Comment: This work confirms majority opinion that the anesthetic molecules *per se* do not possess molecular characteristics of sensitizing agents. Although, a few years ago, the "sensitization" theory was popular, so far there is little conclusive evidence in that regard. There are several case reports in which the following sequence has occurred: first a halothane anesthetic with no problem; second exposure with development of jaundice; a third exposure with no hepatic problems. This clinical experience appears to mitigate against hypersensitivity, since immune responses are not considered to be off and on phenomena. Perhaps, if the entity of halothane hepatitis exists, metabolism of the anesthetic may play a role. It will be of considerable interest to see further developments in studies of antigenicity of halothane metabolites.

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DOSAGE/SIDE-EFFECT RELATIONSHIPS OF MORPHINE AND MEPERIDINE

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Anesth. Analg., *52:* 536–541, July–August, 1973

Morphine and meperidine are among the most commonly used analgesic drugs. Data from a large number of administrations were reanalyzed to see what dose-response relationships might emerge with respect to such side effects as nausea and/or vomiting, dizziness, hypnosis, and relief of preoperative anxiety.

Patients undergoing cervical dilation and uterine curettage were premedicated with morphine (0.051 to 0.5 mg. per kg.) or meperidine (0.4 to 3.3 mg. per kg.) and were left undisturbed except for observer visits after 20, 40, 60, and 90 minutes. In addition, the incidence of nausea in the first 6 postoperative hours was assessed.

Emesis and nausea showed a consistent tendency to increase in incidence as dosage increased; however, after meperidine the incidence was low until a dose of 0.75 mg. per kg. was attained. At this point it increased rapidly to a dose of 2.25 mg. per kg. and then fell off. Emesis after morphine was relatively constant at 57 per cent, whereas after meperidine it varied from 31 to 58 per cent.

Drowsiness increased from 12.5 to 85 per cent for morphine and 20 to 86 per cent after meperidine. For both drugs, drowsiness rose steeply in lower dose ranges and then plateaued above 0.275 mg. per kg. for morphine and 2 mg. per kg. for meperidine.

Preoperative anxiety was well controlled by meperidine in therapeutic levels, whereas morphine showed 2 peaks of apprehension at low and high levels of administration.

Dizziness increased linearly with both drugs as dosages were increased.

These findings indicate that there is not a similar dose-response relationship for each aspect of a drug's action. The establishment of such a relationship for one aspect of action does not mean that it may be extrapolated to other possible effects. For example, analgesic dose-response curves and those of respiratory depression may not be similar.

Comment: This study is helpful in selection of drugs for premedication. The commentator could not, however, go along with the extrapolation of the results to respiratory depression where in animals, at least, a log dose response curve can be demonstrated for both morphine and meperidine—both for rate and respiratory minute volume (Hunter, A. R., Rees, J. M. H. and Pleuvry, B. J., Anaesth., *40:* 927, 1963).
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ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA.

XIII: NIKETHAMIDE, DOXAPRAM, AND NALOXONE

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Br. J. Anaesth., *45:* 497–500, May, 1973

Adult women scheduled for minor gynecologic procedures were studied prior to surgery, without premedication, by the tibial pressure algesimetric method (Dundee and Moore, 1960) wherein gradually increasing pressure applied to the anterior surface of the tibia is reported as an initial feeling of pain (threshold) and then as intolerable (response).

These studies were carried out in 30 subjects who received meperidine 100 mg. per 60 kg. i.v., followed 5 minutes later by nikethamide 250 mg., doxapram 60 mg., or naloxone 0.4 mg. In a second series of 50 patients, morphine 10 mg. alone, or in association with 1 of the 3 above drugs was compared with a saline control group. The drug mixtures were not known to the investigators.

Analgesia was noted in 70 to 80 per cent of the patients who received meperidine. Doxapram had no effect on the degree of analgesia, nikethamide reduced it somewhat but not significantly, and naloxone almost entirely abolished the analgesic effects of meperidine within 3 to 5 minutes of administration.

The results associated with morphine were similar. There were several analgesic responses associated with saline injection.

Naloxone was shown by this method to be capable of anatogonizing the analgesic effects of both morphine and meperidine. Doxapram had no antanalgesic effects and nikethamide showed a transient and fleeting effect on analgesia.