Abnormalities in Central Regulation of Respiration in Acute and Convalescent Poliomyelitis

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Clinical differences between the respiratory disturbances resulting from spinal cord involvement and the breathing defects produced by brain stem lesions have been recognized in poliomyelitis for over 50 years. Despite this long recognition, there have been comparatively few detailed studies of the mode of development, frequency, or pathological physiology of "central respiratory failure" in poliomyelitis.

The earliest reference to supraspinal lesions causing respiratory difficulties in poliomyelitis appears to have been that of Wickman,[1] who stated in 1905 that respiratory paralysis could result from involvement of either "the centre for the intercostal muscles" or "the nucleus of the pneumogastric nerve." Petren and Ehrenberg,[2] in 1909, more correctly designated "the bulbar centre for respiration" as the source of supraspinal respiratory defects in poliomyelitis. Subsequently, a number of authors made direct or passing reference to shallow, irregular breathing with marked variation in rate and depth as characteristic of central respiratory failure. Pathological studies, particularly by Baker and co-workers [3,4] confirmed the belief that patients who showed this type of respiratory defect suffered major damage in the lateral medullary reticular formation. As a matter of fact, damage to the medullary reticular formation has been so common a finding in patients dying of poliomyelitis [5-7] that it is surprising that centrogenic respiratory abnormalities have not been more frequently noted as a clinical problem.

Quantitative measurements of the defect in respiratory regulation which occurs in acute bulbar poliomyelitis are limited to Sarnoff, Whittenberger, and Affeldt's observations.[8] Sarnoff et al. presented clinical, pneumotachographic, and blood gas observations on four subjects with central respiratory failure. Retention of carbon dioxide without dyspnea, correction of hypoventilation upon command, and reduction of ventilation on oxygen therapy were demonstrated. It was advanced that bulbar poliomyelitis produced three defects in respiration: (1) irregularity in rate and depth; (2) incoordination of respiratory muscles, and (3) reduction in sensitivity to carbon dioxide as a respiratory stimulus. The frequency of these defects in bulbar poliomyelitis was not presented, and little comment was made on

the physiological implications of correction of hypoventilation upon arousal and command.

The present report details the clinical and physiological findings on 20 patients who developed centrogenic respiratory disturbances due to acute poliomyelitis. Pathological material was available for correlation in two of these subjects. In addition, abnormalities are described in the central control of respiration, which persisted beyond the acute phase of illness, to produce problems in the management of convalescence. These physiological defects in respiration, which appear during both acute and convalescent stages of Poliomyelitis appear to have relevance in evaluating current theories of the neurogenesis of normal human respiration.

Material and Methods

Patients with acute central respiratory failure were studied in the ward s of the King County Hospital Seattle, and the Providence Hospital, Anchorage, Alaska. - Patients with respiratory in- sufficiency convalescing from poliomyelitis were studied in the Northwest Respirator and Rehabilitation Centre. The entire brain was obtained for pathological study from one of the subjects observed in Anchorage, and brain tissue blocks on another patient were sent us by Dr. James W Stephens, of the University of Colorado Medical Centre.

Patients with cranial nerve paralyses or respiratory difficulties not explained by involvement of spinal motoneurons or airway obstruction were or study from over 250 admissions with selected for study from over 250 admissions with acute poliomyelitis from 1954 to 1956, inclusive. Control studies were performed on healthy medical and nursing students, as well as on patients with spinal and nonparalytic poliomyelitis. (The patients with the clinical diagnosis of nonparalytic poliomyelitis had virus isolated from the stools.) All patients had frequent clinical examinations, and the vital capacity was measured twice daily during their acute illness. Additional studies were performed on selected patients. Respiratory patterns were monitored by a comfortably fitting chest band to which was attached a strain gauge connected with an oscillograph, shielded from the patient's view (inspiration reads up on all tracings in the illustrations). The vital capacity (VC) and maximal breathing capacity (MBC) were measured with a 9-liter Benedict-Roth spirometer with valves and CO_2 absorber removed by the technique described by Baldwin et al.[9] The predicted normal VC and MBC were calculated from the formulae of the same authors. [9] The partial pressure of carbon dioxide in alveolar air ($PAco_2$) was measured with an instantaneous, continuously recording infrared gas analyser (Liston-Becker). End-expiratory and forced-expiratory samples were obtained at either the nares or the orifice of a tracheotomy tube. The arterial carbon dioxide content and oxygen saturation were determined by the manometric method of Neill and Van Slyke.[10] The arterial pH was measured with a Cambridge Research Model glass-electrode pH meter. The partial pressure of carbon dioxide

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in arterial blood (PA_{CO_2}) was calculated from the normograph of Singer and Hastings.[11] Alveolar and arterial P_{CO_2} values corresponded within a range of 2 to 5 mm Hg, the alveolar always being the lower of the two. The respiratory response to oxygen and to carbon dioxide was determined by a modification of the technique described by Nielsen.[12] Air, 100% oxygen, and quantitatively analysed mixtures of 3%, 5%, and 6% CO_2 in air, respectively, were breathed for successive 20-minute periods from a Tissot balanced spirometer. Minute ventilation was recorded for the last five minutes of each period and the PA_{CO_2} was monitored continuously by sampling the expired air at the mouthpiece. Minute alveolar volume was calculated by subtracting the dead-space ventilation assuming 130 cc, for female and 150 cc for male subjects plus 55 cc for the valve. To graph the respiratory response to CO_2, the increase in minute ventilation was plotted as a multiple of resting ventilation in (V/R) on the ordinate, and the increase in PA_{CO_2} in millimetres of mercury, was plotted on the abscissa.

