ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA

VII: THE EFFECTS OF NINE PHENOTHIAZINE DERIVATIVES

BY

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In the original publication on chlorpromazine, Courvoisier and her associates (1953) reported that this phenothiazine potentiated the intensity and duration of action of analgesic drugs in animals. They did not, however, show that chlorpromazine itself possessed any analgesic action. Schneider (1954) also found that it increased the duration of morphine analgesia in mice. Kopera and Armitage (1954), on the other hand, were unable to demonstrate any potentiation of morphine analgesia by either chlorpromazine or promethazine. All these workers used the same species of animals in their studies, employed the same technique for the measurement of analgesia and injected the same dosage of chlorpromazine (10 mg/kg). More recently, Tripod and Gross (1957), using a similar experimental technique, found that chlorpromazine increased the duration of morphine-induced analgesia, and demonstrated that promazine had a similar action.

Despite the widely publicized claims for the potentiation of analgesic action by phenothiazines, the authors were unable to find reports of any other animal experiments which have a direct bearing on the subject. Controlled observations in man are also very few. Using the Hardy, Wolff and Goodell (1948) technique for measuring pain, Hougs and Skouby (1957) found that the chlorinated phenothiazines possessed an analgesic action which was not present in the nonchlorinated compounds. The most extensive study has been that of Boreus and Sandberg (1959) who also used the thermal method for measuring analgesia and carried out investigations in 184 subjects aged between 20 and 25 years. They found that 15 mg of chlorpromazine had some analgesic action and that it augmented the analgesic effect of methadone 6 mg. No analgesic activity could be demonstrated for pecazine 15 mg and when combined with methadone it antagonized the analgesic action of the latter. Acetylpromazine was studied in 5-mg doses and was found to have no analgesic effect but it did not antagonize the action of methadone.

Judging by the amount of data in the literature, the unsubstantiated claims made for the phenothiazines may be based on observations of the amount of analgesic drugs required in the postoperative period in patients to whom the drugs have already been given either in pre-anaesthetic medication or during anaesthesia. In 1950, Laborit, who popularized the use of these drugs, found that postoperative analgesic drugs were not required when diethazine and promethazine had been given before and after operation. This was attributed to the "central analgesic and hypnotic" properties of these drugs.

Dripps et al. (1955) reported that the addition of 5 to 12 mg of chlorpromazine to the usual premedication increased its efficacy and augmented the anaesthetic action of nitrous oxide and oxygen mixtures. The use of several oral doses of 25 mg of chlorpromazine before and after anaesthesia was studied in patients undergoing thoracic surgery by Boulton (1955). He found that this drug made patients indifferent to pain, reducing the postoperative requirements of pethidine by 23 per cent in females and by 6 to 7 per cent in males. He concluded that chlorpromazine potentiated the action of analgesic drugs. In a well organized trial, in which variables were reduced to minimum, Dryberg and Johannsen (1958) could find no difference in the requirements of analgesic drugs in the postoperative period between patients premedicated with morphine 10 mg or chlorpromazine 50 mg. The results of these clinical studies
suggest that chlorpromazine may have some analgesic action of its own and that it increases the efficacy of analgesic drugs.

Sadove (1956) reported that a combination of promethazine and an analgesic drug gave the same degree of relief from pain as was obtained using a larger dose of analgesic alone. The pre- and postanaesthetic use of promethazine reduced the requirements of analgesics to one-sixth to one-half of normal. Watrous (1957), although finding that promethazine was an unsatisfactory sedative drug for premedication, noted that it decreased the dose of thiopentone and of analgesic drugs required during anaesthesia. He gave no figures to support his claim. Contrary to the above findings, Bergner and Ma (1960) did not find evidence of any analgesia in 271 patients premedicated with promethazine and noted that both the frequency and intensity of their reactions to stimuli were similar to those of patients who had been given a barbiturate. Similarly, Pitcher (1959) found that the intravenous use of promethazine during anaesthesia did not "settle" patients in a manner which would be expected from the opiates.

