MEDICAL GRAND ROUNDS

March 8, 1962

Case 1. A 64-year-old obese businessman had severe kyphoscoliosis and chronic inflammatory obstructive bronchopulmonary disease with a history of severe pulmonary insufficiency and carbon dioxide narcosis. He was admitted to the hospital with a 6-day history of progressively increasing somnolence and cyanosis, preceded by symptoms of an upper respiratory infection. On examination, he was markedly obtunded and exhibited very shallow respiration at a rate of 8 to 12 per minute. Because of profound cyanosis, the attending physician administered oxygen by mask. The patient exhibited markedly increased somnolence to the point of an unresponsive coma after several minutes of oxygen without breathing assistance. Even with intermittent positive pressure oxygen with air mix, the patient's respiratory pattern was irregular with periods of apnea. At this point, an arterial puncture was performed and the physiological studies shown in the first column of table 2 were made. Ethamivan, 100 mg., was administered intravenously; prompt arousal, greatly increased depth of respiration and coughing with evacuation of considerable mucoid sputum were immediately noted. From this point on the patient remained intermittently drowsy but responsive. He was maintained on continued controlled breathing with about 40 per cent oxygen, and continuous tepid mainstream nebulization. A vigorous program of postural drainage and coughing assistance by exsufflation with negative pressure was pursued. By the third hospital day, the patient had improved sufficiently so that he would not tolerate continuous controlled or assisted breathing. However, without assistance, his ventilatory status deteriorated (Table 2) and during sleep marked depression of respiration was apparent. Therefore, on the third hospital day, oral ethamivan, 40-80 mg. every 6 hours, was instituted. This produced improved wakefulness of the patient but, with proper adjustment of the dose, did not interfere with normal sleep. Physiological studies were done daily but only the results of the 5th and 10th days are shown in table 2. Continuation of the program of intermittent assistance and vigorous bronchial hygiene was accompanied by progressive improvement. The patient was discharged on 20 mg. of oral ethamivan at 6:00 A.M. and 12:00 noon with 40 mg. at 6:00 P.M. and 12:00 midnight. This dosage was continued for a period of 1 month following discharge at which time a gradual reduction in dosage was undertaken by his local physician. On the last report from his private physician, nearly two years later, he was still on one to 2 20 mg. tablets daily at bedtime. His alveolar carbon dioxide tension had remained within normal limits, whereas in the past this patient was known to have chronic carbon dioxide retention.

This case is an example of one of the early experiences with this agent. Today we would have continued this patient on intravenous drip medication as needed during the first 24-48 hours, then oral medication and continued much as was done. This would have provided greater stability of respiratory function

Case 2. This 58-year-old white male retired engineer gave a long history of recurrent bronchopulmonary infection, usually of suppurative nature. This was accompanied by a history of smoking and inhaling 2-3 packages of cigarettes per day over a 35-year period. Several years earlier, he had had a pulmonary resection for bronchiectasis and pulmonary fibrosis of the right middle lobe and a portion of the right lower lobe. He had experienced progressive exertional dyspnea over a period of at least 10 years. Associated with recurrent episodes

