

spiration, 3 l./minute; expiration, 2½ l./minute) the resistance of the valve is negligible.

We have combined the valve with a single canister (taken from an adult Roswell-Park double canister) to make a pediatric circle system. § This canister (filled with Baralyme 4-8 mesh) with the breathing hose (19 mm. diameter, 70 cm. long) has a pressure drop of 1 mm. H<sub>2</sub>O at a flow of 20 l./minute of oxygen. Similar resistances have been reported for other adult canisters.<sup>3,4</sup> A spring-loaded pop-off is placed just distal to the expiratory valve seat. The tapers on the inspiratory and expiratory valve units are not the same. Thus, it is impossible to attach directly two inspiratory or two expiratory units instead of one of each (fig. 1). The circle has been used satisfactorily in several thousand pediatric anes-

thesia cases in patients ranging in size from small premature newborns to children 12 years of age.<sup>5</sup>

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### The Effects of Fentanyl and Droperidol, Alone and in Combination, on Pain Thresholds in Human Volunteers

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The advantages of neuroleptanalgesia and the pharmacologic effects of the drugs used to produce this state have been reported widely.<sup>1-4</sup> The drugs most commonly used for this purpose in the United States are droperidol, a potent ataractic, and fentanyl, a potent narcotic, combined (Innovar®) in a fixed 50-to-one ratio. It has been reported that droperidol markedly potentiates the analgesic effects of narcotics in both man<sup>1</sup> and animal.<sup>5</sup> To demonstrate this potentiation, we decided to measure algesimetric responses to fentanyl, droperidol, a droperidol-and-fentanyl mixture, and a saline placebo.

## METHOD AND MATERIALS

Eight female and six male volunteers between the ages of 20 and 35 served as subjects. Studies were conducted on a double-blind basis. All drugs and the saline placebos were injected intravenously in a total volume of 10 cc. over a period of two minutes. The end of the injection was designated zero time. An earlobe algesimeter was used to determine pain threshold, using a technique previously described.<sup>6</sup> After pre-drug control determinations of pain thresholds were obtained, each of six subjects (Group I) received 0.0015 mg. per kg. fentanyl, 0.075 mg. per kg. droperidol, a combination of these two drugs and a saline placebo, at intervals of not less than one week. Pain thresholds were determined at five-minute intervals for 30 minutes and at ten-minute in-

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tervals thereafter for a total test period of three hours. Using the same technique, the analgesic response to two dose levels of fentanyl (0.0015 and 0.0022 mg. per kg.) and a saline placebo were compared in the remaining eight subjects (Group II). On the day following the test the subjects were interviewed and their comments noted.

RESULTS

In Group I, a significant analgesic response lasting 40 minutes followed the administration of 0.0015 mg. per kg. fentanyl. Administration of droperidol alone produced a statistically insignificant diminution of pain threshold. Administration of droperidol and fentanyl combined was associated with an analgesic response which did not differ significantly in degree, but was of shorter duration (20 minutes) than with fentanyl alone. Average pain thresholds for the saline placebos were within 10 per cent of pre-test controls throughout the study.

In Group II significant analgesic responses were seen with both doses of fentanyl. Although the degrees of analgesia in the two dose ranges were not significantly different, the duration of significant analgesia was 50 minutes with the larger dose compared with 25 minutes with the smaller dose.

The average pain thresholds for both groups appear in table 1 and figs. 1 and 2. Since average pain thresholds recorded during the third hour did not differ significantly from pre-test controls with any of the drugs used, they are omitted from the tables and figures.

Following droperidol, with or without fentanyl, all but one subject in Group I experienced restlessness during the remainder of the test day and moderate-to-marked insomnia during the night after the test. Following the combination, one subject experienced vertigo till noon of the following day and a second subject was nauseated during the evening. This subject experienced no nausea following the administration of fentanyl alone. Nausea did not occur following the administration of fentanyl alone or in combination with droperidol in the other subjects. Noteworthy responses following the saline placebo were absent except for one subject who reported a headache during the evening following the test.

TABLE 1. Pain Thresholds, Expressed as Per Cent of Control, in Two Groups of Human Volunteers Receiving Fentanyl and Droperidol, Alone or in Combination, and a Saline Placebo

