

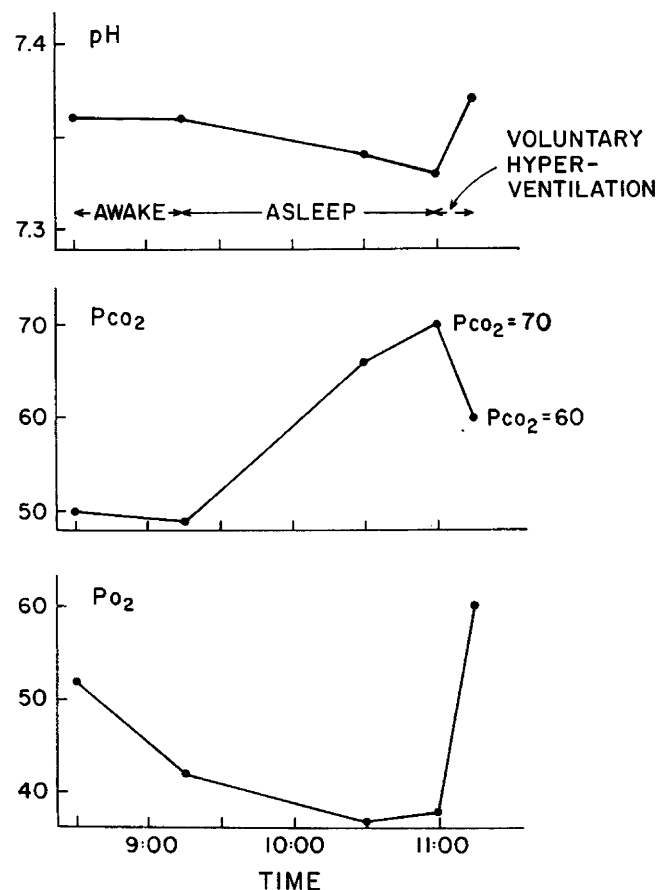
Radio-Frequency Electrophrenic Respiration

Long-Term Application to a Patient With Primary Hypoventilation

John P. Judson, MD, and William W. L. Glenn, MD

Radio-frequency electrophrenic respiration (EPR) has been used successfully on a long-term intermittent basis to manage a patient with primary hypoventilation. The ability to use it only when desired, to adjust the amplitude of stimulation, and to control the rate of stimulation externally, has been made possible by use of the technique of radio-frequency transmission. Electrophrenic respiration by stimulation of one phrenic nerve has been carried out each night for ten months. Moderate fatigue of the stimulated diaphragm could be demonstrated after ten hours of stimulation. Further observation is required to determine if such fatigue is progressive. The future uses of radio-frequency electrophrenic respiration may include any condition of hypoventilation associated with an intact phrenic nerve and diaphragm. Whether its use will be of long-term benefit in the early stages of some hypoventilatory situations secondary to parenchymal disease is under study.

It has been known for almost 20 years that adequate ventilation may be effected by unilaterally stimulating the phrenic nerve.¹ In this technique, an external "thimble electrode" is placed over the cervical motor point of the phrenic nerve, or electrodes and percutaneous wires are implanted surgically. The technique was the subject of many reports between 1948 and 1951 when it was used successfully for up to 3½ days to manage the ventilatory insufficiency, respiratory irregularities, and hypertensive episodes of bulbar poliomyelitis.²⁻⁴ It was better tolerated by the circulatory system than positive pressure endotracheal respiratory assistance in patients with apnea due to high spinal anesthesia, bar-



1. Patient before EPR. Deterioration of arterial gas tensions during sleep and prompt return to control levels with voluntary hypoventilation, March 11, 1966.

biturate intoxication, and hemorrhagic shock.⁵⁻⁶

During the past five years, numerous experiments with more than 75 dogs have expanded our knowledge of the physiology involved in this technique. The experiments have resulted in the development of a permanently implantable system without percutaneous wires, with which electrical stimulation

From the Department of Surgery, Yale University School of Medicine. Dr. Judson is a Public Health Service fellow in cardiovascular surgery.

