The drug which is now known officially as Mephenesin ("Myanesin," "Tolserol") was introduced by Berger and Bradley (1946), who showed that it antagonizes strychnine convulsions, counteracts pre-narcotic excitement, and increases the duration of barbiturate anaesthesia. Small doses depress the reflex excitability of the spinal cord, and larger doses have an ascending depressant action on the central nervous system. When Berger (1947) found that doses with little effect on voluntary power restored deranged reciprocal innervation to normal, he suggested that mephenesin might be useful in spastic and hypertonic conditions.

Much attention has been given to the muscle-relaxing effects of mephenesin, which were also described by Berger and Bradley (1947). Stephen and Chandy (1947) in clinical studies found that there was no change in voluntary motor power or in the E.E.G. when mephenesin was given intravenously. Mental reactions noted included slowing of speech, and complaints of feeling "dopey," "relaxed" or "heavy." Most patients exhibited a mild euphoria during the relaxed period of about one hour. The drug had a pronounced effect on pain of central or "thalamic" origin, and beneficial effects on extrapyramidal diseases.

Schlesinger et al. (1948) considered that the main use of mephenesin was in true muscle spasm. Tremor could be influenced with a low concentration of the drug, and in some cases would disappear for as long as rigidity. In others a certain suggestion of decomposition of movement persisted, or it was necessary to produce mild weakness in order to maintain absence of tremor.

Henneman et al. (1949) mention that clinically mephenesin is somewhat disappointing. They concluded that the site of action is probably the internuncial cell.

Kaada (1950) found that the more complex multisynaptic pathways are particularly vulnerable to mephenesin.

The use of the drug is now established in certain neurological syndromes, particularly those with rigidity and tremor. It has also been used as a relaxant in E.C.T.
Reports of mephenesin in more purely psychiatric conditions will now be briefly reviewed.

Gammon and Churchill (1949) found suggestions of a differential depression in the basal ganglia, brain stem and thalamus. In view of the results of thalamotomy and leucotomy, mephenesin was tested in psychotic cases with "promising results," and is being studied further. They found that 2.0 gm. orally would give the characteristic effect, with relief from tremor lasting 30 to 60 minutes. However, they encountered inconstant responses, finding 3.0 gm. orally to be occasionally ineffective.

Dinenberg and Hecker (1950) reported no definite therapeutic response to mephenesin in 27 psychotic patients.

Using a dose of 0.5 to 1.5 gm. q.i.d., Schian and Unna (1951) reported alleviation of anxiety in three women, the effects occurring within one hour and not being accompanied by sleepiness. Eight cases of acute alcoholism showed reduction or abolition of gross tremor, and severe anxiety was as promptly relieved. The use of sedation was found to be no longer necessary. Withdrawal symptoms in 2 morphine addicts were alleviated, 2 hypomanics became calmer, a case of agitated depression showed diminished activity, and an overactive patient became quiet.

Dixon et al. (1950) found oral mephenesin useful in teaching the sensation of relaxation to patients with anxiety tension states who were learning Jacobson's relaxation technique.

Following this work, Paul (1952) reported the use of mephenesin in anxiety tension states which were being treated by brief psychotherapy. Of 30 anxious neurotic patients all had one or more anxiety tension symptoms—vague diffuse uneasiness, restlessness, irritability, startle reaction, muscle tightness or tension, or psychological tension. Paul gave 1.0 to 2.0 gm. 2, 3 or 4 times daily. Four patients experienced no benefit, but he points out that these had absence of feeling of appreciable muscle tension, and were severely inhibited persons with rigid unconscious control over all affect—even alcohol did not affect their feeling of tension. Twenty-six patients achieved relaxation of tense muscles, leading to a feeling of reduced muscle tension and diminished psychic tension.

It is pertinent to point out that in both series of tests just reviewed the factor of suggestibility seems to be prominent. Apparently subjects knew what to expect from the use of the drug.

Freudenberg (1950) studied the manner in which mephenesin raises the threshold for E.C.T. and leptazol. He noted that any beneficial effect on psychoses or anxiety neuroses often subsided after 2 to 3 weeks of 1.0 gm. t.d.s. One patient with marked startle reaction improved, and 1.0 gm. intravenously relieved the tremors of delirium tremens. One patient in delirium tremens also lost his haptic and visual hallucinations.