of pulmonary infection were reported episodes of profound respiratory insufficiency with cyanosis and carbon dioxide narcosis twice requiring the use of a tank respirator. On this occasion, he was hospitalized at another institution because of a similar episode of respiratory difficulty. Because his condition deteriorated and coma developed, he was transferred to this hospital. Examination revealed a deeply cyanotic, semi-comatose, middle-aged man with slow, shallow respiration and an increased antero-posterior diameter of the chest but with diminution in the volume of the right chest, apparently secondary to previous surgery. There was moderate clubbing. On assisted breathing, respiratory sounds gave evidence of diffuse obstructive disease with marked accumulation of secretions. No specific areas of consolidation were noted. The x-ray examination of the chest was compatible with the clinical evidence of diffuse pulmonary emphysema and fibrosis. Assisted ventilation by intermittent positive pressure with 60 per cent oxygen was instituted. After a few moments, the patient's respirations virtually ceased and he failed to respond even to endotracheal suctioning. Moreover, secretions were virtually impossible to aspirate because of their marked viscosity. Along with periods of controlled forced ventilation, direct instillation of tepid saline and detergent solution into the tracheobronchial tree was used to facilitate evacuation of tenacious secretions but the patient still failed to respond. At this point, 50 mg. of ethamivan were given intravenously and a transient increase in respiration with a slight arousal of the patient was observed. Several minutes later, the patient was given 100 mg. intravenously. This resulted in a profound increase in the depth of breathing with a regular respiratory rate of 16 per minute and also transient but marked arousal accompanied by vigorous coughing and expectoration of large amounts of mucopurulent sputum. Thirty minutes later the patient exhibited signs of depression again; 100 mg. of ethamivan were given and again the dramatic response noted above was observed. Physiological studies are listed in Table 3. The patient was continued on controlled respiration and an intensive program consisting of intermittent bronchodilator aerosol with continuous heated mist mainstream nebulization of a detergent agent, appropriate antibiotic therapy, vigorous intermittent endotracheal suctioning as well as exsufflation with negative pressure. Further injections of ethamivan at about 2-hour intervals were required to prevent recurrence of somnolence and hypoventilation which appeared in spite of controlled ventilatory assistance. Such episodes were felt to be due to the gradual accumulation of secretions which obstructed the airways and led to carbon dioxide retention and narcosis. Each time arousal, vigorous coughing and deep breathing resulted from the ethamivan administration. This program was continued for 24 hours during which time 1.5 gm. of the drug had been given. By then his condition had improved sufficiently so that further injections were not required. By the 3rd hospital day, the patient had shown considerable improvement (Table 3). However, he exhibited a persistent tendency toward marked somnolence and profound hypoventilation during sleep if breathing was not assisted and controlled continually. At any time oxygen was administered, with or without assistance, somnolence and hypoventilation tended to recur. Nevertheless, the patient complained of fatigue and restlessness and was requesting sedatives. On the 5th day, after attempts to withdraw assistance, the studies listed in table 3 were done and ethamivan was instituted, 40-60 mg. every 4 hours. There was a definite improvement in the patient's clinical alertness and an improvement in the effectiveness of ventilation as indicated by the studies on the 8th day (table 3). With the improvement of ventilation, sleep improved since the patient was not disturbed by hypoxic, hypercapnic episodes. As the patient's condition improved between the 8th and 20th hospital days, ethamivan dosage was decreased gradually to 20 mg. every 6 hours. The patient was later discharged on 20 mg. at 8:00 P.M. and 200 A.M. under the care of his local physician. It was possible for the patient to sleep unassisted but he still

continued his intermittent program of nebulization therapy with assisted breathing. Three months later, the patient discontinued all of his treatment voluntarily. One month later he was taken again to his home town hospital in a state of profound ventilatory insufficiency where he expired five days after admission, in spite of being placed in a tank respirator to assist his breathing. He did not receive any ethamivan on that admission.

This is also an example of one of our early patients who, today, would receive a continuous intravenous drip of ethamivan at a rate of 2 to 4 mg. per minute for several days and, as the intravenous medication was withdrawn, oral medication would be substituted and then continued essentially as was done in this case. It is quite apparent that the necessity for tracheostomy was obviated in this case as well as case 1, because of the effective respiratory stimulation observed following administration of ethamivan.