Results

Observations During Acute Poliomyelitis

The pattern of development and progression of centrogenic respiratory decompensation in acute poliomyelitis was similar in most patients and could be divided into three stages. In Stage 1, respiratory irregularity appeared only during sleep and was unnoticed by the patient. Stage 11 was marked by more serious physiological defects in respiration, which persisted during waking hours. Effort or concentration was required to maintain compensation for oxygen and carbon dioxide. Stage 111 was that of respiratory decompensation; hypoxia or hypercapnia rapidly appeared unless artificial respiration was started. The clinical and physiological observations made during these three stages are detailed below.

Centrogenic respiratory abnormalities were observed in 20 patients. The major associated clinical findings in these subjects are given in Table 1. Every patient had other clinical manifestations of bulbar poliomyelitis, although at times the cranial-nerve weaknesses were minimal in degree. Seven patients progressed no further than Stage I during their illness. Five subjects progressed to Stage II, and eight others advanced to Stage III. Thirty-eight patients acutely ill with respiratory failure caused by spinal paralysis were also treated during this same period of time. It is possible that some of the last group also had minor centrogenic defects which were masked by the more overwhelming problem of diaphragmatic and intercostal paralysis. In order to keep the observations as clear as possible, however, the present studies on centrally induced respiratory abnormalities were performed only on patients in whom spinal paralysis was insufficient to account for respiratory failure.

Stage I.

Derangement in central respiratory regulation developed insidiously, and patients were unaware of any breathing abnormality. Breathing patterns were normal

during wakefulness, but irregularity in rate and depth, with periods of apnoea lasting from 4 to 12 seconds, appeared during drowsiness or sleep (Fig. 1). Arousal promptly eliminated the abnormal patterns. Because of this disappearance of irregularity after arousal, respiratory difficulties were not apparent during ward rounds, direct examination, or vital capacity testing. Alveolar P_{CO_2} determinations were normal during both waking and sleeping hours, and ventilation remained unchanged with oxygen therapy. Four of the seven patients who remained in Stage I throughout illness experienced no serious impairment of swallowing. All seven subjects were free of airway obstruction.

Respiratory irregularities were frequent in bulbar poliomyelitis. Of 15 consecutively studied patients with cranial-nerve paralyses, 7 showed decided irregularities of sleeping respiratory rhythm, with restoration of regularity upon awakening. Of 12 consecutive patients with spinal or nonparalytic poliomyelitis, 3 evinced some minor variation in rate and depth of breathing during sleep. These latter changes were not considered significant.

Stage II.

The persistence of irregular breathing during wakefulness marked progression into Stage II. Patients were conscious of irregular breathing, and several complained that they had to concentrate continuously on breathing. Concentration of effort restored regularity, at least transiently (Fig. 2A and B). Vital capacities at this stage were recorded at levels ordinarily considered adequate to maintain physiological ventilation (Table 1). Repeated pinching of the Achilles tendon or repeated commands to breathe resulted in regular respiration for the duration of the external stimuli and for several cycles beyond (Fig. 2C). Sleep produced a more marked degree of respiratory irregularity, with longer periods of apnoea, than was seen in Stage I, so that several patients were afraid to attempt sleep. Breathing ceased altogether when one man was induced to try sleeping under supervision (Fig. 3). Although most of the patients were apprehensive about their breathing defect and their need to drive respiration consciously, dyspnea, or air hunger, was usually absent as a specific sensation.

Five patients in Stage II who were given oxygen therapy manifested hyposensitivity to carbon dioxide as a respiratory stimulus. A prompt rise in P_{ACO_2} from resting levels of 32-41 mm Hg to levels of from 45-54 mm Hg was observed within minutes of starting oxygen in these subjects (Fig. 4). This depression of ventilation with oxygen therapy was not universally searched for, since oxygen usually was withheld from the treatment program of non-respirator patients.

Drugs which depress the brain stem worsened the clinical status of patients with centrogenic respiratory disturbances. Reserpine markedly accentuated the respiratory irregularities of one woman in Stage I. A 7-year-old boy (J. B., Table 1)', with swallowing paralysis but without clinically apparent respiratory insufficiency, was given intravenous thiopental anesthesia for tracheotomy. He

remained in coma postoperatively, and his serum bicarbonate rose to 34 mEq. per litre, providing indirect evidence of abnormal CO_2 retention. He was placed on artificial respiration and was unable to initiate any spontaneous breathing for the next eight days, after which he rapidly and completely recovered without respiratory paralytic residua. A 26 year-old man (J.S., Table 1), with mild respiratory irregularity but no severe respiratory difficulties, was given 50 mg of meperidine hydrochloride (Demerol) to allay his apprehension. Within 30 minutes, long periods of apnoea and cyanosis appeared and necessitated immediate artificial respiration. A 36-year-old woman treated in another hospital was reported to have had mild bulbar poliomyelitis, with partial swallowing paralysis and slightly irregular respirations. She was given 50 mg. of meperidine hydrochloride on the eighth day of her illness, when she was afebrile and apparently stable. Thirty minutes later she became apneic and pulseless and died.

Stage III.

