COMPONENTS OF RESPIRATORY DEPRESSION AFTER NARCOTIC PREMEDICATION IN ADOLESCENTS

R. Knill[*], J.F. Cosgrove[†], P. M. Olley, and H. Levison

Narcotic agents are potent depressants of ventilation.[1-5] Although this effect is generally assumed to result from decreased output of the central respiratory "centres," some of the effect could be due to direct action on the ventilatory apparatus itself, by increasing respiratory impendance. For example, both morphine and meperidine can cause bronchoconstriction;[6] furthermore they can increase the tonic activity of abdominal and intercostal muscles.[7-10] The mechanical effects of this increase in abdominal wall tone have not been assessed after therapeutic doses of these agents, but large doses of narcotics administered intravenously produce board-like rigidity of the abdominal wall [7-10] and markedly decrease total respiratory compliance.[9] As the magnitude of this effect appears to be dose related[10], it may well be present to a lesser extent after therapeutic doses of these agents.

The purpose of this work was to determine whether the ventilatory depression associated with morphine and a meperidine–phenothiazine mixture is solely the result of impairment of the neuromuscular or force-generating mechanisms, or is in part due to increased impedance of the ventilatory pump. Even small increases in ventilatory load with narcotics probably contribute to ventilatory depression, as load compensation is poor when central neural mechanisms are pharmacologically impaired.[11,12]

The conventional technique for examining the effect of narcotics on ventilation is to apply rebreathing and steady-state methods before and after medication, to measure changes in minute ventilation ($\dot{V}_E$) and tidal volume (V_T).[13,14] However, these measurements depend on both central output and the properties of the ventilatory apparatus,[15,16] without distinction between them. A newer method, formulated by Grunstein, Younes and Milic-Emili[17] and modified for use in man by Whitelaw and Milic-Emili,[18] provides more direct assessment of respiratory-centre output. This technique requires occlusion of the airway at functional residual capacity (FRC) for less than 200 msec; mouth pressure is measured at 100 msec (P_{m100}). Occlusion is too brief for a cortical response to interrupt the inspiratory effort, and since there is no gas flow or change in volume, the measure-

449

ment is not influenced by changes in resistance or compliance of the lungs or chest wall.[19] P_{m100} can be measured as part of a CO_2-rebreathing study; combined with the ventilatory response to CO_2, it gives more detailed information about ventilation control.

In the presence of constant length and geometry of the diaphragm occlusion pressure is directly related to the isometric tension developed by the diaphragm; and, in the presence of normal phrenic nerve activity, neuromuscular and diaphragm muscle function is directly related to integrated phrenic neuronal discharge and therefore the output of the respiratory centres.[19] Thus, the occlusion pressure (P_{m100}) provides a convenient and simple index of the "generator" function of medullary respiratory "centres," but can be used as such only when certain neural and neuromuscular functions and diaphragm geometry remain constant. If, for instance, during an experiment there are changes in lung volume (FRC) or configuration of the chest wall, the length or curvature of the diaphragm will vary, and as a result there will be an inconstant relationship between airway occlusion pressure and diaphragm tension and, therefore, medullary drive.[20] However, even with such factors varying P_{m100} continues to represent neuromuscular drive; that is, it is an index of the forces being generated by the neuromuscular system on the chest wall. For the purpose of this study, P_{m100} is interpreted in this manner.

MATERIALS AND METHODS

We studied 13 patients (7 male, 6 female), aged 12 to 19 years (mean age, 15 ± 2 yr), who were undergoing elective cardiac catheterization. They were assessed clinically by a cardiologist before study. The only criterion of selection was the patients' ability to co-operate with the investigators. Premedication, injected intramuscularly, consisted of morphine sulphate (0.1 mg/kg body weight) or 2 ml of CM_3;[21] each ml of the latter contains promethazine HCl 6.25 mg, chlorpromazine 6.25 mg, and meperidine HCl 25 mg.