Case 3. This 58-year-old white female was 65" tall and weighed 230 pounds. She gave a history of cigarette smoking, more than a package a day for 40 years, accompanied by frequent periods of persistent productive cough following upper respiratory infections. Exertional dyspnea had first appeared 10 years before and the principal increase in her weight, nearly 70 pounds, had occurred since that time. One week prior to admission, she developed low grade fever, headache, and increased fatigue, accompanied by more severe coughing and difficulty in raising sputum. She was taken to her local physician who gave her an injection of penicillin and some cough medicine, but she failed to improve. Increasing somnolence to the point of unresponsiveness appeared by the morning of admission. In the emergency room the patient was noted to be obese, cyanotic, comatose and breathing very shallow at a rate of 8-10 per minute. When the patient was placed on an intermittent positive pressure breathing device with oxygen and an air-mix valve, she became apneic in a few minutes. Controlled ventilation was continued with intermittent bronchodilator aerosol. Wetting agent was administered by continuous mainstream mist technique. She failed to respond even after instillation of saline and detergent mixture into the trachea followed by suctioning on several occasions. It seemed certain a tracheostomy would be necessary. An arterial puncture was done and functional studies shown in table 4 were performed before and after a trial administration of 100 mg. of ethamivan by the direct intravenous route. In addition to the changes noted, after 6 minutes (table 4) the patient exhibited an immediate response characterized by transient itching and flushing followed by deep breathing, coughing, expectoration of large amounts of mucopurulent sputum and arousal to the point of being able to converse with the examiners. Twenty-five minutes later the patient was again somnolent and unresponsive. An intravenous drip of ethamivan in 5 per cent dextrose and distilled water was started and run at 4 to 5 mg. per minute, to keep the patient responsive so she would cough on demand. As the patient's state of alertness improved, slight muscular twitching appeared occasionally and the rate of the ethamivan drip was decreased until the muscular twitching disappeared. It is of interest to note that the twitching could be controlled voluntarily if thepatient were requested to do so. During the first day when the patient became drowsy, the drip was speeded up periodically, to deliver about 50 mg. in a few minutes. This produced an intense reaction accompanied by the same manifestations mentioned above, including vigorous coughing and expectoration. Over the next 3 days, the dose of ethamivan was decreased to only intermittent use. A total of 22.4 gm. was given intravenously, then oral medication was started, 40 mg. every 4 hours with extra 20 mg. doses at night if the patient exhibited evidence of shallow breathing during sleep. After 4 days, the schedule was changed to every 6 hours, then over the next 4 weeks, the dose was gradually reduced to 40 mg. at 10:00 P.M. and 2:00 A.M. while intensive

programs of bronchial therapy, weight reduction and exercise were carried on. After 6 weeks of hospitalization, she was discharged to be followed in the chest clinic. Her weight was 201 lb. and ventilatory function studies revealed forced vital capacity of 2.3 L. (68% of predicted), $FEV_{0.5}$ sec. of 1.1 L. (48% of vital capacity) and $FEV_{1.0}$ sec. of 1.4 L. (61% of vital capacity). These studies indicate a restrictive and small airway obstructive ventilatory defect.

In this case the necessity for a tracheostomy was obviated by the use of ethamivan.

Case 4. This 38-year-old white female was known by previous admissions to have a long record of psychiatriac difficulties and intermittent narcotic addiction. She was brought to the emergency room with a history of ingesting some capsules and pills within 12 hours prior to admission. She was comatose with a diminished pupillary reflex and faintly detectable deep tendon reflexes. The pulse rate was 68, blood pressure 80/50 and respirations were very shallow at a rate of 8 per minute. All routine blood chemistry determinations were within normal limits and the blood barbiturate level was 5.42 mg.%. A cuffed endotracheal tube was inserted, gastric lavage was performed, and she was given IV fluids. Respiration was maintained with an auto-cycled intermittent positive pressure, oxygen air-mix apparatus with constant mainstream mist. Because the patient had evidence of chronic bronchitis and recent aspiration was suspected, it was deemed advisable to have the patient more alert and able to cough effectively so as to avoid respiratory complications. Ethamivan was given intravenously to accomplish this. Arterial blood and ventilation studies were done with the patient on room air breathing and before and after 100 mg. of ethamivan (table 5). The patient showed only slight arousal; after 10 minutes she was given 150 mg. of ethamivan. 15 seconds later she exhibited scratching motions as if she felt intense itching. She became flushed and very active, thrashing about. A few seconds later, she awakened and started coughing. Suctioning through the endotracheal tube produced copious amounts of mucoid secretions. She remained responsive for nearly 20 minutes. It was decided to start an IV drip of ethamivan in an attempt to arouse the patient sufficiently so the endotracheal tube could be removed. The IV solution was given initially at a rate of 6 mg./min. After 1 hour the endotracheal tube was removed. The patient, although somewhat agitated emotionally, was surprisingly cooperative and revealed the details of her suicidal attempt. She remained awake except for periods of normal sleep, on diminishing doses of ethamivan by intravenous drip. On the 4th hospital day, she was transferred to a psychiatric division for continued psychotherapy, her convalescence being uneventful. She received a total of 9.6 gm. of the drug.