In his technique of "ataralgesia", in which he attempted to produce total analgesia without loss of consciousness, Hayward-Butt (1957) combined pethidine, pecazine and amiphenazole and attributed his success to the potentiating effect of pecazine on pethidine. However, Boreus and Sandberg (1959), as already mentioned, demonstrated an anti-analgesic effect of pecazine but found that amiphenazole potentiated the analgesic action of methadone. These results suggest an alternative explanation for the good results reported by Hayward-Butt (1957), which is supported by the findings of Davies (1959). When trying to evolve a suitable technique of analgesia for dressing of burns, she found that pethidine with amiphenazole was superior to a mixture of pethidine, amiphenazole and pecazine.

Despite the number of publications which deal with the effects of promethazine and pecazine, there is much less concrete evidence in support of their having an analgesic action, or a potentiating effect on analgesic drugs, than there is for chlorpromazine. None of the newer phenothiazine derivatives appears to have been studied in any detail and it has been possible to find references to the use of perphenazine and triflupromazine only. Phillips et al. (1958) in two comparable groups of patients found that the addition of 5 mg of perphenazine to the standard premedication reduced the incidence of requirements of analgesic drugs in the postoperative period from 20 per cent to 9.2 per cent. Lear and his colleagues (1959), also in a carefully controlled trial, found that triflupromazine 10 to 20 mg halved the requirements of postoperative analgesic drugs.

Space does not permit a detailed discussion of the findings relating to the use of phenothiazine derivatives in chronic pain or in obstetrics. Furthermore, it is difficult to be certain whether any beneficial effect which they may have under these circumstances is indicative of a true analgesic action or is due to a potentiation of analgesic drugs. It must be remembered that an ataractic action, with decrease in anxiety reactions, can be produced in experimental animals with doses of chlorpromazine and morphine which are insufficient to cause a detectable degree of analgesia (Ambrus et al., 1957). It is worthy of note that the drug which has proved most beneficial as an adjuvant in the management of chronic pain is chlorpromazine (Sadove et al., 1954; Dundee, 1957). In the field of obstetrics beneficial effects have been reported following the use of chlorpromazine (Browne and Mannion, 1955; Karp, Lamb and Benaron, 1955; Savage, 1955), promethazine (Hobbs and Carroll, 1958; Adelman et al., 1959; O'Sullivan, 1960), promazine (Macvicar and Murray, 1960), and perphenazine (Harer, 1958).

When investigating the reliability of a method of analgesimetry the present authors found that a mixture of pethidine 100 mg and promethazine 50 mg (Pamergan P.100) was almost devoid of analgesic activity, whereas by the same technique they consistently demonstrated an analgesic action following the administration of pethidine alone. This led to an investigation of the action of promethazine on the patients' appreciation of pain which has been reported recently (Moore and Dundee, 1961a). Irrespective of the route of administration, it was found that 50 mg of promethazine was followed by an increased sensitivity to pain and that it consistently antagonized the analgesia produced by pethidine. These findings prompted a study of the action of a smaller (10 mg) dose of promethazine and also of other phenothiazine derivatives used in anaesthetic
practice. This report describes the results of this investigation and attempts to relate their actions to the chemical structure of the drugs. It will be apparent from the preliminary discussion that similar comparative data on this action of the phenothiazine derivatives is not available in the literature.