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Reprint requests to 333 Cedar St, New Haven, Conn 06510 (Dr. Glenn).

of the phrenic nerve can be effected when desired by an external pocket-sized radio-frequency transmitter.^{7,8} Such a system was used initially 14 months ago in a patient with primary hypoventilation of central origin and has been in use for a ten-hour period each night for the past ten months.

Report of a Case

A 38-year-old white man was admitted to the medical service in February 1966 for intense cyanosis, leukocytosis, polycythemia, pneumonia of the right lower lobe, cor pulmonale, and a two-year history of increasing lethargy. He was afflicted during the first two weeks of life with a severe viral illness, probably encephalitis, and has been mentally retarded since early infancy. His large family, which included a twin sister, had no history of mental deficiency. The patient has a stocky build but has never been obese. The admitting diagnosis was cyanotic congenital heart disease, but one month later, this could not be confirmed by catheterization.

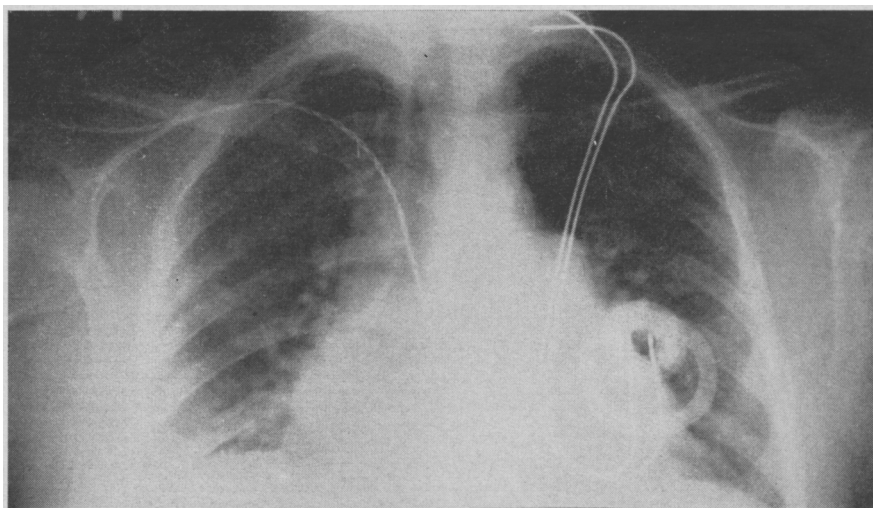
Instead, moderately severe pulmonary hypertension (60 mm Hg) was demonstrated without evidence of cardiac defect. The pneumonia was treated successfully with antibiotics, but hypercapnia, hypoxia, and respiratory acidosis persisted. Ventilatory function studies demonstrated reduced tidal volumes, hyperpnea, and normal minute volumes that were not significantly affected by inhalation of 7% carbon dioxide. During sleep, arterial gas tensions (Fig 1) deteriorated markedly.

With use of an external cardiac pacemaker with impulse of 0.1 msec duration, response of the diaphragm to electrical stimulation of the phrenic nerve was determined with an electrode catheter in the superior vena cava. Active conduction to the right side of the diaphragm following transaxillary stimulation of the nerve indicated an intact neuromyal system. In May, a bipolar, platinum cuff electrode was placed on the left phrenic nerve in the neck and attached to a radio-frequency receiver capsule placed in the left pectoral area (Fig 2). The capsule was tuned to 2 megacycles and contained a single diode to produce half-wave rectified pulses and a resistor-capacitor combination in the output stage to effect a biphasic wave form. A pocket-model, radio-frequency transmitter was designed to deliver 0.1 msec biphasic pulses at 60 cycles per second in trains of 1.7 second duration. A smooth diaphragmatic contraction was produced by adjusting the wave form to rise sharply to submaximal levels before falling rapidly to zero.