Hecker et al. (1951) found that an average dose of 2.5 gm. of elixir of mephenesin produced spontaneous nystagmus, which they regarded as a criterion of adequate dosage. They group the responses found as follows:
1. Release of blocking to recall, or revelation of painful experiences, with or without emotional release. A violent abreaction was seen in one case.

2. Control of vivid emotional reactions (rage) or manic type of release. Various patients became more calm.

3. Relief of overt anxiety with more logical sequential alignment and expression of mental content.

4. Combination of responses.

5. No response occurred in 9 out of 26 patients.

These workers confirmed the lack of effect in schizophrenia. In the same study 24 patients were graded by psychological evaluation as to the presence of anxiety, and it was found that cases with anxiety did show better response to mephenesin. The indicators of anxiety used were lowered intellectual efficiency in digit span; also diffusion and toned down shading effects, evasiveness, compulsiveness and constriction in the Rorschach.

Mercer and Hecker (1951) later described how mephenesin might be useful in distinguishing between loss of efficiency due to impact of existing anxiety and that resulting from the inroads of a disease process.

Herman and Effron (1951) tested mephenesin in the immediate post-alcoholic state. They found decided benefit from doses of 2.0 to 2.5 gm. per day. Tremulousness and gastro-intestinal symptoms were reduced or eliminated, and patients' subjective states improved. This is, incidentally, one of the very few clinical studies in which controls of any sort were used, one group being given phenobarbitone instead of mephenesin.

**The Present Study.**

Because of the extreme lack of adequately controlled work on the psychological effects of mephenesin, we started the investigation of which this article describes the first part.

It was felt that the most interesting aspect of the drug psychiatrically was its reported effect of reducing anxiety, and an attempt was made to test this.

**Method.**

The subjects used were male voluntary patients in the North Carolina Alcoholic Rehabilitation Centre. These men are treated purely by a régime of good diet and vitamins, community life, and daily psychotherapy; none of them was receiving any drug apart from the test doses of mephenesin and of the inert control tablets. All the patients were sober from the time of admission, and were not admitted to the centre in acute alcoholic conditions.

As the drug was not being tested for any specific effect on alcoholism there was no particular virtue in testing this group, except that we had here a suitable sample for the experiment. Patients in the centre are given various psychological tests and psychiatric interviews, so that the tests with mephenesin were readily accepted as being merely part of the routine.

At no time did the subjects know that tests were being conducted on mephenesin, nor did the attendants who administered the tablets know the
nature of the drug. Only the authors were aware of this, and not until the end of the experiment did we correlate the tables to show which patients received which tablets on which test day. When administering the tests we did not know whether active or control tablets had been given to each subject.

The tablets were known simply as "A" and "B," and which tablets were to be given first to each patient was determined from a table of random numbers to which the chief attendant added the patient's name at the time of admission. Tablets "A" and "B" were similar in appearance.

Each patient was tested between the fifth and eighth day after admission. He received first one set of tablets on one test day, and the other tablets on the following test day. The digit span test was given to each patient on both test days, and on each occasion he was asked to record his subjective sensations on a questionnaire.

Tablets were administered to small groups of 2 or 3 patients daily, and were always taken on an empty stomach immediately before breakfast, being washed down with 3 oz. of water. The digit span test was administered one hour later, and immediately after this each patient was asked to fill in the questionnaire.

In the first series of tests 15 patients received 1.0 gm. of mephenesin and 1.0 gm. of control tablets. Analysis of the results in this series showed such little difference in the two groups (see below) that it was felt desirable to increase the dose. Accordingly a second series of 101 patients received 2.0 gm. each of active and control tablets on alternate days. At the conclusion of this series further small groups of 19 received 0.5 and 1.5 gm. of tablets, and 5 more patients received 1.0 gm. to bring this group's total to 20.

**PSYCHOLOGICAL TESTING.**

The problem of measuring psychometrically the effects of mephenesin on anxiety involved the selection of a method, or methods, which would allow a reasonable amount of objectivity. We also required a quantitative measurement of any reduction of anxiety which might be brought about by the administration of the drug. Two methods were given serious consideration: (a) Test-retest with the Digit Span test, and (b) test-retest with the Rorschach test, using the various anxiety factors suggested in the literature.

