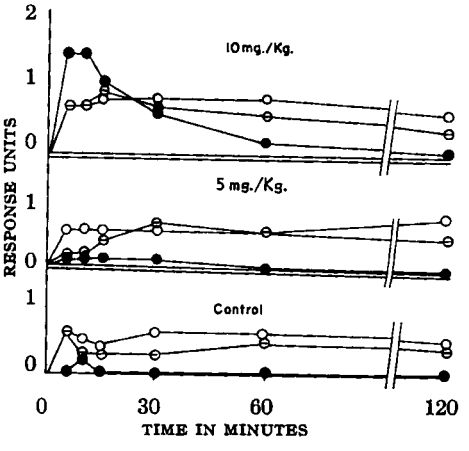


Fig. 2.—Time-response curves for pentobarbital (response components). Key: O, loss of spontaneous motion; ⊖, response to stimuli; ●, degree of ataxia.

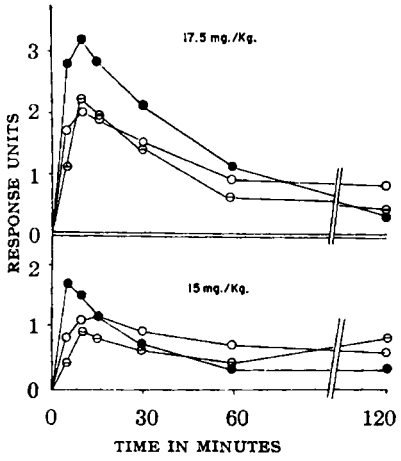


Fig. 3.—Time-response curves for pentobarbital (response components). Key: O, loss of spontaneous motion; ⊖, response to stimuli; ●, degree of ataxia.

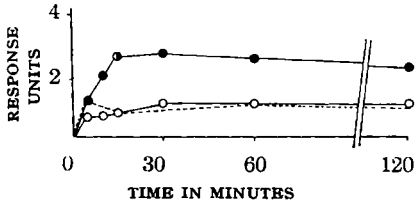


Fig. 4.—Time-response curves for chlorpromazine (total response). Key, -----, control; O—O, 1 mg./Kg. chlorpromazine; ●—●, 5 mg./Kg. chlorpromazine; ◑, significant difference from control ($P = 0.05$).

respectively. Figures 8 and 9 illustrate the dose-response relationships obtained for pentobarbital alone and in combination with chlorpromazine.

The doses used were chosen because each one brought about a particular behavioral response. In the case of chlorpromazine, only two dose levels were found where distinct behavioral responses could be elicited. Chlorpromazine in a dose of 0.5 to 3 mg./Kg. gave essentially the same response as 1 mg./Kg., while doses of 4 to 7 mg./Kg. gave the same type of response as 5 mg./Kg. Doses higher than 7 mg./Kg. did not increase the intensity of drug action, but only affected the duration of action.

Controls were run with saline (4 ml./Kg.) to determine the effect of the evaluation procedure on behavior. Control animals showed a score ranging from 0–3 with an average of 1.6. This was found to be significantly greater than an ideal response of zero for the administration of saline. Significance was determined by the Mann-Whitney U test for independent samples (9) at the 0.05 level of probability. The words "significant" and "significance" are used throughout this paper to mean statistical significance. Calculation of the regression coefficients (slopes) for the dose-response curves in Figs. 4 and 5 was accomplished using the method of least squares (10). Table II summarizes the data obtained by this method. Table III gives the average maximum response obtained with each drug and drug combination used as well as the contribution of each response component to this total.

An analysis of the response component curves for chlorpromazine used alone and pentobarbital used alone indicated that increasing doses of chlorpromazine exerted the most depressant effect on responses to stimuli. Ataxia and loss of spontaneous motion were produced to a lesser, but approximately equal, extent. Pentobarbital was found to exert its greatest depressant effect on ataxia while responses to stimuli were least affected. These data are summarized in Table III. Combinations of pentobarbital with 1 mg./Kg. of chlorpromazine produced no detectable change in the response components when compared to the responses produced by pentobarbital alone. Combinations of pentobarbital with 5 mg./Kg. chlorpromazine produced marked effects on all response components. In comparison with the responses produced by pentobarbital given alone, response to stimuli was affected to the greatest extent. Combinations of pentobarbital with 1 mg./Kg. chlorpromazine produced a duration of action that was slightly greater than the duration of action of pentobarbital given alone. Combinations of pentobarbital with 5 mg./Kg. chlorpromazine produced a greatly increased duration of action when compared with the effects of pentobarbital administered alone.