In September, after four months of studying electrophrenic respiration (EPR) in this patient, a program of long-term EPR was begun. Pacing has been done regularly ten hours each night (henceforth identified as nocturnal pacing). There has been no recurrence of respiratory infection or of cor pulmonale. At two-to-four-week intervals during the past ten months, the patient has been admitted to the Clinical Research Unit for a period of 24 to 48 hours for reevaluation. On each admission, values were obtained twice a day for blood gases, hematocrit, and hemoglobin; measurements were also obtained twice a day for spontaneous and induced minute and tidal volumes while the patient was supine. Every few months, complete ventilatory function studies have been carried out in the upright position. Cinefluoroscopy has been performed once during each admission. After six months of nocturnal EPR, differential bronchspirometry was performed and a catheterization of the right side of the heart was done again.

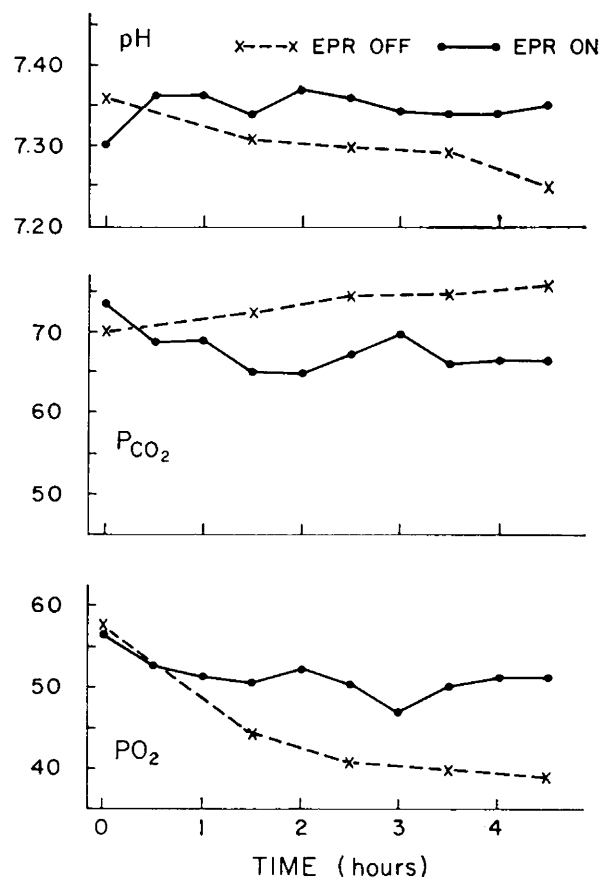
Results

Certain facts were noted during electrophrenic respi-



2. Subcutaneously placed radio-frequency receiver in postoperative (14 months) roentgenogram of chest. Platinum wire electrodes terminate in bipolar cuff electrode surrounding phrenic nerve in neck. Antenna lies on skin over receiver.