We decided to employ the Digit Span test-retest in the first part of the investigation (which is described here), because of the greater ease of quantification of any changes brought about by the drug, as opposed to the more subjective and poorly quantified Rorschach test. The validity of the Digit Span test as a measure of the effects of anxiety has been widely reported in the literature, perhaps the most complete exposition of the subject being that of Rapaport (1946). We employed a similar test to that contained in the Wechsler-Bellevue test, following the technique outlined by Wechsler (1944).

The results are shown in Table I. It is seen that none of the differences between the means reached the 5 per cent. level of significance, although twice the 10 per cent level was exceeded. It is noted that there seems to be as much (though not significant) variation due to the practice effect as variation which might be attributable to the administration of the drug. There does, however,
Table I.—Digit Span Scores of Subjects Receiving Mephenesin and Inert Control Tablets on Alternate Days.

(We used the formula: \( SED = \sqrt{SEM_1^2 + SEM_2^2 - 2r(SEM_1, SEM_2)} \) for the standard error of the difference between two correlated means. The Critical Ratio (C.R.) was \( D \) where \( D \) is the mean difference.)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Group</th>
<th>Number of subjects</th>
<th>Number of digits repeated</th>
<th>S.D.</th>
<th>Mean diff.</th>
<th>C.R.</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 gm.</td>
<td>Inert</td>
<td>19</td>
<td>10-65 8-14 1.59</td>
<td>.48</td>
<td>2.09</td>
<td>.5%</td>
<td>not significant</td>
</tr>
<tr>
<td></td>
<td>Mephenesin</td>
<td>19</td>
<td>11-11 8-15 1.94</td>
<td>.89</td>
<td>.84</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st day</td>
<td>19</td>
<td>11-00 8-14 1.74</td>
<td>.26</td>
<td>.84</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>19</td>
<td>10-74 8-15 1.94</td>
<td>.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 gm.</td>
<td>Inert</td>
<td>20</td>
<td>11-20 7-15 2.17</td>
<td>.20</td>
<td>.50</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mephenesin</td>
<td>20</td>
<td>11-40 7-14 1.83</td>
<td>.63</td>
<td>.84</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st day</td>
<td>20</td>
<td>10-90 7-14 1.84</td>
<td>.20</td>
<td>.44</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>20</td>
<td>11-70 7-15 2.5</td>
<td>.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 gm.</td>
<td>Inert</td>
<td>19</td>
<td>11-64 8-17 2.51</td>
<td>.09</td>
<td>.23</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mephenesin</td>
<td>19</td>
<td>11-73 9-16 2.56</td>
<td>.75</td>
<td>.84</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st day</td>
<td>19</td>
<td>11-37 8-16 2.34</td>
<td>.63</td>
<td>1.99</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>19</td>
<td>12-00 9-17 2.62</td>
<td>.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0 gm.</td>
<td>Inert</td>
<td>101</td>
<td>11-03 7-17 2.63</td>
<td>.03</td>
<td>.19</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mephenesin</td>
<td>101</td>
<td>11-00 7-17 2.24</td>
<td>.77</td>
<td>.84</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st day</td>
<td>101</td>
<td>10-82 7-17 2.36</td>
<td>.37</td>
<td>1.17</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>101</td>
<td>11-21 7-17 2.51</td>
<td>.76</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

seem to be a trend towards significance where the dose of mephenesin was small (0.5 gm.).

It may be concluded from this material that, if the Digit Span test is a reliable measure of anxiety and its effects, mephenesin produced no significant reduction of anxiety.

It is, of course, quite possible that the ability to do digit span may be affected by the drug, in that it may produce a subtle clouding of consciousness or an inability to attend. For this reason the further investigation noted at the end of this paper was commenced as a cross-check of the validity of this study.

**Subjective Aspects of Mephenesin Administration.**

We did not attempt any clinical evaluation of the effects on muscle tension or tremor in the present study. Although aware of the inherent defects of the questionnaire system we used one experimentally, and we believe that the results are sufficiently interesting to warrant a brief statement.

The questionnaire was worded as follows:

1. How do you feel at present?
2. Are you often nervous? If so, in what way?
3. Are you nervous at present?
4. Have these tablets affected you in any way?