In this stage respiratory homeostasis was lost. Gross irregularities in the rate and depth of breathing produced a chaotic respiratory pattern with varying periods of apnoea. Some patients continued to initiate a few breaths each time they were commanded to breathe: others responded only transiently and ineffectively to commands or other external stimuli. At times, there was a complete inability to initiate any respiratory act. If artificial respiration was not started promptly, carbon dioxide retention and arterial oxygen desaturation developed rapidly and

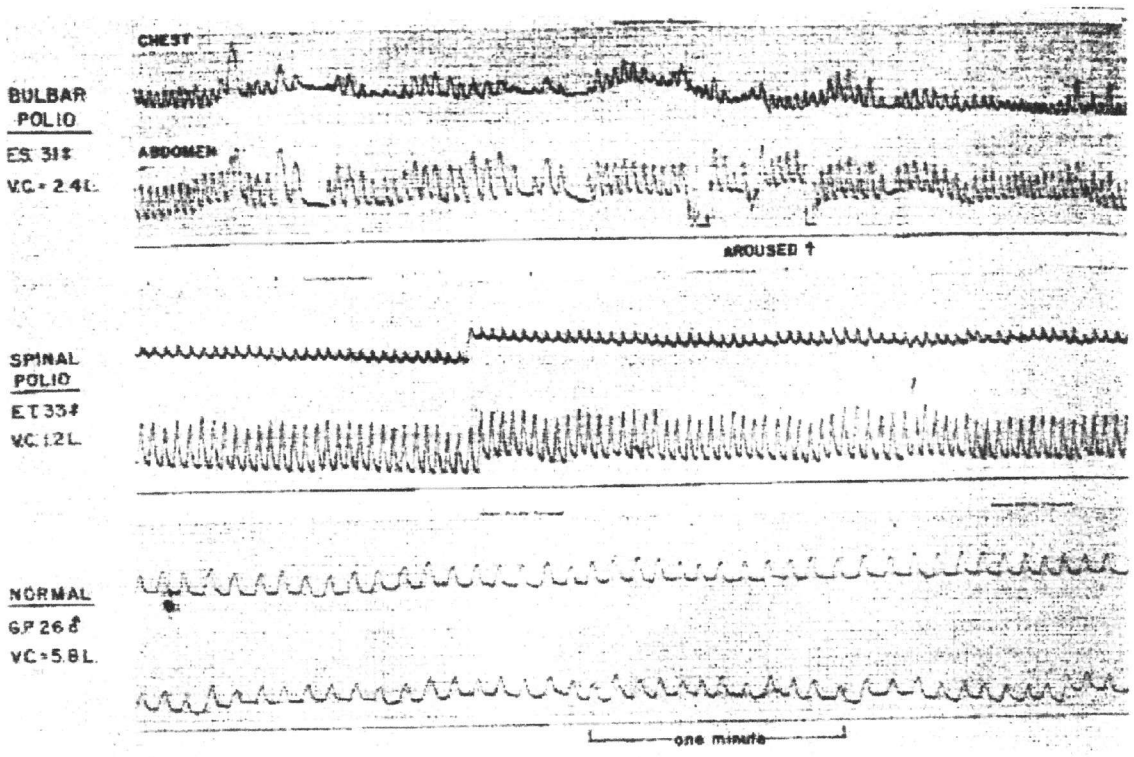
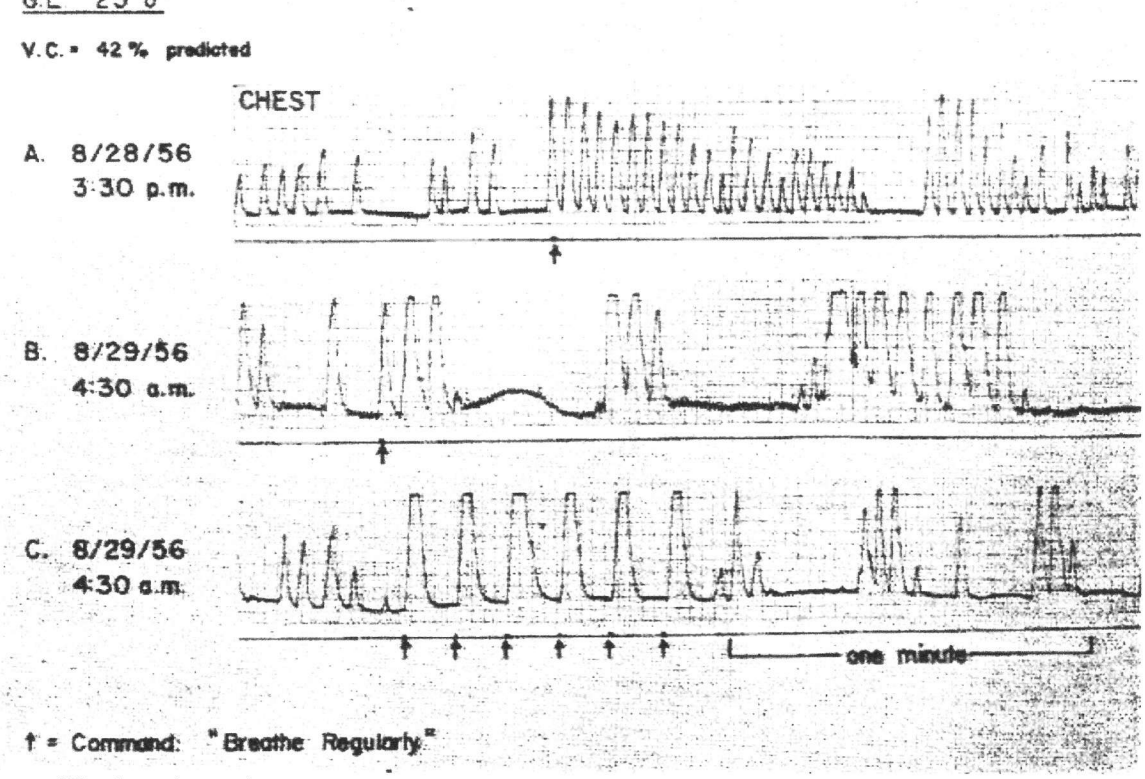


Fig. 1.—Stage I: Irregular respiration during sleep. Upper tracing (E. S. Table 1): characteristic pneumogram of Stage I of central respiratory failure in poliomyelitis. Note the irregularity in rate and depth of breathing during sleep, with improved regularity upon arousal. The middle tracing (E. T., Table 3) was taken at a time when the patient had already developed moderate diaphragmatic and intercostal paralysis but had not yet developed respiratory failure. The lower tracing (G. P.) was taken on a healthy laboratory worker during sleep.

impaired consciousness.