With all the combinations of pentobarbital and 1 mg./Kg. chlorpromazine, the responses of the combined drugs were not significantly greater than the responses to the predominant individual depressant,

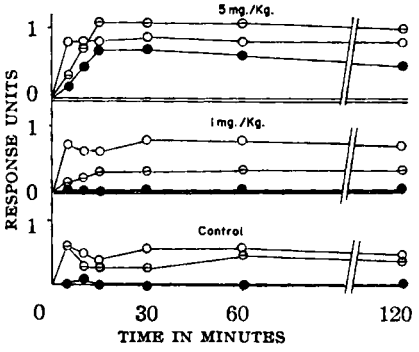


Fig. 5.—Time-response curves for chlorpromazine (response components). Key: O, loss of spontaneous motion; ⊖, response to stimuli; ●, degree of ataxia.

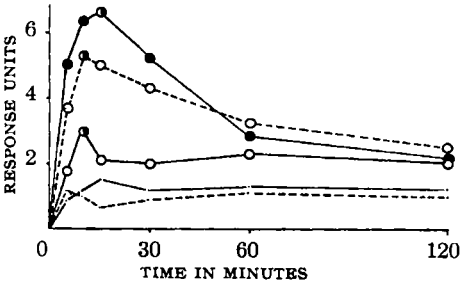


Fig. 6.—Time-response curves for combinations of pentobarbital with 1 mg./Kg. chlorpromazine. Key: ----, control; —·—, 5 mg./Kg. pentobarbital; O—O, 10 mg./Kg. pentobarbital; O----O, mg./Kg. pentobarbital; ●—●, 17.5 mg./Kg. pentobarbital; ◑, significant difference of the maximum response from control ($P = 0.05$).

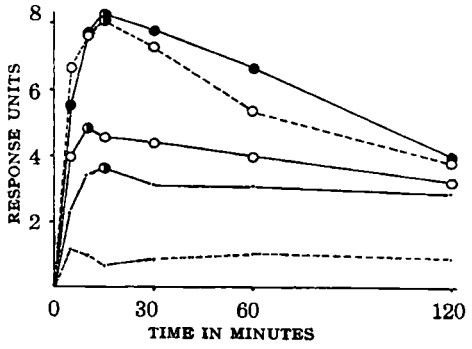


Fig. 7.—Time-response curves for combinations of pentobarbital with 5 mg./Kg. chlorpromazine. Key: ---, control; —·—, 5 mg./Kg. pentobarbital; O—O, 10 mg./Kg. pentobarbital; O---O, 15 mg./Kg. pentobarbital; ●—●, 17.5 mg./Kg. pentobarbital; ◑, significant difference of the maximum response from control ($P = 0.05$).

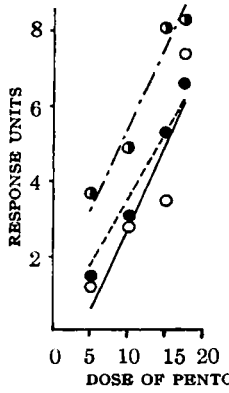


Fig. 8.—Dose-response curves for pentobarbital-chlorpromazine (combinations (total response). Key: O—O, pentobarbital; ●---●, pentobarbital + 1 mg./Kg. chlorpromazine; ◑---◑, pentobarbital + 5 mg./Kg. chlorpromazine; each point represents the maximum response seen.

*i.e.*, the drug in the combination that produced the greater degree of depression when given alone. In two of the four combinations of pentobarbital with 5 mg./Kg. chlorpromazine (the combinations with 10 and 15 mg./Kg. pentobarbital), the responses of the combination were significantly greater than the response to the predominant individual depressant.