This case illustrates the valuable adjunct role of an agent such as ethamivan in the treatment of respiratory depression in drug intoxication.

Case 5. This 70-year-old Negro male who had a mild residual left hemiparesis was admitted with an acute right hemiparesis and was said to have been in a semi-comatose state for 2 days. He was known to have chronic bronchitis and was believed to have aspirated secretions during his coma. His breathing was shallow at a rate of 12/min. and he was obviously pooling secretions. The patient was given O_2 to insure adequate cerebral oxygenation and then 100 mg of ethamivan were administered. In 30 seconds, he exhibited intense scratching motions of his upper trunk, slight flushing and vigorous coughing accompanied by deep breathing. He readily evacuated large amounts of mucous. He regained consciousness but could not talk. After an hour, he again became uncooperative and nearly unresponsive. Ethamivan, 100 mg. was injected at hourly intervals for 4

doses after which the patient remained responsive and cooperative with induced coughing and other bronchial therapy procedures. The patient's recovery was good and his voice returned prior to discharge several weeks later.

This case is an example of a good result using ethamivan on a patient with a specific central nervous injury. Our results were poorest in this group of patients where increased respiratory activity cannot be expected in response to the drug unless nerve tracts are intact from the respiratory center.

Case 6. This case, a 51-year-old white male who was hospitalized at another institution, was reported to us as follows. He was said to have been treated for thyroid carcinoma $1\frac{1}{2}$ years prior to this illness. He was thought to have metastases to the liver and had definite metastases to the lungs although there was no functional disability. The lung lesions cleared after treatment of the primary lesion and no evidence of hepatic dysfunction was detected. He developed myxedema after surgical removal of his thyroid carcinoma and required supplemental thyroid.

Several days prior to this admission, the patient was noted to be showing increasing somnolence, irritability, withdrawn behavior, and ultimately paranoia considered at first to be a functional psychosis. After several days, cyanosis, complete collapse, and coma developed. He exhibited slow, shallow respirations without evidence of respiratory distress and there was no evidence of pulmonary disease. His arterial pCO_2 was 114 mm. Hg, pH 7.18, CO_2 content 47 mEq, BUN 20 mg., potassium 6.4 There was pitting edema of the lower extremities, the heart was not enlarged, electrocardiogram showed slight prominence of the P waves and right axis deviation but no other striking abnormalities. The patient was placed on ventilatory assistance by IPPB device and oxygen which was immediately accompanied by further hypoventilation. Therefore, he was placed on IPPB by compressed air. This resulted in adequate oxygenation. He was given large doses of IV Hydrocortisone, a mercurial diuretic, digitalis, and intravenous glucose and water. After 24-36 hours, marked clinical improvement was noted. The patient became alert, more cooperative, and no longer showed a tendency to hypoventilate without assistance. Between 48-72 hours, he began to complain of weakness, again developed irritability, and abnormal mental behavior and hypoventilation developed followed by hypotension. At that time his arterial pCO_2 was found to be 80 mm. Hg, his pH 7.34, and his serum potassium 3.1, in spite of supplemental potassium intravenously for a period of 24 hours prior to this determination. Recommendations were made and executed essentially as follows: Supportive ventilatory assistance was continued with the addition of Emivan, 3-4 mg./min. intravenously, and vigorous doses of parenteral potassium. Aramine was used for a brief period of time to correct the hypotension and the patient's improvement was rapid. Emivan oral was continued during the convalescence with the dose varied according to the patient's need. He was ultimately established on a nocturnal dose of Emivan which prevented further hypoventilation during sleep.