**Phenothiazine derivatives studied.**

The chemical structure of these is shown in figure 1, in which the drugs have been grouped according to the classification described by Rees (1960). Some difficulty was encountered in deciding upon equipotent doses of different phenothiazine derivatives and eventually it was decided to use the dosage of each drug most commonly employed in anaesthetic practice. Since different publications have described the use of phenothiazine derivatives in anaesthesia for a variety of purposes (pre-operative sedation, antisialogogue effect, production of hypothermia, potentiation of anaesthetics and anti-emetic action) it is not

<table>
<thead>
<tr>
<th>Dimethyl amino propyl side chain</th>
<th>Proprietary name</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chlorpromazine</td>
<td>Largactil</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; N(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; HCl</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>2. Promethazine</td>
<td>Phenergan</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH(CH&lt;sub&gt;3&lt;/sub&gt;) N(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; HCl</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>3. Promazine</td>
<td>Sparine</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; N(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; HCl</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>4. Trifluopromazine</td>
<td>Vespral</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; N(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt; HCl</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
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</tr>
<tr>
<td>5. Trimeprazine</td>
<td>Vallergan</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH(CH&lt;sub&gt;3&lt;/sub&gt;) CH&lt;sub&gt;2&lt;/sub&gt; N(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Piperazine side chain</th>
<th>Proprietary name</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Stemetil</td>
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<td>Cl</td>
<td></td>
</tr>
<tr>
<td>2. Perphenazine</td>
<td>Fentazin</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; N N CH&lt;sub&gt;2&lt;/sub&gt; CH&lt;sub&gt;3&lt;/sub&gt; OH</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>3. Trifluoperazine</td>
<td>Stelazine</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; CH&lt;sub&gt;2&lt;/sub&gt; N N CH&lt;sub&gt;2&lt;/sub&gt; 2 HCl</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Piperidine side chain</th>
<th>Proprietary name</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pecazine</td>
<td>Pacatal</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt; N CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 1**

Chemical structure of phenothiazine derivatives studied.
certain that the dosages of the different drugs used in this study are strictly comparable as regards any single one of their various facets of action.

**METHOD**

The patient's appreciation of pain was estimated by the method of analgesimetry described by Dundee and Moore (1960). This consists of the gradual application of pressure to the anterior surface of the tibia. Two endpoints were determined (a) when the feeling of pressure changed to pain (threshold) and (b) when the pain became unbearable or when the limb was moved in response to the stimulus (response). Previous tests have determined the degree of error associated with this method and have demonstrated its reliability on repeated usage.

**RESULTS**

*Intravenous injection.*

This would seem to be the most suitable route of administration for this study but unfortunately in the doses used the phenothiazine derivatives caused an appreciable degree of hypotension. Apart from the difficulties in reversing the falls in blood pressure and their frequent persistence during the course of the subsequent anaesthesia, it was found repeatedly that the scatter of duplicate readings became more marked during profound hypotension and thus the significance of the findings became less. In addition to this, the intravenous injection of most of the phenothiazine derivatives caused a marked degree of restlessness and agitation in the conscious subject. This phenomenon occurred within 10 minutes of injection and frequently persisted for 15 to 20 minutes. The restlessness was so severe in some patients that it was necessary to abandon the study and induce anaesthesia.

Figure 2 shows the average deviations of threshold and response readings from the control with five of the phenothiazine derivatives under study.
This represents the average of five observations with promethazine 50 mg and of two with each of the other drugs. The average of seven readings with pethidine 100 mg is included for comparison.

Bearing in mind the limitation of these findings it would appear that all the compounds studied increase sensitivity to pain and that this effect seems to be more marked with promethazine 50 mg than with the other drugs. The maximum "anti-analgesic" effect appeared about 20 minutes after intravenous injection but it was not possible to prolong the investigations and thus obtain an estimate of its duration of action. There was no correlation between the onset of restlessness and increased appreciation of pain, and in fact many patients had passed through the stage of extreme agitation and were calm and drowsy when the greatest decrease in pain readings was noted.

**Intramuscular injection.**

In these studies the phenothiazine derivatives were given in combination with atropine 0.6 mg, as pre-anaesthetic medication before the operation of uterine curettage. The patients were all of good physical status, conforming to the requirements of grades 1 and 2 risks of the American Society of Anesthesiologists' classification as described by Dripps, Eckenhoff and Vandam (1957).