Each of ten patients performed FVC expiration into a 9-litre water-filled Collins spirometer. The test of three breaths were analyzed for FVC in one sec. ($FEV_{1.0}$), and the results were expressed as a percentage of predicted normal values from standards obtained in this laboratory.[22] Total lung capacity (TLC) and its subdivisions were measured in a variable-pressure body plethysmograph, using the technique described by DuBois, et al.[23]

In all 13 patients, Read's rebreathing technique[24] was used to determine the ventilatory response to carbon dioxide and P_{m100} was measured simultaneously. The subjects, comfortably supine, breathed 7 per cent CO_2 in 93 per cent O_2. A rapid-acting low-resistance solenoid valve was inserted into the circuit. It was activated periodically during expiration and remained closed for 200 msec during the next inspiration. Occlusion was repeated 6 to 10 times during the four-minute rebreathing procedure. The following indices were recorded on a Beckman type S2 Dynograph; end-tidal carbon dioxide (PA_{CO_2}), tidal volume (V_T), gas flow, inspiratory time (T_I) and total time (T_{tot}) of each breath, and the mouth-occlusion pressure at 100 msec (P_{m100}). Volumes were corrected for body temperature and pressure saturated with water (BTPS). The responses of $\dot{V}_E$, V_T and P_{m100} to increases in PA_{CO_2} were plotted, and the slope of each response was found by the

TABLE I

PERSONAL, CLINICAL AND RESTING PULMONARY FUNCTION DATA AND PREMEDICATION OF THE 13 PATIENTS STUDIED

| Case No.	Age (yr)	Sex	Height (cm)	Weight (kg)	Diagnosis	Cyanosis	FVC (% of predicted normal)*	$FEV_{1.0}$	RV/TLC (%)	Premedication
1	19	F	167	57.9	Aortic stenosis	no	—	—	—	CM₃
2	14	M	155	38.6	Pulmonary stenosis	no	—	—	—	CM₃
3	14	M	154	43.6	Coarctation of aorta	no	119	104	26.9	CM₃
4	17	F	155	52.1	Aorto-pulmonary window	no	73	80	38.6	CM₃
5	14	M	170	53.6	Subaortic stenosis	no	110	113	18.5	CM₃
6	14	M	157	56.7	Functional murmur	no	109	109	22.1	CM₃
7	15	F	162	51.3	Aortic stenosis	no	86	99	26.2	CM₃
8	18	F	152	48.6	Tetralogy of Fallot	yes	80	86	34.7	CM₃
9	13	M	152	43.0	Tricuspid atresia	yes	79	71	32.4	Morphine
10	13	F	130	42.1	Tetralogy of Fallot	yes	—	—	—	Morphine
11	14	M	162	57.3	Pulmonary valve stenosis	no	108	106	23.8	Morphine
12	17	F	154	50.0	Aortic stenosis	no	102	83	37.4	Morphine
13	13	M	160	46.6	Aortic stenosis	no	93	90	33.6	Morphine

*Standards established in our laboratory.[22]
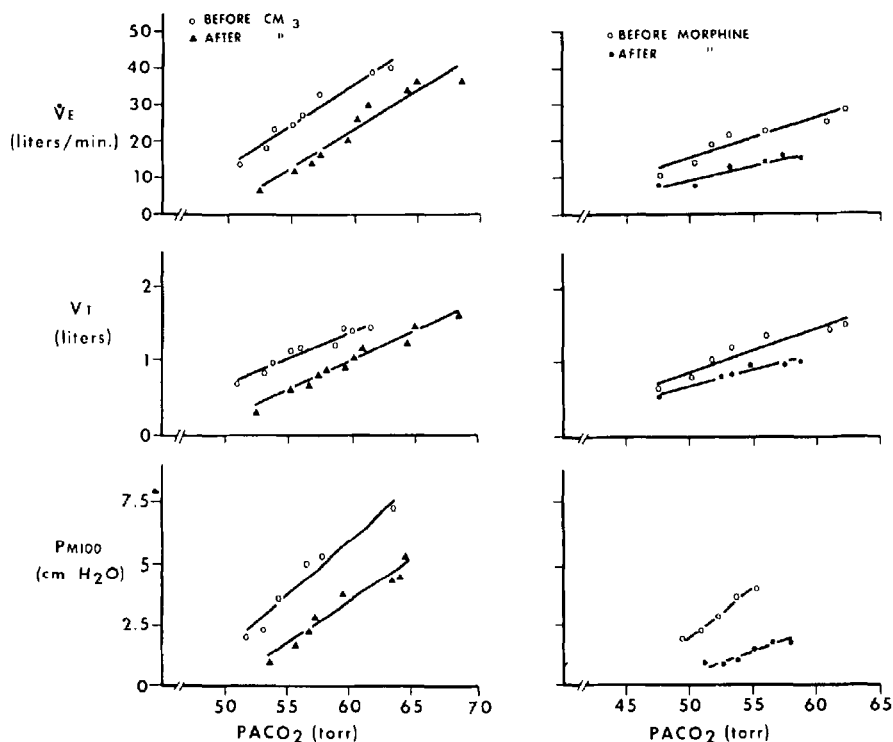
FIGURE 1. Regression lines for $\dot{V}_E$, V_T, and P_{m100} plotted against P_{ACO_2}. A: Case 6: before and after injection of CM_3. B: Case 11: before and after injection of morphine.