3. Beneficial effect on blood gases of electrophrenic respiration (nocturnal studies).



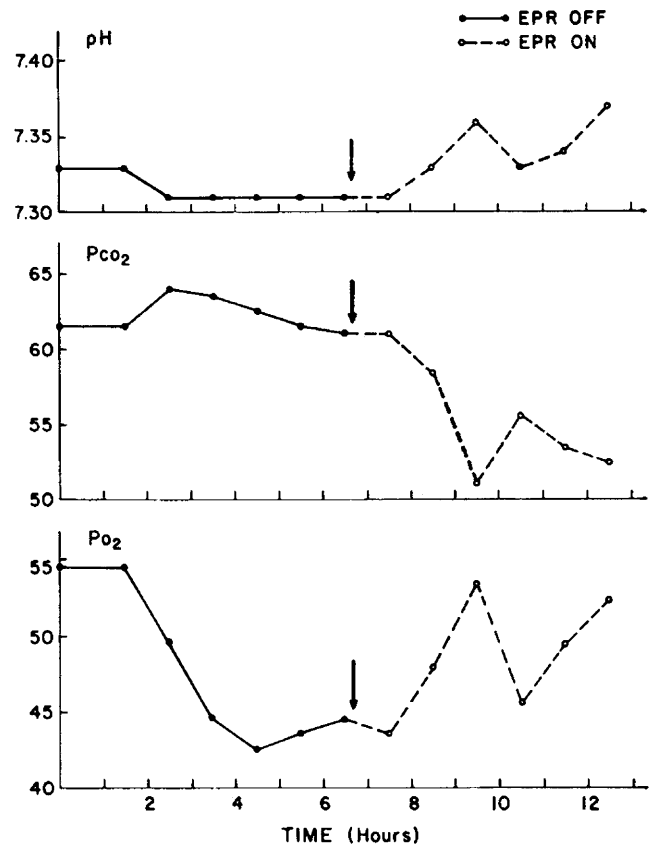
ration carried out during the four-month control period preceding institution of regular nocturnal EPR. During unilateral EPR, all spontaneous ipsilateral and contralateral respiratory effort was abolished, and a moderate paradoxical motion of the contralateral dia-

phragm was observed fluoroscopically. When the patient was asked to hyperventilate, however, there was normal motion of the contralateral hemidiaphragm. Eating and drinking during EPR resulted in mild choking, but after a few minutes of adjustment, there was no other associated discomfort. Stimulation was performed continuously on one occasion for 20 hours. At the end of this time, there was a marked diminution of induced and spontaneous ipsilateral hemidiaphragmatic motion. This evidence of fatigue had completely disappeared after 35 hours without EPR. Ten- to 12-hour periods of EPR were at that time, however, well tolerated.

One major beneficial effect of nocturnal EPR (Fig 3 and 4) was the avoidance of marked nocturnal deterioration of arterial gas tensions. The broken line (Fig 3) represents values obtained during spontaneous ventilation on the night preceding institution of regular nocturnal EPR in September. The solid line represents values obtained after six months of nocturnal EPR. A similar study was done in which the patient breathed spontaneously for five hours, then by EPR, for the remaining five hours of that night (Fig 4). Improvement in the arterial gas tensions during EPR is obvious, though normal levels were not reached. Secondary polycythemia (Fig 5), with a hematocrit reading of 65 to 67, was treated with phlebotomy in June but during the next four months the hematocrit reading slowly increased until regular nocturnal EPR was begun. During the ten months since then, the hematocrit reading has fallen and now ranges between 50% and 55%.

Catheterization of the right side of the heart, six months after the start of nocturnal EPR, demonstrated no change in pulmonary artery pressure compared to the findings one year before EPR was begun. Differential bronchspirometry was carried out 6½ months after the start of nocturnal EPR (Table 1). As can be seen, spontaneous ventilation still resulted in a normal left-to-right ratio of tidal and minute volumes. During EPR, the total tidal and minute volumes were increased bilaterally, and though the percentage contribution by the ipsilateral lung had increased slightly, the percentage of ventilation of the contralateral lung remained nearly normal. The oxygen intake was not increased by EPR, indicating that the mechanical benefit of EPR was not being offset by increased oxygen demands.

Fluoroscopy during the ten months of stimulation initially demonstrated a barely detectable reduction of spontaneous ipsilateral diaphragmatic motion after ten hours of EPR. This was completely abolished after 10 to 12 hours without EPR, while after ten months, there was practically no spontaneous motion of the ipsilateral diaphragm after 10 hours of EPR, and full recovery took 36 to 48 hours. Induced motion of the left diaphragm, however, remained strong even after ten hours of stimulation. On cessation of EPR, the contralateral diaphragm, suppressed during EPR, immediately