We felt that the use of the very general term "nervous" was justified as nearly all of our patients use it, at least when first admitted to the Centre. During the course of the group psychotherapy we analyse the meaning of the term and the origin of the sensations implied. However, the patients answering the questionnaire had attended group psychotherapy for only one week, and most had not yet discussed the subject of "nervousness."
84 per cent. of the subjects answered question 2 positively, to indicate that they often felt sensations they called "nervousness." This was variously described in question 2 as "shaky all over," "jittery," "restless," "stomach all upset," "breathe deeply," etc. Approximately half of the symptoms were of the "external" type, e.g., "hands shake," "restless," and half of them of the "internal" type, e.g., "tensed up inside," "stomach tied in knots."

To find that over four out of five patients often suffer from such feelings is not surprising in a group of alcoholics. Quite apart from the physical effects of alcohol, it is a common experience of alcoholics to suffer much tension and uneasiness while in the remorse and guilt stages of a hangover. Then again, when we consider that alcoholism is a symptom of underlying chronic maladjustment, we are not surprised that a high percentage of the group should have suffered from attacks of anxiety.

In a future publication we hope to give statistical data of the types of psychological problems present in alcoholism. In the meantime we know that many alcoholics have used alcohol as a means of relief from psychological and physical tension. Here, then, we have a group of men who should at once appreciate any relaxing effects that mephenesin might give.

All patients had been sober for at least a week at the time of testing, and in the relatively neutral environment it is natural to expect that some patients will be already less tense at the end of that week. Actually 50 per cent of the subjects answered question 3 positively, to indicate that they were "feeling nervous" at present. Possibly the fact that they had just completed an interview for administration of the digit span might account for this.

Detailed analysis of the questionnaires would be very lengthy, but it is found that the answers can be classified into four broad groups:

1. No subjective effects noticed with either active or control tablets.
2. Similar effects noticed with both active and control tablets.
3. Effect only noticed with the control tablets.
4. Effect only noticed with the active (mephenesin) tablets.

The effectiveness (as regards subjective sensation) of either or both tablets is shown at the various dose levels in Table II. As can be seen, the greatest effectiveness of mephenesin occurred with the 2.0 gm. dose, but even here only 22.8 per cent. could define any definite subjective feeling.

The table also shows that a considerable degree of suggestion was operating

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of subjects</th>
<th>No effect with either tablets</th>
<th>Similar effect with both tablets</th>
<th>Effect only with control tablets (inactive tablets)</th>
<th>Effect only with active tablets (mephenesin) tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 gm.</td>
<td>19</td>
<td>11 (58%)</td>
<td>3 (15.75%)</td>
<td>2 (10.5%)</td>
<td>3 (15.75%)</td>
</tr>
<tr>
<td>1.0 gm.</td>
<td>20</td>
<td>9 (45%)</td>
<td>6 (30%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>1.5 gm.</td>
<td>19</td>
<td>11 (58%)</td>
<td>2 (10.5%)</td>
<td>4 (21%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>2.0 gm.</td>
<td>101</td>
<td>55 (54.5%)</td>
<td>17 (16.8%)</td>
<td>8 (7.9%)</td>
<td>23 (22.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>84 (52.8%)</td>
<td>28 (17.6%)</td>
<td>16 (10.1%)</td>
<td>31 (19.5%)</td>
</tr>
</tbody>
</table>

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in many cases. Undoubtedly the patients discussed these tablets among themselves, but they were unaware that the tablets were not identical or what effects were to be expected of them.

The quality of the effects noted is of considerable interest.

Of the 28 patients reporting similar effects from tablets "A" and "B," only one mentions any beneficial or desirable effect. He claimed to feel "Calm, quiet and with no worries" with 1.0 gm. of mephenesin, and "As if I had had an ounce of whisky" with 1.0 gm. of inert tablets. The other 27 patients felt similar effects with each set of tablets, such as "nervousness," "shakiness" or "weakness."

Of the 16 patients reporting an effect from the inert tablets only, one mentions an effect which suggests relaxation. He felt no effect with 1.0 gm. of mephenesin, but, "As if I had had a drink" with 1.0 gm. of control tablets. The other 15 patients reported feelings such as "nervousness," "shakiness" and "weakness" with the inert tablets only.