Control readings in duplicate were made before injection of the drug and on two or more occasions before the induction of anaesthesia. It was observed that the peak effect of the phenothiazine derivatives occurs 75 to 90 minutes after intramuscular injection and it was necessary to make certain that readings were made at this time.

Since the actions of nine phenothiazine derivatives were studied and since two of these were studied at more than one dose level, it was not possible to present the findings in the same detail as for promethazine 50 mg in the earlier publication. We therefore calculated the percentage incidence of changes in both the threshold and response readings which we observed 75 to 90 minutes after administration of the phenothiazine derivatives. These are shown in table I, which also includes data for pethidine 100 mg to illustrate the different effects of the phenothiazine and analgesic drugs.

In order to arrive at a single figure for each drug, which would give some guide as to its analgesic or anti-analgesic action the "analgesia index" has been devised. This is calculated as follows:

\[
\text{Analgesia index} = \frac{(\text{Incidence of decrease in readings})}{(\text{Incidence of increase in readings})} - 1
\]

Total number of observations.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>No. of patients</th>
<th>Percentage incidence of alteration in pain readings</th>
<th>Analgesia index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>50</td>
<td>11</td>
<td>Increase 22, No change 70, Decrease 8</td>
<td>+0.14</td>
</tr>
<tr>
<td>Trimeprazine</td>
<td>25</td>
<td>10</td>
<td>Increase 48, No change 38, Decrease 14</td>
<td>+0.34</td>
</tr>
<tr>
<td>Promazine</td>
<td>100</td>
<td>22</td>
<td>Increase 25, No change 64, Decrease 11</td>
<td>+0.14</td>
</tr>
<tr>
<td>Promazine</td>
<td>25</td>
<td>20</td>
<td>Increase 17, No change 75, Decrease 8</td>
<td>+0.09</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>12.5</td>
<td>17</td>
<td>Increase 0, No change 83, Decrease 17</td>
<td>-0.17</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>5</td>
<td>30</td>
<td>Increase 7, No change 67, Decrease 26</td>
<td>-0.19</td>
</tr>
<tr>
<td>Trifluperazine</td>
<td>1</td>
<td>9</td>
<td>Increase 0, No change 67, Decrease 33</td>
<td>-0.33</td>
</tr>
<tr>
<td>Triflupromazine</td>
<td>20</td>
<td>24</td>
<td>Increase 0, No change 63, Decrease 37</td>
<td>-0.37</td>
</tr>
<tr>
<td>Promethazine</td>
<td>50</td>
<td>56</td>
<td>Increase 2, No change 30, Decrease 68</td>
<td>-0.66</td>
</tr>
<tr>
<td>Promethazine</td>
<td>10</td>
<td>12</td>
<td>Increase 8, No change 20, Decrease 72</td>
<td>-0.64</td>
</tr>
<tr>
<td>Pecazine</td>
<td>50</td>
<td>11</td>
<td>Increase 0, No change 27, Decrease 73</td>
<td>-0.73</td>
</tr>
<tr>
<td>Pethidine</td>
<td>100</td>
<td>80</td>
<td>Increase 62, No change 31, Decrease 7</td>
<td>+0.55</td>
</tr>
</tbody>
</table>
It can be seen from table I, that none of the phenothiazine derivatives showed the same degree of analgesic action as pethidine. The findings in this table enable them to be classified into three groups as follows:

1. Those showing some analgesic activity, as judged by a positive analgesia index. (Chlorpromazine, trimeprazine, and promazine.)

2. Those with a mild anti-analgesic action, in which the majority of changes in readings fell within the accepted range of error of the method of analgesimetry but where analgesia index has a negative value. (Prochlorperazine, perphenazine, trifluperazine, trifluromazine.)

3. Markedly anti-analgesic drugs, with a preponderance of decrease in pain readings and a negative analgesic index. (Promethazine and pethazine.)

There was no significant difference in the distribution of the incidence of changes in readings between individual drugs in any of the above groups.