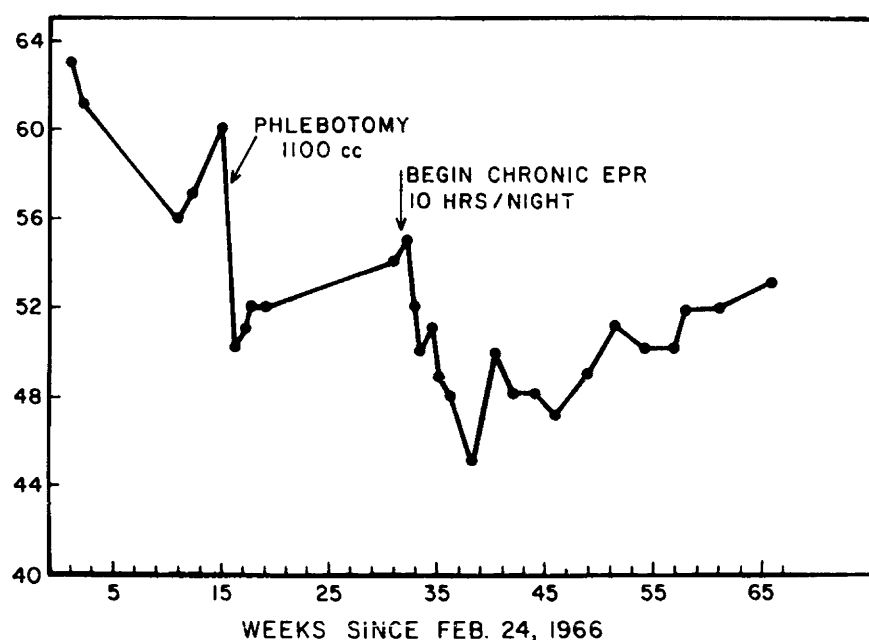


4. Beneficial effect of nocturnal electrophrenic respiration. Patient was dozing or sleeping from second to 12th hour.

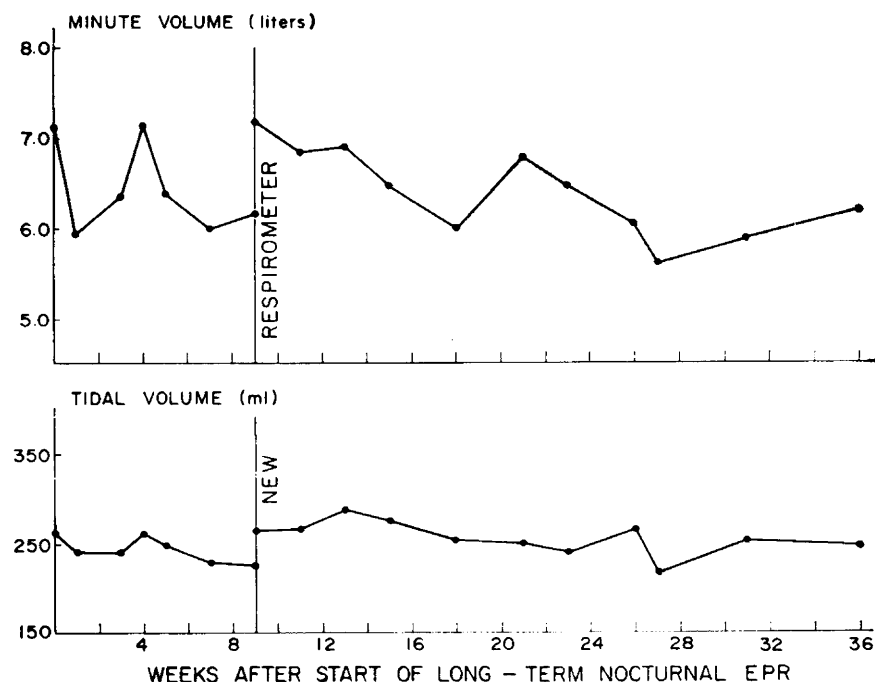
began to contract with each respiratory effort. The apparent fatigue of the left side had no effect on ventilatory function studies carried out in the sitting position (Table 2). Although there are fluctuations between individual determinations, it can be seen that there is no significant overall difference between the four studies carried out after six to ten months of nocturnal EPR and the two studies carried out four to six months before the start of nocturnal EPR. On the other hand, studies of spontaneous minute and tidal volumes, while the patient was supine (Fig 6) after nine hours of EPR, do show some progressive diminution which correlates with the increasing carbon dioxide pressure (Pco₂) values of arterial samples over the past ten months (Fig 7). But it must also be noted that the oxygen pressure (Po₂) and pH values have been well maintained. The threshold to stimulation has remained unchanged between 0.5 and 0.6 v since the beginning of regular EPR.