With combinations of pentobarbital and 1 mg./Kg. chlorpromazine, pentobarbital was the predominant depressant over the 10 to 17.5 mg./Kg. dose range. In the lowest doses used, both chlorpromazine (1 mg./Kg.) and pentobarbital (5 mg./Kg.) produced responses that were not significantly different from those obtained with saline. With the combinations of pentobarbital and 5 mg./Kg. chlorpromazine, the latter was the predominant depressant when pentobarbital was given at a dose of 5 or 10 mg./Kg., while pentobarbital became the predominant depressant in doses of 15 and 17.5 mg./Kg. These results are summarized in Table IV.

The response to the combination of 17.5 mg./Kg. pentobarbital and 5 mg./Kg. chlorpromazine was found to be not significantly greater than the response to pentobarbital alone. However, other evidence tended to modify a conclusion based solely on the statistical results. At these high dose levels, hypnosis began to appear. A comparison of the number of animals losing their righting reflex with the combination and with pentobarbital alone indicated that an increased degree of depression had occurred. After the administration of 17.5 mg./Kg. pentobarbital, 5 out of 12 animals lost their righting reflex, while the combination of 17.5 mg./Kg. pentobarbital and 5 mg./Kg. chlorpromazine caused 8 out of 12 animals to lose the righting reflex. Hypnosis was also seen with the combination of 15 mg./Kg. pentobarbital and 5 mg./Kg. chlorpromazine. In this case, 7 out of 12 animals lost the righting reflex.

## DISCUSSION

The results of this study of pentobarbital and chlorpromazine interaction indicate that the time-response scoring method is capable of giving a consistent and readily interpretable visualization of the effects of two types of central depressants. The effectiveness of the method appears to be limited at the extreme ends of the subhypnotic dose-response scale, *i.e.*, at doses producing a barely detectable response and at doses that begin to cause a loss of the righting reflex. Between these two extremes, the results obtained have been satisfactory.

Pentobarbital was shown to be a rapidly acting central depressant that affected motor components of behavior more rapidly and earlier than sensory components. Chlorpromazine was shown to be a relatively slow acting depressant that affected

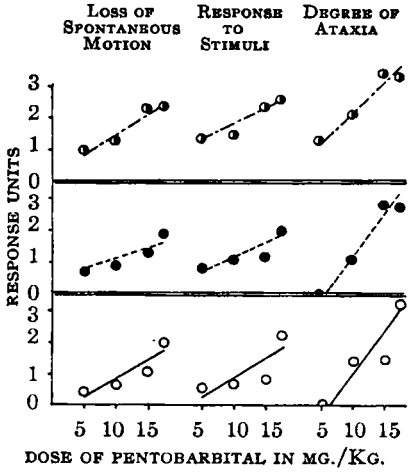


Fig. 9.—Dose-response curves for pentobarbital-chlorpromazine combinations (response components). Key: O—O, pentobarbital; ●---●, pentobarbital + 1 mg./Kg. chlorpromazine; ◑---◑, pentobarbital + 5 mg./Kg. chlorpromazine; each point represents the maximum response seen.

TABLE II.—SLOPES OF DOSE-RESPONSE CURVES FOR CHLORPROMAZINE-PENTOBARBITAL COMBINATIONS

| | Pentobarbital | Pentobarbital + 1 mg./Kg. Chlorpromazine | Pentobarbital + 5 mg./Kg. Chlorpromazine |
|---|---|---|---|
| Total response | 0.45 | 0.35 | 0.43 |
| Loss of spontaneous motion | 0.12 | 0.06 | 0.13 |
| Response to stimuli | 0.12 | 0.09 | 0.10 |
| Degree of ataxia | 0.25 | 0.26 | 0.20 |