method of least squares. To correct for variations in respiratory frequency, the ratio of V_T to inspiratory time (V_T/T_1) was determined for the breath preceding an occlusion; V_T/T_1 was plotted against the P_{m100} value of the respective occluded breath, and the slope of this relationship also found by the method of least squares.

After completion of the first rebreathing procedure, five patients received morphine and eight were given CM_3. After an interval of 47 ± 5 min (mean $\pm$ 1 SD) the rebreathing procedure was repeated. The patients remained awake throughout the study.

RESULTS

In most cases, routine pulmonary function values were within normal range for age (Table I). The mean FVC was 96 ± 16 per cent of predicted normal, in the range 79 per cent to 119 per cent; mean $FEV_{1.0}$ was 94 ± 14 per cent of predicted normal, in the range 71 per cent to 113 per cent, RV/TLC was in the range of 18.5 per cent to 38.6 per cent, in two cases slightly above the upper limit or normal established in our laboratory.[22]

The composite plot of pulmonary responses to CM_3 shown in Figure 1A is typical of the findings recorded in all eight patients who received this drug. Similarly, the plot shown in Figure 1B is typical of the responses seen in the five patients given morphine. Both drugs depressed $\dot{V}_E$, V_T, and P_{m100}, the conventional responses to CO_2 (Table II). Comparison of the ventilatory and occlusion responses