		Time in Minutes											
		5	10	15	20	25	30	40	50	60	80	100	120
Group I	Fentanyl 0.0015 mg./kg.	132 ± 22.1*	121 ± 14.1	124 ± 18.0	122 ± 12.7	128 ± 20.0	119 ± 11.1	116 ± 14.8	111 ± 13.3	103 ± 7.0	101 ± 11.2	102 ± 7.2	
	Droperidol 0.075 mg./kg.	90 ± 14.2	90 ± 17.1	92 ± 11.7	86 ± 14.6	97 ± 12.5	95 ± 11.0	98 ± 13.7	95 ± 14.0	100 ± 10.2	105 ± 7.4	98 ± 16.2	90 ± 12.1
	Droperidol 0.075 mg./kg. + fentanyl 0.0015 mg./kg.	117 ± 20.3	121 ± 12.9	127 ± 27.4	124 ± 18.5	107 ± 17.4	109 ± 17.3	103 ± 22.8	114 ± 20.4	108 ± 18.0	107 ± 24.3	102 ± 27.1	103 ± 10.6
	Saline control	97 ± 15.0	91 ± 12.3	99 ± 10.4	94 ± 11.2	96 ± 7.5	100 ± 9.8	101 ± 11.3	90 ± 9.8	94 ± 15.7	100 ± 10.0	101 ± 11.2	100 ± 14.5
Group II	Fentanyl 0.0015 mg./kg.	130 ± 22.3	122 ± 10.2	134 ± 22.2	130 ± 23.1	125 ± 25.9	128 ± 11.9	110 ± 28.3	112 ± 21.4	109 ± 22.5	88 ± 25.4	104 ± 20.4	85 ± 18.0
	Fentanyl 0.0022 mg./kg.	138 ± 32.5	134 ± 18.2	150 ± 33.5	136 ± 11.2	130 ± 35.8	131 ± 31.2	132 ± 35.1	133 ± 20.4	111 ± 16 ± 31.3	128 ± 20.4	100 ± 20.7	107 ± 23.1
	Saline control	90 ± 15.2	94 ± 12.2	104 ± 13.2	99 ± 13.8	101 ± 8.1	99 ± 12.6	109 ± 10.1	99 ± 9.1	94 ± 13.5	101 ± 17.0	94 ± 10.7	90 ± 11.2

\* Standard deviation.

## DISCUSSION

Criticism of algesimetry as a technique for the study of pain-relieving drugs has been based upon the dissimilarity between pain of organic origin and experimental pain.<sup>7</sup> Obviously, there are pertinent differences between the subject of an experimental pain study and a "sick and anxious patient whose pain is mysterious, unpredictable and of unknown causation."<sup>7</sup> Other limitations on the interpretation of algesimetric studies are suggested by the recent work of Robson and his associates,<sup>8</sup> who reported that the same drug may produce opposite results when different modalities of pain are tested. It is possible that different results might have been obtained with droperidol using a different modality of pain, but reports of such work are not available.

Recruitment of volunteers for this study became progressively more difficult because of unpleasant side effects following the administration of droperidol, either alone or in combination with fentanyl. These effects included feelings of uneasiness, apprehension and insomnia characterized by the inability to find a comfortable position which, in some instances, extended for periods of 24 to 36 hours. In addition to the subjects reported, these effects were seen in four others who

withdrew from the study before its completion. Such subjective responses to droperidol have been observed by others<sup>9</sup> in studies utilizing conscious volunteers. In a recent study<sup>10</sup> in which neuroleptanalgesia was used in more than 100 pneumoencephalograms, such side effects were not a prominent feature during the 36 hours following the procedure. The conscious volunteers were ambulatory following the study, whereas the patients following pneumoencephalography almost uniformly were confined to bed. This suggests that ambulatory patients are not good candidates for this technique.

We were unable to demonstrate potentiation of fentanyl's analgesic effect by droperidol in the subjects studied. These findings suggest that the clinical efficacy of the mixture may be the result of other mechanisms. It has been suggested that the reticular formation exerts inhibitory as well as excitatory influences on the cerebral cortex.<sup>11,12</sup> If the inhibitory effects are depressed, the excitatory influence (Forbes response<sup>13</sup>) predominates.<sup>14</sup> Brazier<sup>14</sup> has discussed excitatory predominance as a feature of early barbiturate anesthesia; as anesthesia deepens the excitatory influence also becomes depressed, and ultimately the cortex becomes unresponsive.

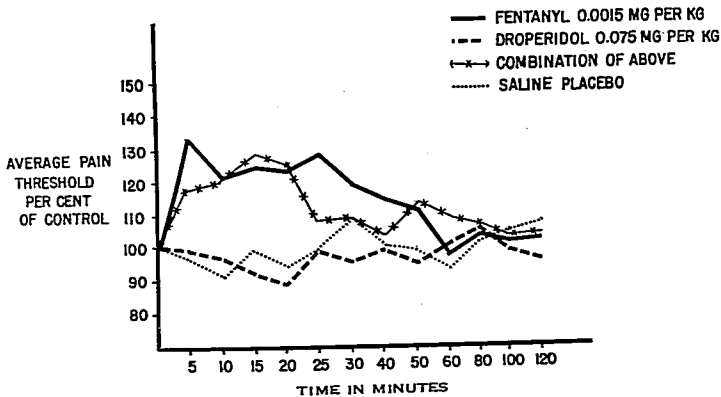
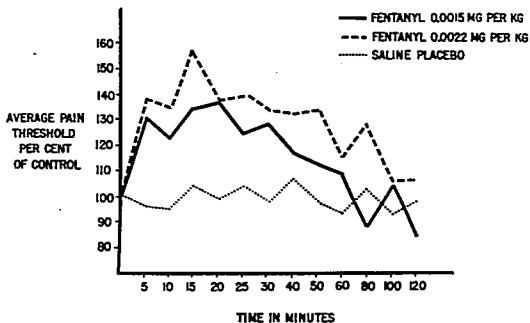