TABLE III.—RESPONSES OBTAINED FOR CHLORPROMAZINE-PENTOBARBITAL COMBINATIONS

| Pentobarbital, mg./Kg. | Chlorpromazine, mg./Kg. | Average Maximum Response | Response Components | | |
|---|---|---|---|---|---|
| | | | Loss of Spontaneous Motion | Response to Stimuli | Degree of Ataxia |
| ... | ... | 1.2 | 0.6 | 0.6 | 0.0 |
| 5 | ... | 1.2 | 0.5 | 0.6 | 0.1 |
| 10 | ... | 2.8 | 0.7 | 0.7 | 1.4 |
| 15 | ... | 3.5 | 1.1 | 0.9 | 1.5 |
| 17.5 | ... | 7.4 | 2.0 | 2.2 | 3.2 |
| ... | 1 | 1.1 | 0.8 | 0.3 | 0.0 |
| 5 | 1 | 1.5 | 0.7 | 0.8 | 0.0 |
| 10 | 1 | 3.1 | 0.9 | 1.1 | 1.1 |
| 15 | 1 | 5.3 | 1.3 | 1.2 | 2.8 |
| 17.5 | 1 | 6.6 | 1.9 | 2.0 | 2.7 |
| ... | 5 | 2.7 | 0.9 | 1.1 | 0.7 |
| 5 | 5 | 3.7 | 1.0 | 1.4 | 1.3 |
| 10 | 5 | 4.9 | 1.3 | 1.5 | 2.1 |
| 15 | 5 | 8.1 | 2.3 | 2.4 | 3.4 |
| 17.5 | 5 | 8.3 | 2.4 | 2.6 | 3.3 |

TABLE IV.—DEPRESSANT EFFECTS OF CHLORPROMAZINE-PENTOBARBITAL COMBINATIONS

| Pentobarbital, mg./Kg. | Chlorpromazine, mg./Kg. | Response to Individual Drug | Response to Combination | Drug in Combination Exerting Predominant Response |
|---|---|---|---|---|
| ... | 1 | 1.1 | ... | ... |
| 5 | ... | 1.2 | ... | ... |
| 10 | ... | 2.8 | ... | ... |
| 15 | ... | 3.5 | ... | ... |
| 17.5 | ... | 7.4 | ... | ... |
| 5 | 1 | ... | 1.5 | Neither |
| 10 | 1 | ... | 3.1 | Pentobarbital |
| 15 | 1 | ... | 5.3 | Pentobarbital |
| 17.5 | 1 | ... | 6.6 | Pentobarbital |
| ... | 5 | 2.7 | ... | ... |
| 5 | 5 | ... | 3.7 | Chlorpromazine |
| 10 | 5 | ... | 4.9 | Chlorpromazine |
| 15 | 5 | ... | 8.1 | Pentobarbital |
| 17.5 | 5 | ... | 8.3 | Pentobarbital |

sensory components of behavior more rapidly and earlier than motor components.

In both series of pentobarbital-chlorpromazine combinations, the increased duration of action of the combinations over the individual drugs seemed to be due to the chlorpromazine component. The data suggested that pentobarbital exerted its predominant effect within 30 minutes after the administration of low doses (5 and 10 mg./Kg.) and within 60 minutes after the administration of higher doses (15 and 17.5 mg./Kg.). Additional evidence for the predominance of chlorpromazine at these times and after is seen by the sharp break in the time-response curves at the above-mentioned times for the different chlorpromazine-pentobarbital combinations (see Figs. 6 and 7). Such breaks have been interpreted by Bliss (1) as being indicative of independent additive action in drug combinations. As applied to this study, the interpretation of Bliss would seem to indicate that chlorpromazine and pentobarbital exert independent depressant actions, the predominance of one or the other being a direct function of its depressant ability when used alone.

While many of the above conclusions are well known from numerous other studies (6, 11–13), very few attempts have been made to quantitate the responses seen. A major reason for this is inherent in the nature of the responses being studied. Quantitation to any degree, no matter how small, can give more clues to mechanisms and sites of drug action than can qualitative data. The time-response scoring method appears to accomplish this with a minimum of equipment, time, and training. It appears to be useful as a screening method and as a tool for more theoretical studies when appropriate modifications are made for different types of pharmacological agents.

## SUMMARY

A new method for the evaluation of central nervous system depression is presented. It is based on the scoring of behavioral responses to subhypnotic doses of central depressants. The application of the method to the study of two different types of depressants, pentobarbital and chlorpromazine, both alone and in combination, is shown.

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