Comment

At the time when bulbar poliomyelitis and its respiratory irregularities were prevalent and EPR seemed to have its greatest application, the syndrome of primary hypoventilation was essentially unknown. Effective treatment of this disorder has not been particularly successful, and the fact that a majority of such patients have central nervous disorders makes most complicated exercises or



5. Hematocrit determinations from seven months before start of nocturnal EPR to nine months afterwards.



6. Spontaneous ventilation after nine hours of EPR (supine position.)

treatment methods extremely difficult.⁹ The patient herein described had a history compatible with a respiratory center lesion and classic evidence of primary hypoventilation in his failure to increase his minute volume of ventilation in response to inhalation of 7% carbon dioxide.¹⁰ The suppression of spontaneous respiratory effort during EPR has been noted both experimentally, with contralateral diaphragmatic and intercostal action potentials, and clinically, with the control of the respiratory irregularities of bulbar poliomyelitis.^{11,12} The choking, possibly indicative of near aspiration, occurring with eating or drinking during EPR, may be a peculiarity of this patient since it has not been observed by others.¹³ Fatigue following prolonged continuous stimulation has been described in experiments, but it occurred only after several days of stimulation.^{8,14} The other characteristics of this patient's fatigue, including its total reversibility, are similar to those observed in the canine.

Objective criteria of improvement during the ten months of nocturnal EPR were as follows: The nocturnal studies of arterial gas tensions demonstrate relief of the augmented hypercapnia and hypoxia seen in this patient with sleep, and the avoidance of prolonged periods of nocturnal hypoxia is probably responsible for the prevention of recurrent secondary polycythemia. Also, the absence of recurrent respiratory infection and of cor pulmonale during the period of treatment is indicative of clinical benefit. Differential bronchspi-

Table 1.—Differential Bronchspirometry,* 4/7/67

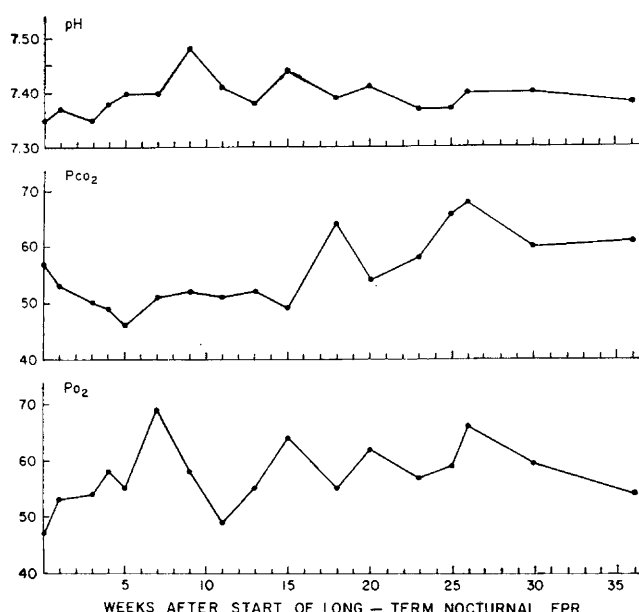
	EPR	Total, ml	Right, ml	Left, ml	Right, %	Left, %
Tidal volume	Off	258	142	116	55	45
	On	332	169	163	51.2	48.8
Minute volume	Off	7,711	4,244	3,467	55	45
	On	8,035	4,115	3,920	51.2	48.8
Vital capacity	Off	1,708	930	778	54.5	45.5
	On	1,639	907	732	55.3	44.7
Oxygen uptake	Off	382	208	174	54.4	45.6
	On	301	154	147	51.1	48.9