Fig. 2.—Respiratory stimulation by command. G. L. was in the fourth day of acute bulbospinal poliomyelitis when pneumogram *A* was recorded. He had moderate weakness of the legs and swallowing paralysis but was awake and alert. At the arrow he was asked to concentrate on breathing regularly. Note the ultimate return to a totally irregular pattern.

Tracings *B* and *C* were recorded 12 hours after *A*. He had not been able to sleep. The vital capacity was unchanged, but only brief regularity in breathing followed command. In tracing *C*, repeated commands to breathe showed a 1:1 response.



Stage III developed precipitously in cases with fulminating disease of the brain stem or when depressant drugs were administered to patients in Stage II.

> D D., a 23-vear-old man, admitted 14 hours after the onset of swallowing paralysis, had irregular respiratory efforts with an inspiratory "cogwheel" pattern on spirometric tracings. His vital capacity was 2.8 litres, and his minute volume was 7.2 litres. A tracheotomy under local anesthesia provided a clear airway but failed to eliminate the respiratory irregularity. Within six hours respirations became more irregular in rate and depth, and the blood pressure rose from 145/80 to 168/98. He was placed in a body respirator. For a few hours he was able to make single vigorous respiratory efforts upon command, but then he lapsed into total apnoea. Bilateral paralysis of the 5th, 7th, 9th, 10th, 11th, and 12th cranial nerves developed. He died five days after admission, of a perforated duodenal ulcer with haemorrhage.

A less rapid development of Stage III was seen when artificial respiration was delayed for patients in Stage II. Progressive fatigue appeared to be an important factor in the gradual loss of ability to drive respiration consciously. However, evaluation of fatigue in producing total respiratory failure was limited, as patients treated by us from the onset of their disease usually were provided with artificial respiration whenever they progressed significantly into Stage II.

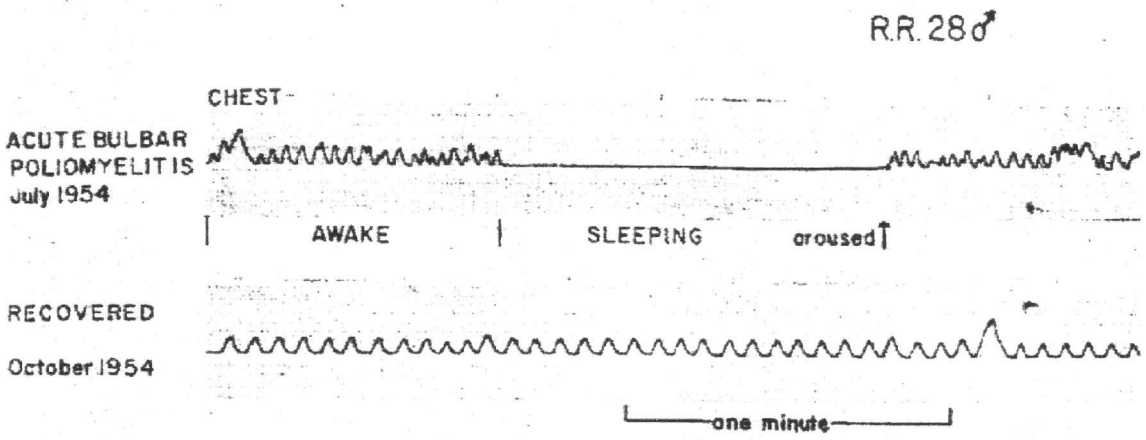


Fig. 3.—Apnea developing during sleep (Stage II). R. R. developed an irregular breathing pattern on the third day of his acute illness. The VC was 26% of the predicted normal. There were no definite cranial nerve paralyses. He spontaneously complained that he had to stay awake to keep breathing. Reassured that he would be supervised for any difficulty, he dozed (upper tracing). Apnea ensued and persisted for 75 seconds, until he was forcibly aroused by shouting. Note the lack of hyperpnea at the end of the apneic period. Completely normal ventilation was regained in convalescence (Table 3). The lower tracing demonstrates his breathing pattern three months after the acute illness.