TABLE II
VENTILATORY RESPONSES TO CO_2 BEFORE AND AFTER PREMEDICATION WITH CM_3 OR MORPHINE

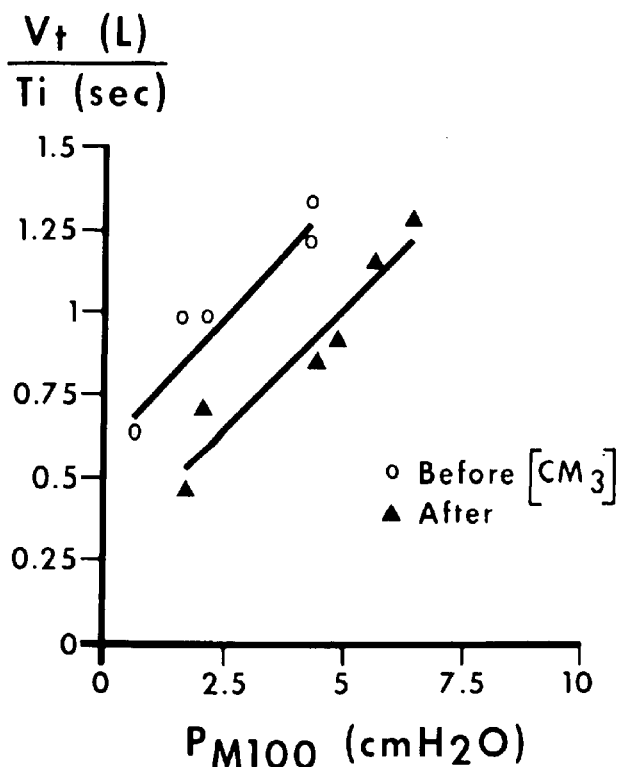| Case No.		$S\dot{V}_E$ (1/min/torr)	SV_T (1/torr)	SP_{m100} (cm H_2O/torr)	At Pa_{CO_2} = 55 torr				
					$\dot{V}_E$ (litres/min)	V_T (litres)	P_{m100} (cm H_2O)	Breath, per min	V_T/V_I at P_{m100} = 2 cm H_2O
Premedication with CM_3									
1.	Before	1.92	0.057	0.60	27.27	0.85	4.43	32	0.637
	After	1.16	0.060	0.69	14.53	0.55	0.63	26	0.509
2.	Before	1.19	0.048	0.33	23.76	0.91	3.93	26	0.643
	After	1.58	0.070	0.37	14.39	0.77	2.05	19	0.590
3.	Before	2.39	0.068	0.46	31.21	1.18	4.95	27	—
	After	2.98	0.060	0.21	17.54	0.68	1.26	26	—
4.	Before	3.06	0.062	0.47	49.99	1.61	7.66	31	—
	After	1.07	0.030	0.12	22.27	0.91	2.95	25	—
5.	Before	5.34	0.220	0.87	55.28	2.27	6.88	24	0.904
	After	5.27	0.180	1.27	30.37	1.51	5.22	20	0.524
6.	Before	2.27	0.070	0.45	24.35	1.03	3.64	24	0.592
	After	2.15	0.080	0.35	12.98	0.60	1.75	22	0.487
7.	Before	1.32	0.090	0.26	26.61	1.49	2.75	18	0.740
	After	0.94	0.060	0.26	14.56	0.74	1.51	20	0.454
8.	Before	3.65	0.090	0.95	88.42	2.60	20.88	34	0.754
	After	2.03	0.060	0.55	49.47	1.92	11.36	26	0.624
Premedication with Morphine									
9.	Before	2.93	0.13	0.84	42.84	2.14	10.40	20	0.634
	After	1.99	0.07	0.37	28.28	1.34	5.36	21	0.458
10.	Before	3.17	0.08	0.41	53.69	1.66	8.14	32	0.773
	After	2.82	0.08	0.34	42.43	1.44	6.21	30	0.606
11.	Before	1.10	0.06	0.39	20.69	1.16	3.85	18	—
	After	0.79	0.04	0.16	13.42	0.90	1.27	15	—
12.	Before	2.34	0.10	0.40	37.48	1.72	5.06	22	0.662
	After	2.20	0.06	0.43	32.12	1.24	4.88	26	0.629
13.	Before	1.99	0.09	0.52	26.03	1.11	5.35	24	0.520
	After	1.73	0.11	0.39	24.45	1.19	0.39	21	0.721

$$\frac{V_t \ (L)}{Ti \ (sec)}$$

FIGURE 2. Case 5: Regression line for V_T of a breath preceding occlusion divided by inspiratory time plotted against P_{m100}, before and after injection of CM_3.

showed a significant decrease ($p < 0.05$) in V_T/T_I at a P_{m100} of 2 cm. H_2O after premedication in ten of the patients. (Three subjects did not achieve this level of drive after receiving the narcotic.)

The plot of time-corrected V_T (V_T/T_I) of breaths preceding occlusions during rebreathing vs P_{m100} of the respective occlusions showed a shift to the right after premedication with CM_3 (Figure 2).

As shown in Table III, the only significant change in magnitude of the slopes after premedication was a decrease in $S\dot{V}_E$ after morphine ($p < 0.05$). At $P_{ACO_2} = 55$ torr, there was a significant shift in all slopes after premedication with CM_3, but in only $\dot{V}_E$ and P_{m100} after morphine.