FIG. 1. The effects of fentanyl and droperidol, alone and in combination, and a saline placebo on pain thresholds in human volunteers.

FIG. 2. The effects of two dose levels of fentanyl and a saline placebo on pain thresholds in human volunteers.



Clutton-Brock's<sup>15</sup> original description of "antanalgesia" referred to the ability of pentobarbital to depress pain thresholds previously elevated by meperidine. A similar effect on narcotic-induced analgesia was noted by Dundee *et al.*<sup>16</sup> and the present authors<sup>17</sup> for certain phenothiazines. It is possible that during algometric studies such decreases in pain threshold may be associated with increased cortical responsiveness secondary to decreased influence of inhibitory pathways. The occurrence of drowsiness with a decrease in pain threshold suggests unequal depression of both components of ascending reticular influence.

It would be reasonable to speculate that such increased cortical responsiveness bears a relationship to the classical second stage of general anesthesia. Work by the present authors<sup>18</sup> has demonstrated a fall in pain threshold with the onset of drowsiness and delirium during studies with subhypnotic concentrations of halothane and methoxyflurane. This fall occurred despite blood levels of the agent in excess of those associated with previously elevated thresholds. This sequence is similar to that reported by Artusio,<sup>19</sup> who described a stage of analgesia prior to the stage of delirium during the inhalation of ether.

The present studies with droperidol demonstrated no effect on pain threshold when given alone nor any alteration in the expected increase when combined with fentanyl. A similar effect was seen in studies with promazine,<sup>17</sup> suggesting that the site of action of these drugs may differ, at least in part, from that of the

other phenothiazines studied (promethazine and propiomazine) and the barbiturates. However, droperidol, in common with the phenothiazines, produced marked drowsiness.

It is often difficult to extrapolate purely experimental findings to clinical situations. However, the present study and those formerly reported from this laboratory<sup>17</sup> suggest that the term potentiation may have been used inappropriately in characterizing drug combinations such as droperidol and fentanyl or phenothiazines and narcotics. In clinical usage their combined effects may not be due to true potentiation. Rather, the dimension provided by the non-narcotic component of these combinations may reside in their ability to sedate and to tranquilize.

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### A Venturi Circulator for Anesthetic Systems

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The Dual-Venturi Circulator † is designed to move the warm, moist, anesthetic atmosphere at high flow around the circuit of a semi-closed carbon dioxide absorption system. The input of anesthetic gases and oxygen is injected into the system at low flow through two identical, parallel, Venturi jets. This convenient mode of operation thus eliminates any need for an auxiliary source of power. The mechanism is simple in construction, quiet in operation, and unusually free from trouble because there are no moving parts.

Besides these advantages, inherent in Venturi design, the use of such a circulator provides all the benefits of a high-flow circulating system. Gases and vapors are mixed rapidly

within the circuit, eliminating abruptness or undue delay in changes of concentrations in the inspired atmosphere. Resistance to breathing through tubes, valves and soda lime is compensated. Under-mask deadspace is ventilated thoroughly if a partitioned Y piece is used to connect the breathing tubes with the face mask. ‡ Control of temperature and humidity is available. The breathing space becomes, in effect, a miniature air-conditioned chamber. These advantages are progressively more important with the smaller sizes of children and infants.<sup>1</sup>

For pediatric anesthesia, the diversity of apparatus and methods in past use has resulted from a general dissatisfaction with the various answers to the problems of deadspace, resistance, and control of temperature and humidity. A current trend toward the use of adult circle absorbers in preference to the miniaturized versions or the various non-rebreathing systems has been accelerated by the development of halothane as a very expensive but also very desirable anesthetic agent. The problems still inherent in the ap-

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† The Dual Venturi Circulator is available commercially from Ralph Neff Associates, 1441 Flicker Way, Sunnyvale, California 94086.

‡ The partitioned Y or divided chimney Y piece is listed in the catalogs of Dupaco, Arcadia, California 91006, and Ohio Chemical Co., Madison, Wisconsin 53700.