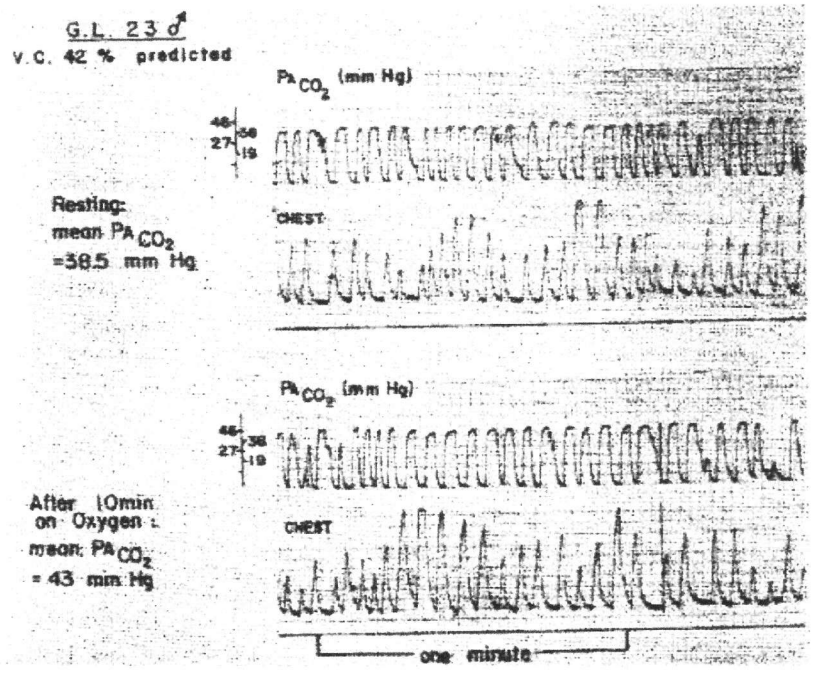


Fig. 4.—Hypoventilation with oxygen therapy. Continuous PA_{CO_2} (at the nares) and pneumogram recorded on Patient G. L. 27 hours after the tracing in Figure 2.4. He had been able to sleep intermittently. The upper tracing shows his resting level of PA_{CO_2}. One hundred per cent oxygen was given by a face cone at 12 liters a minute. Note the rise in PA_{CO_2} demonstrated in the lower tracing. The patient was placed in the respirator after the above observation was made.

TABLE 1.Clinical Data in Twenty Patients with Acute and Convalescent Poliomyelitis

			Extent of Paralysis				Circulation		Treatment				
Name	Sex	Age	Cranial Nerve	Spinal	Swallowing Paralysis	Min VC % predicted	Hyper-tension	Hypo-tension	VC at time of Respiratory Failure	Art Resp Duration	Recovery VC	Trach-eotomy	Manifestations
Stage 1													
ES	F	33	R 10++	±	++	65.5	None	None	No failure	None	78.7%	None	Irregularity in rate and depth when drowsing, with apneic periods of 12 sec.
BW	F	26	R&L 10+	+	+	70.0	None	None	No failure	None	70%	None	Irregularity in rate and depth when drowsing, with apneic periods of 4 sec.
JF	M	28		±	++++ 11 days	100.0	None	None	No failure	None	100%	None	Irregularity in rate and depth when drowsing, with apneic periods of 6 sec.
CS	F	24		-	±	100.0	None	None	No failure	None	100%	None	Irregularity in rate and depth when drowsing, with apneic periods of 7 sec.
OP	F	28		-	++++ 4 days	58.0	None	None	No failure	None	65.2%	None	Irregularity in rate and depth, accentuated after reserpine with apneic periods of 8 sec
MD	F	21		±	++++ 2 days	75.8	None	None	No failure	None	81.5%	None	Irregularity in rate and depth during sleep, with apneic periods of 5 see
JE	M	29		-	+	90.0	None	None	No failure	None	100%	None	Irregularity in rate and depth when drowsing

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Stage 2													
RR	M	28	0	+	-	12.6	135/95	None	26.4%	Tank 10 days; rocking 12 days	104%	None	Irregularity in rate and depth when awake, completely apneic for 70 see. during sleep
RF	M	32	R&L 10+ R&L 11+++	++	++++ 14 Days	11.2	150/90	None	56.2%	Tank 8 days; rocking 10 days	67.2%	Yes	Irregularity In rate and depth breathing; Intermittent apnoea; patient unable to sustain ventilation despite VC 56.2%; spinal paralysis later developed and VC dropped to 11.2%
RS	M	34	R&L 10++	+++	++++	22.9	200/100	None	22.9%	Tank 2 wk.; rocking 60 days	76%	Yes	Irregularity In rate and depth when awake, with apneic periods of 24 sec; only transient response to commands to breathe
GL	M	23	R 7+++ R&L 10+++ R&L 10+++	+++	++++	21.0	170/100	None	42%	Tank 8 days; rocking 21 days	68%	Yes	Rapid progression of irregular breathing, lapsing into semi-stupor; patient later unable to initiate sustained respirations on command when removed from tank respirator; recordable VC never less than 21 %
JC	F	4	R&L 10 R 7	+	+++	40.0	None	80/?	40%	Tank inter mittent 2 days	>50%	None	Totally irregular respiratory pattern; patient unable to sleep during acute Ill ness except in respirator, responded to command with excellent respirations

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Name	Sex	Age	Cranial Nerve	Spinal	Swallowing Paralysis	Min VC % predicted	Hyper-tension	Hypo-tension	VC at time of Respiratory Failure	Art Resp Duration	Recovery VC	Trach-eotomy	Manifestations
Stage 3													
JS	M	26	R&L 7 R&L 10+++ R&L 11 +	++	++++	Not measured	++	None	Not measured	Tank 20 days; rocking 8 mo	43%	Yes	Marked irregularity In rate and depth with prolonged apneic periods and cyanosis after 50 mg. meperidine HCl
JB	M	7	R&L 10+++	++	++++	Not measured	None	+++; Blood & vaso-pressors	Not measured	Tank 22 days	Not measured est. 90%	Yes	Irregularity in rate and depth, accentuated by thiopental anaesthesia; CO_2 retention developed with bicarbonate of 34 MEq.; patient unable to initiate any respiratory effort for 18 days after placed in body respirator
DD	M	23	R&L 5,7,9,10, 11,12	++	++++	62.6 before apnoea	160/90	++++; Blood & vaso-pressors	62.6%	Tank 6 days	Died	Yes	"Cogwheel" irregularity of inspiration, progressing rapidly to total irregularity and apnoea, with complete inability to initiate respiratory act
PG	F	36	R&L 3,4,5,6,7, 9,10,11, 12++++	+	++++	-	None	++++ cardiac arrest	44%	Tank 12 hr.	Died	Yes	Rapid progress to total apnoea with minimal spinal paralysis ; gill-like breathing motions terminally
AW	M	32	R&L 10++	++	++++	11	None	++++; Vaso-pressors	48%	Tank 33 days rocking 120 days	48.6%	Yes	Irregularity In rate and depth and acute awareness of need to drive respiration consciously
FL	M	19	R5 ++ L7 ++ R&L 10,11, 12+++	++	++++	8	150/75	++++; Blood & vaso-pressors	55%	Tank 30 days; rocking at night indef.	42.8%	Yes	Irregularity in rate and depth, progressing rapidly to ineffectual gasps; brief deep breaths on command but patient unable to maintain compensation despite VC of 55%