The average effect of each of the three classes of drugs is shown in table II, and it can be seen that each group is significantly different from the others. Lest it be thought that the title "some analgesic activity" ascribed to group 1 in this table suggests that it is composed of pethidine-like drugs, it is important to note that a highly significant difference in the incidence of alterations in pain readings exists between the effects of these phenothiazines and that of pethidine (table III). The number of observations with trimeprazine was too small to include in this analysis and the reasons for this paucity of cases have been explained (Dundee and Moore, 1961c).

### Table II

*Comparison of analgesic action of groups of phenothiazine derivatives, arranged according to scheme outlined in text.*

<table>
<thead>
<tr>
<th>Group</th>
<th>Class</th>
<th>Percentage incidence of alterations in pain readings</th>
<th>Analgesia index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>1</td>
<td>Some analgesic activity</td>
<td>27</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Mildly anti-analgesic</td>
<td>3</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>Markedly anti-analgesic</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

Groups compared
- 1 and 2
- 1 and 3
- 2 and 3

\[
\chi^2 = 28.232; \quad df = 2; \quad P < 0.001
\]

\[
\chi^2 = 93.006; \quad df = 2; \quad P < 0.001
\]

\[
\chi^2 = 29.989; \quad df = 2; \quad P < 0.001
\]

### Table III

*Comparison of the analgesic action of the group I phenothiazines with that of pethidine 100 mg.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>(\chi^2)</th>
<th>df</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine 50 mg</td>
<td>21.347</td>
<td>2</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Promazine 100 mg</td>
<td>16.075</td>
<td>2</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Promazine 25 mg*</td>
<td>8.952</td>
<td>1</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>All Group 1</td>
<td>35.962</td>
<td>2</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

* With promazine 25 mg it was necessary to pool two groups of effects (increase in readings and no change in readings).
The subdivision of phenothiazine drugs according to analgesic activity bears no relationship to the chemical subdivision in figure 1. A few comparisons of the effects of compounds differing only in one chemical group are shown in table IV. Although only the "analgesia index" is shown in this table, differences were calculated from the absolute figures which form the basis of table I.

It is unwise to draw too rigid conclusions as to the effect of chemical structure on clinical action from observations with a small number of drugs but we have definitely failed to substantiate the finding of Hougs and Skouby (1957) that chlorination increases the analgesic action of the phenothiazines. This is further shown by the presence of two chlorinated compounds (perphenazine and prochlorperazine) in group 2 as classified above, while the group of compounds showing most analgesic activity contained only one chlorinated phenothiazine. The action of fluorination in decreasing analgesic activity appears to be pronounced but observations with more compounds are needed before this can be stated with certainty.

The effect of replacing a dimethylaminopropyl side chain by a piperazine ring on the analgesic action of phenothiazines is not clarified by the data in table IV. It may be of some importance to note that all the piperazine-containing phenothiazines have been classed as having mild anti-analgesic activity in table I, whereas all the ones for which an analgesic action has been demonstrated have a dimethylaminopropyl side chain.

The present findings do not suggest any reason for the strong anti-analgesic action of promethazine, which is demonstrable even with a 10 mg dose. The consistency of this action is shown by the fact that the analgesic index is practically identical for 50 and 10 mg doses of promethazine and, as will be seen, this index was calculated from a fairly large series of observations with both doses. The writers are also unable to suggest any chemical relationship between promethazine and perazine, which might be responsible for the similarity of their actions.

**DISCUSSION**

It is necessary to stress that the main findings in this paper apply to the effects of the phenothiazines as observed 60 to 90 minutes after intramuscular injection. They do not exclude the possibility of a biphasic reaction with an early increase in appreciation of pain followed by a later decrease. Clinical facilities did not permit the authors to carry out observations at longer time intervals. The findings are considered to be of importance to anaesthetists in that they reflect the changes in response to somatic pain which may be

### Table IV

**Comparison of effect of phenothiazines, which differ from each other in only one chemical group, on the patients' appreciation of pain.**