From the point of view of the present study, the most important group is that consisting of patients who felt a definite effect from the mephenesin tablets, but not from the inert tablets:

Of the 19 patients receiving 0.5 gm. of tablets, three felt an effect with mephenesin only: one said, "May have made me feel more nervous"; one said, "Feels like a bottle of beer or a small whisky"; one said, "Kind of dizzy and a feeling of nervousness in the stomach."

Of the 20 patients receiving 1.0 gm. of tablets, three felt an effect with mephenesin only: two said, "More nervous than usual"; one said, "Dizzy for a minute."

Of the 19 patients receiving 1.5 gm. of tablets, two felt an effect with mephenesin only: one said, "Dizziness"; one said, "The tablets made me feel lightheaded."

Of the 101 patients receiving 2.0 gm. of tablets, 23 felt an effect with mephenesin only: 12 felt that the tablets made them dizzy; two complained of "swimming in the head"; two said, "A little sleepy"; one each felt "groggy," "nerves calmed," "sick for a few minutes," "less nervous," "less shaky," "head fulness," "as if I had had one Manhattan."

We cannot be certain that the sensations reported were caused by the mephenesin. However, it is interesting to see that not one patient said outright that he felt relaxed, and that only 5 implied relaxation by reporting being less nervous or shaky, or by comparing the tablets' effect with that of an alcoholic drink. Dizziness was the most commonly felt sensation, and it is not a particularly desirable one in a drug of this nature.

We feel that the evidence is sufficient for us to conclude that even in doses of up to 2.0 gm. of mephenesin on an empty stomach, there is a low incidence of beneficial reactions such as relaxation. Of the 159 patients receiving the drug orally, only 5 might be said to have obtained a feeling of relaxation.

It seems possible that the relaxation effects reported in higher percentage by other workers can be largely attributed to the power of suggestion.

We feel doubtful that mephenesin is likely to prove of lasting value as a relaxant drug in states of anxiety and tension.
Of course we do not dispute the usefulness of mephenesin in neurological syndromes, or its effectiveness when given intravenously in delirium tremens as reported by Freudenberg (1950), or that orally it gives better relief than does phenobarbitone in acute alcoholism (Herman and Effron, 1951).

Suggested Further Study.

While it seems likely that the Digit Span Test employed here is a perfectly adequate means of measuring the effects of anxiety, the validity of this study could be enhanced by employing other psychometric means for measuring the effects of mephenesin on anxiety.

Accordingly we are engaged in repeating the experiment, using the Rorschach test-retest. Various indices of anxiety, such as are mentioned by Klopf and Kelley (1946), are being used.

Summary.

(1) An experiment was devised to test the effects of mephenesin on anxiety in 159 alcoholic patients. Rigid controls were employed, involving the use of inert tablets for comparison purposes, as well as other safeguards to eliminate subjective factors on the part of the examiners.

(2) Using the Digit Span Test-retest as an index of anxiety, it was found that no statistically significant diminution of anxiety was obtained with doses of up to 2.0 gm. mephenesin orally.

(3) Using a simple questionnaire, patients described their subjective experiences with both active and inert tablets. The effects of suggestion were marked throughout. Only 5 subjects out of 159 reported feelings indicating relaxation when receiving mephenesin; 2 of the 159 obtained similar relaxation effects from the control tablets. Undesirable effects from both sets of tablets were frequently encountered, such as complaints of "nervousness," "shakiness" and "weakness" in 42 of the subjective reports from patients receiving inert tablets, and in 53 of patients receiving mephenesin tablets (in each instance, out of a total of 159).

(4) It was concluded, from the psychometric and clinical data obtained, that mephenesin is of little value in alleviating subjective experiences of anxiety. Lack of controls and the effect of suggestion may account for previous encouraging reports of the usefulness of mephenesin in anxiety states.

Acknowledgments.

We are indebted to Mr. C. Keith and his assisting attendant staff of the North Carolina Alcoholic Rehabilitation Centre for their aid in this study. E. R. Squibb & Sons kindly supplied us with control tablets to match their product "Tolserol."

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THE EFFECT OF MEPHENESIN ON ANXIETY