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Name	Sex	Age	Cranial Nerve	Spinal	Swallowing Paralysis	Min VC % predicted	Hyper-tension	Hypo-tension	VC at time of Respiratory Failure	Art Resp Duration	Recovery VC	Trach-eotomy	Manifestations
PD	M	6	R&L 10+++	+	++	-	148/88	++++; Vaso-pressors	40%	Tank 9 $^1/_2$ hr.	Died	Yes	Child with negligible spinal paralysis, swallowing failure, given general anaesthetic for tracheotomy, remained in coma; respirations irregular but intermittently deep; $PAco_2$ climbed to 52 mm Hg; O_2 masked hypoventilation
VJ	M	5	R&L 10, 11 +++	+	+++	Not measured	130/?	None	Not measured	Tank 14 days	Not measured est. 100%	Yes	No spinal paralysis; irregular breathing progressing rapidly to ineffectual respiratory efforts and stupor; incoordination between irregular breathing patterns and respirator a problem until hyperventilation was produced

Treatment

No specific treatment was required for the breathing defect in Stage 1, although the clinical symptoms alerted the staff that more serious problems might develop. It was learned that sedative or tranquillising drugs must be avoided with acutely ill patients, and oxygen therapy could be used safely only in conjunction with artificial respiration. When general anesthesia was employed for tracheotomy, it proved necessary to follow it with artificial respiration.

Artificial respiration by tank respirator was required sooner or later to treat all 13 patients in Stage II or Stage III. Respiratory decompensation was an obvious indication for artificial respiration, but most patients were placed in the respirator before decompensation was reached. Artificial respiration was started whenever patients admitted the need to concentrate in order to breathe, when sleep had been delayed because of apprehension about breathing, or when alveolar CO_2 tensions rose above normal (40-42 mm Hg).

Irregular central respiratory control and laryngeal incoordination sometimes produced chest motion out of phase with the respirator. This problem was overcome by eliminating glottic obstruction by tracheotomy and then increasing respirator pressures and rates to produce hyperventilation (with PA_{CO_2} usually about 28 mm Hg). Respirator pressures then were reduced gradually to maintain just enough ventilation to eliminate the endogenous respiratory drives caused by carbon dioxide.

Complete swallowing paralysis developed sooner or later in 9 of the 13 patients in Stages II and III, and all 9 of them were given tracheotomy. Tracheotomy was performed in several patients in advance of serious swallowing difficulty because artificial respiration was contemplated; with progressive bulbar disease the likelihood of eventual nucleus ambiguus involvement was great. Tracheotomy failed to eliminate abnormal centrogenic breathing patterns, although coughing, gasping, or other irregularities induced by obstructing secretions disappeared after the procedure.

Mortality and Pathology.-

There were 3 deaths in the total series of 51 patients with either central or spinal respiratory failure. All three were in patients with fulminating disease of the brain stem and central respiratory failure. Autopsy was obtained on one of our own subjects (D. D.), and, in addition, examination was made of tissue blocks from the brain of another patient (H. I. S.), who suffered from central respiratory failure. This woman, a patient of Dr. James W. Stephens, died suddenly on the 20th day of her illness. The immediate cause of death was not apparent on autopsy. Dr. Stephens' notes recorded: "It was repeatedly noted that when she was taken out of the tank ... she had a vital capacity ... usually between 1200 and 1500 (cc.); yet when she was left alone, without any sensory stimulus given her outside the tank, her respirations became shallow and very irregular and from time to time would

stop altogether for a period as long as 30 or 45 seconds, only starting again when she was told to breathe, so that repeatedly one would have to stand over her counting in order to make her breathe."

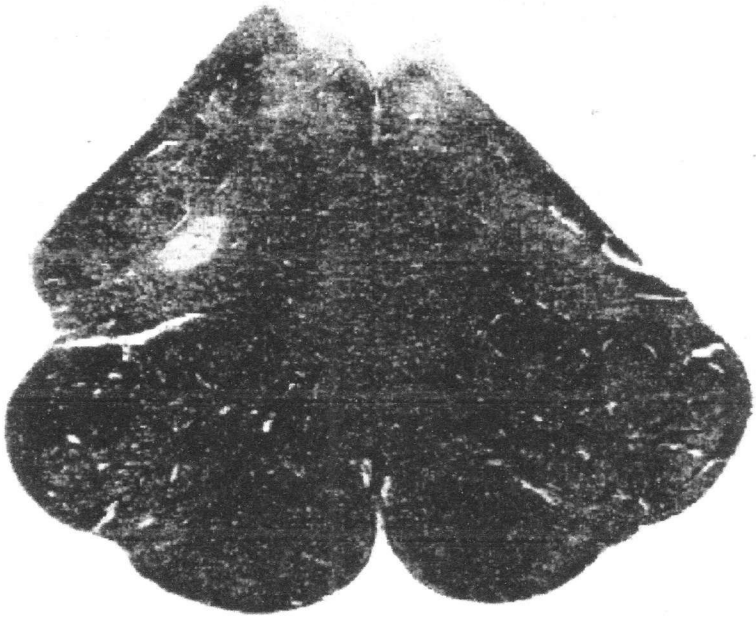

Fig. 5A.—Medulla at the lower level of the inferior olive from H. I. S. Note the pale area of necrosis in the region of the left nucleus ambiguus and surrounding lateral reticular formation. This measured 3 mm. in greatest diameter.