<table>
<thead>
<tr>
<th>Factors under study</th>
<th>Drugs compared</th>
<th>Analgesia index</th>
<th>Significance of difference</th>
</tr>
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<tbody>
<tr>
<td>Dimethylaminopropyl</td>
<td>Triflupromazine 20 mg</td>
<td>-0.33</td>
<td>( \chi^2 = 0.084: df = 1^*: 0.80 &gt; P &gt; 0.70 )</td>
</tr>
<tr>
<td>Piperazine side chains</td>
<td>Trifluperazine 1 mg</td>
<td>-0.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine 50 mg</td>
<td>+0.14</td>
<td>( \chi^2 = 9.404: df = 2: P &lt; 0.01 )</td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine 12.5 mg</td>
<td>-0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triflupromazine + Chlorpromazine</td>
<td>-0.17</td>
<td>( \chi^2 = 3.709: df = 1^*: 0.10 &gt; P &gt; 0.05 )</td>
</tr>
<tr>
<td></td>
<td>Trifluperazine + Prochlorperazine</td>
<td>-0.23</td>
<td></td>
</tr>
<tr>
<td>Chlorination</td>
<td>Promazine 100 mg</td>
<td>+0.14</td>
<td>( \chi^2 = 0.250: df = 2: 0.70 &gt; P &gt; 0.50 )</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine 50 mg</td>
<td>+0.14</td>
<td></td>
</tr>
<tr>
<td>Fluorination</td>
<td>Promazine 100 mg</td>
<td>+0.14</td>
<td>( \chi^2 = 8.591: df = 2: P &lt; 0.02 )</td>
</tr>
<tr>
<td></td>
<td>Triflupromazine 20 mg</td>
<td>-0.33</td>
<td></td>
</tr>
</tbody>
</table>

* Paucity of numbers of cases showing a rise in readings necessitated pooling these with those in whom the drug had no appreciable effect on the pain readings. The significance levels were calculated from the incidence of readings which revealed an increase in sensitivity to pain as compared with the remaining observations.
anticipated with the drugs which are used for routine pre-anaesthetic medication.

These results show that minor alterations in the side chains attached to the phenothiazine nucleus can produce marked differences in their clinical actions. This is known to apply to the barbiturates, ethers, sulphonamides and many other widely used drugs. In the case of the barbiturates the effects of some of the side chains are fairly well understood but, apart from the decrease in analgesic activity produced by fluorination, this does not yet apply to the phenothiazine group. However, although this study is only concerned with one facet of their actions, it demonstrates that it is wrong to consider the phenothiazines as a group of compounds with qualitatively similar actions in which the more recently introduced compounds differ from chlorpromazine only in their potency and toxicity.

This study also prompts reconsideration of the action of the "lytic cocktail" consisting of pethidine, promethazine and chlorpromazine. Moore and Dundee (1961a) found that a mixture of pethidine 100 mg and promethazine 50 mg was almost devoid of analgesic activity and, from the present results it would not be expected that the addition of 50 mg chlorpromazine would enhance the analgesic action of this mixture to any significant degree. However, Smith and Fairer (1953) and Harrison (1955) reported that following the use of the lytic cocktail patients did not require any postoperative analgesic drugs for several hours. They stressed that the pain-free postoperative period was one of the advantages associated with its use. Vialard (1953) found that an infusion of pethidine and chlorpromazine eased pain in patients in whom the opiate alone was ineffective. In the light of the findings in this paper, these observations, together with the beneficial effects of the phenothiazines in obstetrics (including those classed in table I as being markedly anti-analgesic) suggest that the view that they produce a "pharmacological frontal lobotomy" as postulated by Terzain (1952). Detailed studies of the analgesic action of the pethidine, promethazine and chlorpromazine combination are in progress in order to clarify this point.