This is an interesting example of severe hypoventilation secondary to acquired myxedema. This is also a classic example of profound hypokalemia with muscular weakness developing during the recovery period from respiratory acidosis where the degree of hypokalemia was doubtless aggravated by the administration of potassium-free fluids intravenously, the use of mercurial diuretics and Hydrocortisone.

Table 1. Data on dose and mode of administration of ethamivan

Mode of Administration	Dosage Range	Time of Onset	Duration of Action
Intravenous	0.5 - 5 mg/kg	15-45 sec.	10-20 min.
Intramuscular	2-10 mg/kg	8-12 min.	1-2 hrs.
Subcutaneously	1-10 mg/kg	1-5 min.	1-2 hrs.
Oral solution	1-10 mg/kg	1-5 min.	2-3 hrs.
Continuous intravenous	0.05-0.15 mg/kg/min.	30-90 sec.	sustained
Oral tablets	0.5-2 mg/kg	20-30 min.	2-4 hrs.

Table 2. Summary of physiological data on case 1.

Hosp. Day	1	1	2	3	5	10	
	Unasst. Breath.	After 100 mg. Ethamivan IV	IPPB Air	Unassisted Breathing			Predicted
					Oral Ethamivan		
$FEV_{0.5}$ ml.	250	--	--	300	500	700	2200
FVC, ml.	700	--	--	800	900	1100	3400
TV, ml	125	350	500	325	455	480	--
Resp. Rate	8-12	14	14	16	16	16	--
SaO_2%	80	91	93	85	88	90	96
$PaCO_2$ mm Hg	90	70	60	72	56	48	40
pH	7.20	7.28	7.35	7.30	7.40	7.40	7.40

Table 4. Summary of physiologic data on case 2.

Hosp. day	1	1	3	5	8	20	
	Unasst. Breath.	After 100 mg. Ethamivan IV	IPPB Air	Unassisted Breathing			Predicted
					Oral Ethamivan		
$FEV_{0.5}$ ml.	200	--	700	500	900	1100	2500
FVC ml.	800	--	2100	1800	2700	3000	3700
TV ml.	165	520	480	350	450	465	--
Resp. Rate	8	14	16	14	16	14	--
SaO_2%	44	79	87	77	88	89	96
$PaCO_2$ mm. Hg	98	70	58	74	55	50	40
pH	7.23	7.33	7.40	7.32	7.40	7.38	7.40

$FEV_{0.5}$ = Forced expiratory volume, 0.5 second
FVC = Forced vital capacity
TV = Tidal volume
SaO_2 = Arterial O_2 Saturation
$PaCO_2$ = Arterial CO_2 tension

Table 4. Physiologic data on case 3.

	Before Ethamivan	6 minutes after Ethamivan
Respiratory Rate	12/min.	14/min.
Tidal Volume	126 ml.	410 ml.
Minute Ventilation	1.5 L.	5.75 L.
Oxygen Saturation	82%	88%
CO_2 Tension, mm. Hg.	108	80
pH	7.24	7.37

Table 5. Physiologic data on case 4, before and after ethamivan

	Before	After
Respiratory Rate/minute	12	15
Tidal Volume, ml.	213	428
Oxygen Saturation, %	86	93
Carbon Dioxide Tension, mm. Hg	74	56
Arterial pH	7.16	7.31

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