Tissue blocks were taken from the brain of H. I. S. at the level of the decussation of the pyramids, at the level of the hypoglossal nucleus and inferior olive, and at the mid-pontine level. Sections were examined from D.D. at 2-3 mm. intervals from C-1 to the midbrain. Selected blocks also were prepared from other sites. Both patients showed extensive inflammation and neuronal alterations in the medullary reticular formation particularly in the ventrolateral reticular formation, from the level of the acoustic tubercles down to the level of the pyramidal decussation. In both cases, small necrotic foci of 1-2 mm diameter were observed in the ventrolateral reticular formation (Figs. 5A-5D). At pontine levels, inflammatory changes in the reticular formation were moderately intense and consisted predominantly of perivascular infiltration with mononuclear cells without severe neuronal alteration or necrosis. D. D. also showed fairly severe inflammatory infiltration and neuronal loss in the trigeminal motor nuclei.

Figs. 5B, 5C, and 5D—Sections from D. P.

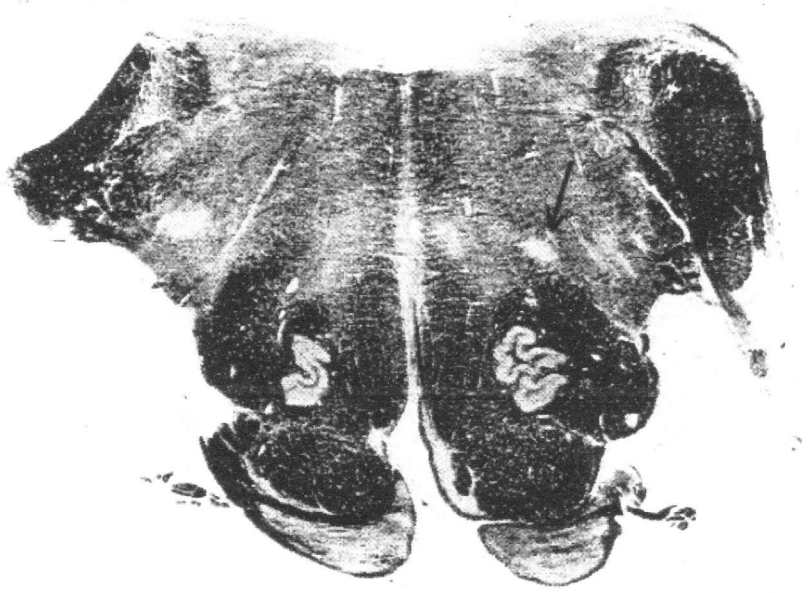

Fig. 5B.—Caudal border of pons. The area of necrosis on the left lies in the region of the nucleus of spinal V. There were several tiny areas of necrosis in the ventral reticular formation on the right, the largest of which is indicated by the arrow.

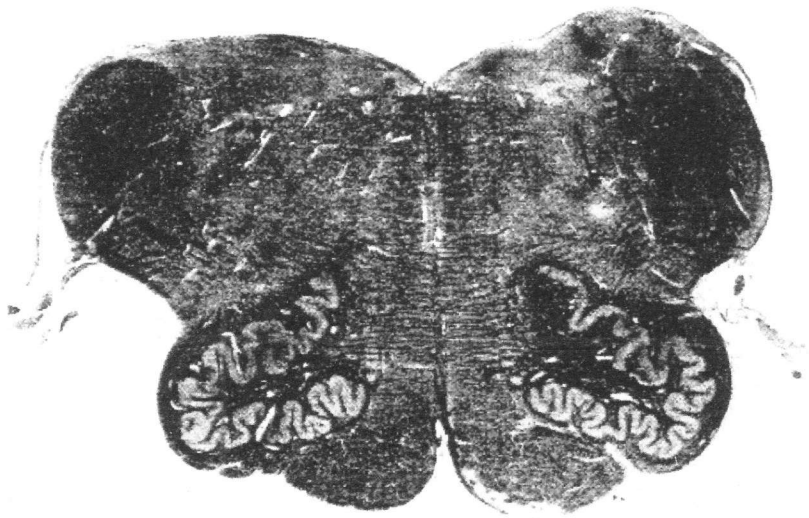

Fig. 5C.—Medulla at level of the inferior olive. The extensive inflammatory changes in the ventral lateral reticular formation extended to this section. An area of necrosis is indicated by the arrow.

Observations During Convalescence from Poliomyelitis

Permanent Respiratory Irregularity and Hyposensitivity to Carbon Dioxide During Sleep.

The characteristic clinical abnormalities in respiration induced by defective central control of breathing seldom lasted more than two weeks after the end of the acute stage of poliomyelitis. However, major disturbances in central respiratory control persisted late into convalescence in at least two subjects. Both these patients progressed to Stage III failure during their acute illness, and it proved difficult during convalescence to emancipate them from respiratory aid, particularly during sleep. Physiological studies showed irregular respirations during drowsiness or sleep, retention of carbon dioxide during sleep, depression of ventilation when

breathing oxygen, and a reduced response to carbon dioxide as a respiratory stimulus. Both subjects demonstrated choreiform movements involving the head and extremities during sleep.

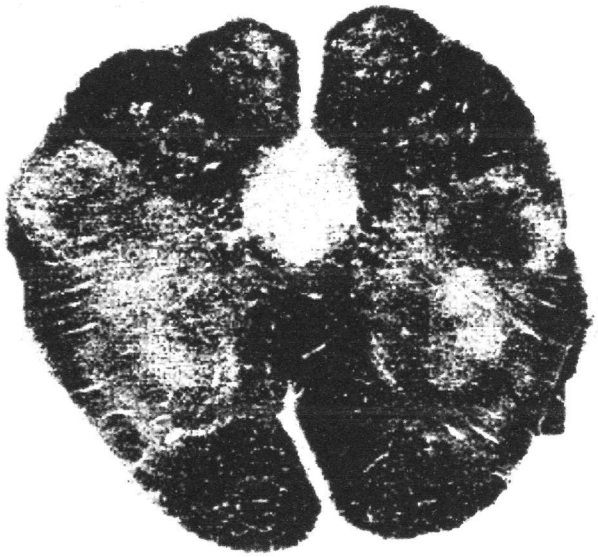

Fig. 5D.—Medulla at the level of the pyramidal decussation. The necrotic focus on the right lies in the reticular formation just ventral to the descending root of spinal V.