DISCUSSION

The depression of ventilation by narcotics is poorly understood. In general, central nervous system depressants which reduce ventilation (e.g., barbiturates, narcotics and inhalational anaesthetics) are usually considered to affect ventilation by acting on the respiratory "centres" in the medulla. However, direct supportive evidence has not been easy to obtain. In one set of animal experiments, respiratory centres under the influence of narcotics showed decreased responsiveness to electrical stimulation.[25]

The main purpose of the present study was to assess the effects on ventilation of two narcotics frequently used as premedication for cardiac catheterization in chil-

TABLE III

PAIRED ANALYSIS OF VENTILATORY RESPONSES, USING THE STUDENT *t* TEST

| Drug | No. of cases | $S\dot{V}_E/P_{ACO_2}$ | SV_T/P_{ACO_2} | SP_{m100}/P_{ACO_2} | At $P_{CO_2} = 55$ torr | | | |
					$\dot{V}_E$ (litres/min)	V_T (litres)	P_{m100} (cm H$_2$O)	Breaths per min
CM$_3$	8	N.S.*	N.S.	N.S.	$p < 0.005$	$p < 0.001$	$p < 0.01$	$p < 0.02$
Morphine	5	$p < 0.05$	N.S.	N.S.	$p < 0.025$	N.S.	$p < 0.05$	N.S.

*N.S.: not significant.

dren. In addition, it provided an opportunity to evaluate the effect of a meperidine–phenothiazine mixture on ventilation. Finally, we assessed two possible modes of action of these narcotics on the respiratory system, one or both of which actions might explain their depressant effect.

Depression of the conventional response to CO_2 by both morphine and CM_3 was best demonstrated by a shift to the right of the $\dot{V}_E/P_{A_{CO_2}}$ and $V_T P_{A_{CO_2}}$ curves (Figure 1). This shift was measured by calculating values for each curve at $P_{A_{CO_2}} = 55$ torr, a method of analysing shifts suggested by Tenney[26] and Read.[24] The results obtained in our patients accord with those reported after the administration of morphine and meperidine to neonates[27] and adults[4]; similar studies have not been reported in older children. The CM_3 mixture was at least as depressant as morphine alone, each narcotic being administered in approximately equipotent amount, supporting Lambertsen et al.'s conclusion[28] that phenothiazine, rather than sparing narcotic depression,[29] usually potentiates it.

Both drugs significantly depressed the mouth-occlusion response (P_{m100}) to CO_2. Since the P_{m100} is a direct measurement of the neuromechanical output of the respiratory centre and there is no evidence that narcotics impair nerve or neuromuscular condition,[30] we conclude that the depressant effect on neuromechanical drive reflects an action on the central nervous system. Any action which would alter the geometry of the diaphragm would also independently affect P_{m100}, the coupling between diaphragm-tension generation and occlusion-pressure generation being highly sensitive to both the length and the radius of curvature of the diaphragm.[20] We have no evidence of an effect of narcotics on diaphragm geometry, but speculate that, if present, it would consist in cephalad displacement of the diaphragm, thereby increasing the curvature of the diaphragm. Such an effect would augment P_{m100}, not decrease it.[20]

The possibility that narcotics also affect the mechanics of ventilation, by increasing resistance or stiffness of the lungs or chest wall, was examined by comparing the ventilation achieved at varying neuromechanical drives before and after each narcotic. As the index of central drive (P_{m100}) was taken at a fixed time of inspiration (100 msec), V_T values were corrected to a fixed time unit dividing them by inspiratory time (V_T/T_I). V_T/T_I was significantly decreased ($p < 0.05$) after either drug for a given P_{m100} (2 cm H_2O), indicating that these drugs decrease the responsiveness of the ventilatory apparatus. A decreased responsiveness of the ventilatory pump must represent a change in the compliance or resistance characteristics of either the lungs or the chest wall. The only known consistent effect of narcotics on these structures is an increase in the tonic activity of abdominal and intercostal muscles.[7-10] Changes in this activity might increase respiratory impedance. Increased tonic activity directly reduces chest-wall compliance, an effect which has been documented after large doses of narcotics.[8,9] Alternatively, increases in intercostal and abdominal activity could disrupt the normal coupling of the motions of the diaphragm and the rib cage. This coupling usually acts to move the entire chest wall along its "relaxation characteristic," keeping the work of breathing at a minimum.[31] If the tonic activity disrupted this relationship, the relative motions of the rib cage and diaphragm would change, so increasing the work of breathing and respiratory impedance.[31] Studies of chest-wall motion under the influence of narcotics are needed to determine this point.

