Although it has never been claimed that the phenothiazines have an analgesic action comparable to that of the opiates, it is frequently inferred that they have some effect on pain. They are widely used to potentiate analgesic drugs in the management of intractable pain and have enjoyed great popularity in the treatment of the terminal stages of malignant disease.

Apart from their anti-emetic effect, the rationale of the pre-operative use of the phenothiazines has never been clearly defined. Here they are usually administered in combination with analgesics and their sedative and tranquillizing properties are considered to be highly desirable. This popularity is evidenced by the marketing of the "Pamergan" preparations which contain pethidine and promethazine. When these first became available the authors were evaluating a method of analgesimetry, using pethidine 100 mg as the standard drug. It was expected that Pamergan P.100 (pethidine 100 mg and promethazine 50 mg) would produce a more marked and consistent degree of analgesia than pethidine alone. As will be shown later, this was not the case and this surprising finding led us to study the effects of promethazine 50 mg and the above mentioned mixture in more detail.

This paper reports the results of this study and compares the findings with those reported for pethidine alone by Dundee and Moore (1960). For the sake of clarity, the mixture of pethidine 100 mg and promethazine 50 mg is referred to by its proprietary name of "Pamergan P.100".

METHOD
All observations were made in patients prior to the induction of anaesthesia and where the intramuscular route was employed, atropine 0.6 mg was given in addition to the drug under study. (This is known to have no appreciable effects on the readings.) The patients' reaction to pain was measured by the application of variable pressure to the anterior surface of the tibia and two endpoints were elicited:
1. threshold: first appreciation of pain.
2. response: pain unbearable.

The technique and reliability of this method of analgesimetry has been previously described in detail by Dundee and Moore (1960).

RESULTS

Promethazine.
The effect of the intravenous injection of promethazine 50 mg on pain threshold and response readings in five patients is shown in figure 1. This injection was followed by a high incidence of restlessness which limited the number of observations but it can be seen that it resulted in a consistent increase in sensitivity to pain.

Studies were carried out at varying intervals following its intramuscular use in 42 patients (fig. 2). These also demonstrated a high incidence of increases in sensitivity to pain which were detected 20 minutes after administration and persisted for as long as 3 hours.

Comparison with pethidine.
Figure 3 compares the percentage incidence of the effects of the intramuscular injection of 50 mg promethazine with the data for pethidine 100 mg referred to above. This figure does not include patients in whom the alteration in readings was within the accepted experimental error of the method used in the studies and it shows that the effect of the two drugs appears to be antagonistic and the duration of their action is similar.

It was possible consistently to demonstrate an antagonism of pethidine-induced analgesia by
promethazine and one such finding is shown in figure 4. The blood pressure and the heart rate are shown in this figure in view of a previous observation that marked hypotension interferes with the reliability of the readings.

_Pamergan P.100._

This mixture was administered intravenously to six patients and produced no consistent pattern of change in the pain readings (fig. 5). Likewise when the intramuscular route was used in 60 patients (fig. 6), the results were very inconclusive and it seemed that the antagonism between the constituents demonstrated in figures 3 and 4 produced a mixture which had no effect on the appreciation of pain. No relationship between dosage and effect can be demonstrated in figure 6.

However, it was shown by Dundee and Moore (1960) that the response to the intramuscular injection of pethidine 100 mg, as measured by the method used in this study, varied with the patients' initial control threshold reading. This was more consistent and marked in those subjects who had a low initial pain threshold. The incidence of changes with pethidine 100 mg and Pamergan P.100 related to dosage and the patients' control reading is shown in figure 7 and the significance levels of the differences between the drugs is given in table I. This demonstrates that with low dosage of Pamergan (in mg/kg) the "anti-analgesic" action of the promethazine appears to more than counteract the analgesic effect of the pethidine. It suggests that a more beneficial mixture which would retain some of the analgesic action of pethidine and yet contain sufficient promethazine to exert an anti-emetic effect might be achieved by a decrease in the amount of the latter drug.

**DISCUSSION**

In view of the widely held belief that the phenothiazines potentiate the action of analgesics, these findings were somewhat unexpected. They show that one member of this group of drugs (promethazine), rather than increasing the analgesic action of pethidine, markedly antagonized the effect of the analgesic on the patient's appreciation of pain.

Despite the enormous literature on the phenothiazines we are unable to find any concrete data showing that promethazine does, in fact, increase the action of analgesics, although this may occur with other phenothiazines (Courvoisier et al., 1953; Hougs and Skouby, 1957). This has led the authors to extend their studies to include other phenothiazines and the findings will be published at a future date. A discussion on possible explanations of our findings will be reserved until our data is complete.
Alterations in pain threshold and response readings following the intramuscular injection of promethazine 50 mg in 42 patients.

--- Accepted range of error with the method of analgesimetry.

**Fig. 2**
Percentage incidence of increases and decreases in pain threshold and response readings following intramuscular injection of pethidine 100 mg and promethazine 50 mg.

The effect of promethazine 50 mg (I.V.) on the analgesic induced by pethidine 100 mg given by intravenous injection.

Upper curve—pain response readings.
Lower curve—pain threshold readings.

The effect of the intravenous injection of a mixture of pethidine 100 mg and promethazine 50 mg on pain threshold and response readings. Figures refer to dose of pethidine in mg/kg.
Alterations in pain threshold and response readings following the intramuscular injection of Pamergan P.100 in 60 patients.

Dosage (in mg/kg pethidine in mixture) indicated as follows:
- △ low dosage, under 1.5 mg/kg
- ○ medium dosage, 1.5–2.0 mg/kg
- X high dosage, over 2.0 mg/kg

--- accepted range of error associated with the method of analgesimetry.
Using a method of analgesimetry which employs the application of graded pressure to the tibia, the authors have studied the effect of promethazine 50 mg, and a mixture of pethidine 100 mg and promethazine 50 mg (Pamergan P.100) on the appreciation of pain. The results have been compared with published data on the action of pethidine alone.

Irrespective of the route of administration, promethazine consistently increased the patients' sensitivity to pain and its action was directly opposite to that of pethidine. Pamergan P.100 produced no consistent pattern of changes and had much less analgesic action than pethidine.

The significance of these findings will be discussed in a further publication when data from all the phenothiazines is available.

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REFERENCES