*Electrophrenic respiration—differential bronchspirometry. The electrodes are attached to the left phrenic nerve.

Table 2.—Ventilatory Function Studies*

		Before Nocturnal EPR		With Nocturnal EPR Since 9/21/66			
	Norm	3/7/66	5/5/66	3/23/67	3/30/67	4/26/67	6/2/67
Vital capacity, liters	2.5-5	2.24	1.33	2.7	2.67	2.51	2.44
Maximum mid-expiratory flow rate, liters per sec	4	1.9	2.65	1.77	1.82	0.953	3.45
Residual volume, liters	0.8-1.5	1.81	1.013	0.85	1.13	1.75	1.6
Total lung capacity, liters	3.3-6.5	3.42	2.34	3.55	3.8	4.26	4.04
Residual volume/total lung capacity	0.25	0.34	0.43	0.24	0.3	0.41	0.4
Maximum breathing capacity, liters per min	100	44.4	52	54.7	48.5	51.4	49.5
Total volume, liters	0.5	0.35	0.24	0.35	0.31	0.38	0.28
Minute volume, liters	5-8	12	6.89	9.4	7	11.4	7.7

*Ventilatory function studies, sitting position. The patient was breathing spontaneously during these studies. The last four studies were made in the afternoon approximately eight hours after EPR had been discontinued.



7. Arterial gas tensions after 8½ hours of continuous EPR. Each study was carried out in the early morning.

rometry confirmed experimental observations that, despite the absence of contralateral diaphragmatic and intercostal motion, contralateral ventilation at nearly normal levels occurs during unilateral EPR, and that mediastinal shifting is probably the mechanism responsible.¹⁵ The slight diminutions of vital capacity during EPR is explained by the fact that voluntary efforts on the part of the patient resulted in competition with the induced respiratory pattern. Less can be said about the data on catheterization of the right side of the heart, since it is not known what changes would have occurred in the ten months without treatment.

The fluoroscopic observation of increasing fatigue on the ipsilateral side is not at all unlike that observed in experiments, but its origin and significance are not yet known. Since the normal response of a muscle to stimulation is hypertrophy and augmented contraction, not diminished function, it would seem that the diaphragm itself was not becoming fatigued. De Villiers et al¹⁴ claimed that the neuromyal junction was not the site of fatigue, since low-frequency stimuli easily produced twitches in the diaphragm. Furthermore, in one animal, with fatigue following prolonged stimulation, we noted no response to the administration of edrophonium chloride (Tensilon Chloride) which would be expected to compensate fatigue secondary to depletion of the synaptic neurohumors. The fact that the stimulation threshold has remained constant and that the observed fatigue is reversible would indicate that there has been no permanent damage to the nerve. The remaining possibilities are fatigue of the nerve itself and central inhibitory reflexes. Indeed, both may be responsible in view of the fact that the observed fatigue appears to have two components, ie, diminished induced motion of the diaphragm after prolonged continuous stimulation and

diminished spontaneous movement of the ipsilateral hemidiaphragm after discontinuation of long-term intermittent stimulation. Thus far, the reduced spontaneous motion of one hemidiaphragm does not appear to have adversely influenced the course of the patient herein reported, since ventilation in the upright position, ie, during daytime hours, has not been significantly reduced. The matter is one of continuing observations.

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Generic and Trade Names of Drug

Edrophonium chloride—*Tensilon Chloride*.

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