SUMMARY

The effects of narcotics on ventilatory control were assessed in 13 adolescents and young adults. Both a narcotic and narcotic–phenothiazine significantly depressed the CO_2 response curve. Using an occlusion pressure technique (P_{m100}) to evaluate those neuromuscular processes that generate forces acting on the ventilatory pump, it was found that narcotic agents reduced neuromuscular drive. In most subjects, narcotics had an additional action that contributed to the overall ventilatory depression. Using carbon dioxide to vary neuromuscular drive before and after drug administration at constant levels of neuromuscular drive the drugs reduced tidal-volume responsiveness of the pump. We conclude that narcotics impair ventilation through a combination of two effects; first, reduced neuromuscular drive, most probably due to central depression, and second, increased impedance of the ventilatory pump, most probably due to a decrease in chest-wall compliance.

RÉSUMÉ

Les effets des analgésiques morphiniques sur le contrôle ventilatoire furent évalués chez 13 adolescents et jeunes adultes. Un analgésique de même qu'un analgésique associé à une phénothiazine dépriment d'une façon significative la réponse au CO_2. A l'aide d'une technique avec pression d'occlusion (P_{b100} = Pression buccale) permettant d'évaluer les mécanismes neuromusculaires générateurs des forces opérant sur la pompe ventilatoire, on a trouvé que les agents analgésiques diminuent la forc neuromusculaire. Chez la plupart des sujets, les analgésiques ont une action additionnelle qui contribue à le dépression ventilatoire globale. En variant la CO_2 pour faire varier la force neuromusculaire avant et après l'administration des drogues, on a trouvé qu'à des niveaux constants de force neuromusculaire, les narcotiques diminuaient le volume courant de la pompe ventilatoire. Nous concluons que les analgésiques modifient la ventilation de deux façons, à savoir une réduction de la force neuromusculaire probablement par dépression centrale et par une augmentation de l'impédance de la pompe ventilatoire, vraisemblablement due à une chute de la compliance thoracique.

REFERENCES

1. KREUGER, H., EDDY, N.B., & SUMMWALT, M. The pharmacology of the opium alkaloids. USPHS, Pulbic Health Rep., Suppl. 165, 1941.
2. EDDY, N.B., HALBACH, H., & BRAENDEN, O.J. Synthetic substances with morphine-like effect. Clinical experience: potency, side-effects, addiction liability. Bull. WHO, *17*: 569 (1957).
3. REYNOLDS, A. & RANDALL, L.O. Morphine and allied drugs. University of Toronto Press, Toronto, Ontario (1957).
4. ECKENHOFF, J.E. & OECH, S.R. The effects of narcotics and antagonists upon respiration and circulation in man. A review. Clin. Pharmacol. Ther. *1*: 483 (1960).
5. HIGGINS, H.L. & MEANS, J.H. The effect of certain drugs on the respiration and gaseous metabolism in normal human subjects. J. Pharmacol. Exp. Ther. 7: 1 (1915).
6. MITCHELL, H.S. & DEJONG, J.D. The effect of morphine on bronchial muscle. J. Allergy, 25: 302 (1954).
7. HAMILTON, W.K. & CULLEN, S.C. Supplementation of nitrous oxide anaesthesia with opiates and a new opiate antagonist. Anesthesiology *16*: 22 (1955).

8. SOKOLL, M.D., HOYT, J.L., & GERGIS, S.D.   Studies in muscle rigidity, nitrous oxide, and narcotic analgesic agents. Anesth. Analg. *51*: 16 (1972).

9. FREUND, F.G., MARTIN, W.E., WONG, K.C., & HORNBEIN, T.F.   Abdominal-muscle rigidity induced by morphine and nitrous oxide. Anesthesiology *38*: 358 (1973).

10. GRELL, F.L., KOONS, R.A., & DENSON, J.S.   Fentanyl in anesthesia: a report of 500 cases. Anesth. Analg. *49*: 523 (1970).

11. MARGARIE, C.E., ISCOE, S., PENGELLY, L.D., COUTURE, J., DON, H., & MILIC-EMILI, J.   Immediate ventilatory response to elastic loads and positive pressure in man. Resp. Physio. *18*: 347 (1973).