One of the most important clinical applications of the findings in this study is the effect of the pre-anaesthetic use of the phenothiazine compounds on the course of barbiturate anaesthesia. Dundee and Riding (1960) demonstrated that opiate premedication reduced the incidence of abnormal muscle movements associated with the use of thiopentone and Inactin. Subsequent investigations showed that anaesthesia with methohexitone (Brietal) was much more influenced by the type of premedication than were the two thiobarbiturates; compared with the use of atropine alone, pethidine very markedly lowers the frequency of muscle movements (Dundee and Moore, 1961a), whereas the anti-analgesic drugs promethazine (Moore and Dundee, 1961a), and hyoscine (Dundee and Moore, 1961b) increases both the incidence and intensity. In a study carried out concurrently with the present one, the authors found that the incidence of abnormal spontaneous muscle movements occurring following the injection of 1.6 mg /kg of methohexitone was directly related to the analgesic index of the phenothiazine derivatives used for pre-anaesthetic medication (Dundee and Moore, 1961c). The extent to which these findings apply to thiopenitone has not yet been determined.

It is tempting to postulate some connection between the findings of these analgesic studies and the anti-adrenaline action of the phenothiazines. Gross et al. (1948) have demonstrated the analgesic effect of adrenaline in man, while Parson and Goetzl (1945) claimed that pain itself raises the pain threshold because of the release of adrenaline. Animal experiments by Goetzl, Burrill and Ivy (1944) showed that amphetamine intensifies morphine analgesia, while there are many convincing reports of the beneficial effects of combinations of amphetamine or dextroamphetamine with mild analgesics (Long, 1950; Coppersmith, 1951; Reed, 1956). An adrenolytic action has been claimed for most of the phenothiazine derivatives but comparative data concerning their potency in this respect is limited to the report of Eggers, Corssen and Allen (1959). Their finding that chlorpromazine has a more marked adrenolytic effect than promethazine, while the action of pecazine is intermediate between these two, cannot be correlated with the observations reported here on the anti-analgesic action of the drugs. It is not possible, however, to dismiss completely some, as yet unexplained, connection between these two facets of the action of the drugs.
SUMMARY AND CONCLUSIONS

Although there is some evidence in the literature to show that chlorpromazine potentiates the action of analgesic drugs, this has not been shown to apply to all the members of the phenothiazine group. This aspect of their actions has been studied by the authors, using a method of analgesimetry in which a measurable degree of pressure is applied to the anterior surface of the tibia until the patient experiences pain.

The findings suggest a division of the phenothiazines into three groups as follows:

1. Those having some analgesic activity: chlorpromazine, promazine, trimeprazine.
2. Those having slight anti-analgesic action: prochlorperazine, perphenazine, trifluoperazine, triflupromazine.

Several unsuccessful attempts were made to correlate the above grouping with the chemical structure of the drugs. Fluorination may decrease analgesic action to some extent.

The degree of analgesia produced by group 1 phenothiazines is not as marked as that produced by pethidine.

Some of the implications of these findings have been discussed.

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CORRESPONDENCE

MUSCLE PAINS AFTER SUXAMETHONIUM AND SUXETHONIUM

Sir,—The investigation reported by Burtles (Brit. J. Anaesth., 1961, 33, 147) showed no appreciable difference in the pain producing powers of these two drugs when used by a group of anaesthetists with differing techniques and anaesthetic drugs. In my investigation (Brit. J. Anaesth., 1959, 31, 530) I tried at first to assess the results obtained by all our anaesthetists in a somewhat similar fashion, but found the results unreliable and certainly not comparable because of the wide variations in techniques, drugs, and of course in the skill of the anaesthetist. I therefore restricted my investigation to my own work entirely, in an attempt to obviate a large number of these variables.

Under these circumstances, therefore, it seems to me that the basis of my comparison made on patients I anaesthetized myself, when almost all the surgery was performed by one surgeon, and at times the two drugs compared on the same patient, is more reliable than that reported by Burtles.

I can state with confidence that the differences I observed have led me to use suxethonium in preference to suxamethonium whenever I require a short-acting relaxant.

G. E. HALE ENDERBY