12. FREEDMAN, S. & CAMPBELL, E.J.M.   The ability of normal subjects to tolerate added inspiratory loads. Respir. Physiol. *10*: 213 (1970).

13. ECKENHOFF, J.E., HELRICH, M., & HEGE, M.J.D.   A method for studying respiratory functions in awake or anesthetized patients. Anesthesiology *17*: 66 (1956).

14. LAMBERTSEN, C.J.   Effects of drugs and hormones on the respiratory response to carbon dioxide. *In*: Handbook of Physiology, Section 3 (Respiration), vol. *1*: W.O. Fenn and H. Rahn (eds.) Washington, D.C. American Physiological Society, p. 545 (1964).

15. CHERNIAK, R.M. & SNIDAL, D.P.   The effect of obstruction to breathing on the ventilatory response to CO_2. J. Clin. Invest. *35*: 1286 (1956).

16. KELLOGG, R.H.   Central chemical regulation of respiration. *In*: Handbook of Physiology, Section 3 (Respiration) vol. *1*: W.O. Fenn and H. Rahn (eds.) Washington, D.C., American Physiological Society, p. 507 (1964).

17. GRUNSTEIN, M.M., YOUNES, M., & MILIC-EMILI, J.   Controls of tidal volume and respiratory frequency in anesthetized cats. J. Appl. Physiol. *35*: 463 (1973).

18. WHITELAW, W.A. & MILIC-EMILI, J.   A new method of evaluating respiratory centre output. Physiologist, *16*: 486 (1973).

19. WHITELAW, W.A., DERENNE, J.P., & MILIC-EMILI, J.   Occlusion pressure as a measure of respiratory center output in conscious man. Respir. Physiol. *23*: 181 (1975).

20. GRASSINO, A.   Influence of chest wall configuration on the static and dynamic characteristics of the contracting diaphragm. *In*: Pengelly, L.D., Rebuck, A.S., & Campbell, E.J.M. (eds.). Loaded Breathing, Toronto, Longmans, Canada p. 64 (1974).

21. SMITH, C., ROWE, R.D., & VLAD, P.   Sedation of children for cardiac catheterization with an ataractic mixture. Can. Anaesth. Soc. J., *5*: 35 (1958).

22. WENG, T.R. & LEVISON, H.   Standards of pulmonary function in children. Am. Rev. Respir. Dis. *99*: 879 (1969).

23. DuBOIS, A.B., BOTELHO, S.Y., BEDEL, G.N., MARSHALL, R., & COMROE, J.H., Jr.   A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J. Clin. Invest. *35*: 322 (1956).

24. READ, D.J.C.   A clinical method for assessing the ventilatory response to carbon dioxide. Aust. Ann. Med. *16*: 20 (1967).

25. PENTIAH, P., REILLY, F., & BORISON, H.L.   Interactions of morphine sulfate and sodium salicylate on respiration in cats. J. Pharmacol. Exp. Ther. *110*: 154 (1966).

26. TENNEY, S.M.   The interpretation of respiratory drug effects in man. Anesthesiology *17*: 82 (1956).

27. WAY, W.L., COSTLEY, E.C., & WAY, E.L.   Respiratory sensitivity of the newborn infant to mepheridine and morphine. Clin. Pharmacol. Ther. *6*: 454 (1965).

28. LAMBERTSEN, C.J., WENDEL, H., & LONGENHAGEN, J.B.   The separate and combined respiratory effects of chloropromazine and meperidine in normal men controlled at 46 mm. Hg alveolar pCO_2. J. Pharmacol. Exp. Ther. *131*: 381 (1961).

29. RECKLESS, D.   Action of chlorpromazine and promethazine. Br. Med. J. *1*: 1035 (1954).

30. GOODMAN, L.S. & GILMAN, A.   The Pharmacological basis of therapeutics, vol. 4, ed. New York, Macmillan, p. 241 (1970).

31. MEAD, J.   Mechanics of the chest wall. *In*: Pengelly, L.D., Rebuck, A.S., & Campbell, E.J.M. (eds.). Loaded Breathing. Toronto, Longmans, Canada, p. 35 (1974).