Report of Cases

F.L., a 19-vear-old youth, developed swallowing paralysis two days prior to admission, on Nov. 15, 1954. He had partial paralysis of the right 5th and left 7th and bi-lateral paralysis of the 10th, 11th and 12th cranial nerves. Respiration was markedly irregular in rate and depth when he was awake, but his vital capacity was 55% of the predicted normal. During his first hospital day a tracheotomy, was done, and he was placed in a body respirator because the marked respiratory irregularity threatened to produce hypoventilation. There were serious complications during the acute illness: Gastrointestinal haemorrhage necessitated transfusion with whole blood, and his blood pressure was supported with vasopressors for 96 hours (Table 1).

During the first six months of convalescence he was seriously and, at times, critically ill. Persistent swallowing paralysis with regurgitation of gastric contents made it difficult to feed him, and he had repeated episodes of pneumonitis and pyelonephritis. His vital capacity gradually increased to 1.7 litres (39% of predicted) by the sixth month, but, in order to sleep, he required respiratory aid in the form of a rocking bed. During drowsiness or sleep his respirations were irregular, and chorieform movements of the head and extremities appeared. He became progressively drowsier during the day, falling asleep when eating or during physical therapy. Residual skeletal muscle strength was sufficient to allow walking and functional use of both arms, but his progress was slow. Ten months after the acute illness, studies were performed (Table 2A) which demonstrated marked arterial hypercapnia and normal O_2 saturation. Breathing pattern is shown Figure 6, upper tracing. He had an audible inspiratory laryngeal stridor and a diminished inspiratory flow rate. At first, airway obstruct was suspected to be the cause of his respiratory difficulty, and the tracheotomy, which had been closed during the seventh month, was re-established. Table 2A records the data following tracheotomy. Ventilation improved, but irregular respiration (Fig. 6, middle and lower tracings)

with retention of carbon dioxide persisted during sleep. His minute ventilation was reduced when he was breathing 100% oxygen. He had adequate pulmonary reserve to overcome CO_2 retention and could ventilate voluntarily into hypocapnic ranges.
The CO_2 retention and overwhelming drowsiness during the day were relieved by the tracheotomy, however, and his rehabilitation program progressed more rapidly.

A follow-up examination nine months later showed persistence of the irregular respiration and choreiform activity during sleep. Sleeping PA_{CO_2} was *53.2* mm Hg (normal mean PA_{CO_2} during sleep=46.3 mm Hg[13]). Numerous attempts to free him from artificial respiration at night were unsuccessful, as they, induced progressive CO_2 retention without dyspnea. His ventilatory response to increased tensions of CO_2 in the inspired air was depressed markedly. (Fig. 8B, F. L., Table 3).

A.W., a 32-vear-old man, was admitted Oct. 23, 1954, with acute poliomyelitis. He complained of stiffness of his neck and a weak left arm. There were no gross cranial-nerve paralyses, but his voice had developed a nasal quality. His vital capacity was 4.2 litres (94% of the predicted normal). During his first hospital day he complained of having to concentrate on breathing, and his respirations were jerky and irregular. The vital capacity fell to 49%, and he was placed in a body respirator in order to provide rest. His disease progressed and coma and swallowing paralysis developed. Partial obstruction of the airway by secretions ensued, although he had a tracheotomy, and arterial oxygen desaturation was present for five days during the acute illness. His blood pressure had to he supported for three days (Table 1).

In early convalescence irregularity in rate and depth of breathing and choreiform movements of the extremities were noted during drowsiness or sleep. The vital capacity returned to 36%; but emancipation from the respirator was slow, and four months were required to eliminate night-time respiratory aid. He was discharged seven months after admission. At that time his trunk and lower extremity muscles were normal but he had severe residual paralysis in his neck, shoulders, and upper extremities.

Nine months later he developed a low-grade tracheobronchitis. A chronic cough and increasing drowsiness persisted for a month before he sought medical care. He did not complain of dyspnea but had a PA_{CO_2} of 55.5 mm Hg. Drowsiness and hypercapnia cleared after three days of artificial respiration and treatment of the tracheobronchitis. Table 2B records ventilators and blood gas data before and after treatment. The sleeping respiratory pattern was irregular in rate and depth (Fig. 7), and he had chorieform movements during sleep. Despite the respiratory abnormalities, he no longer needed a respirator once the infection was clear. He was able to reduce his PA_{CO_2} to hypocapnic ranges by voluntary overbreathing. A follow up examination two months later revealed that the irregular breathing pattern and choreiform movements during sleep were unchanged. His sleeping PA_{CO_2} was 50.8 mm Hg. Measurements of his ventilation while he was inhaling increased concentrations of CO_2 showed depressed response to the CO_2 stimulus (Fig 8) although his MBCwas 51% of the predicted normal (Table 3). Oxygen breathing depressed his minute respiratory volume.

Studies were again repeated in March, 1958. Sleeping PA_{CO_2} was 57 mm Hg, and he was repeatedly awakening from sleep, feeling frightened but not dyspneic. . Because of these findings the patient has been provided permanently with a rocking bed for sleep. This has eliminated both the nocturnal awakening and the elevated PA_{CO_2}.

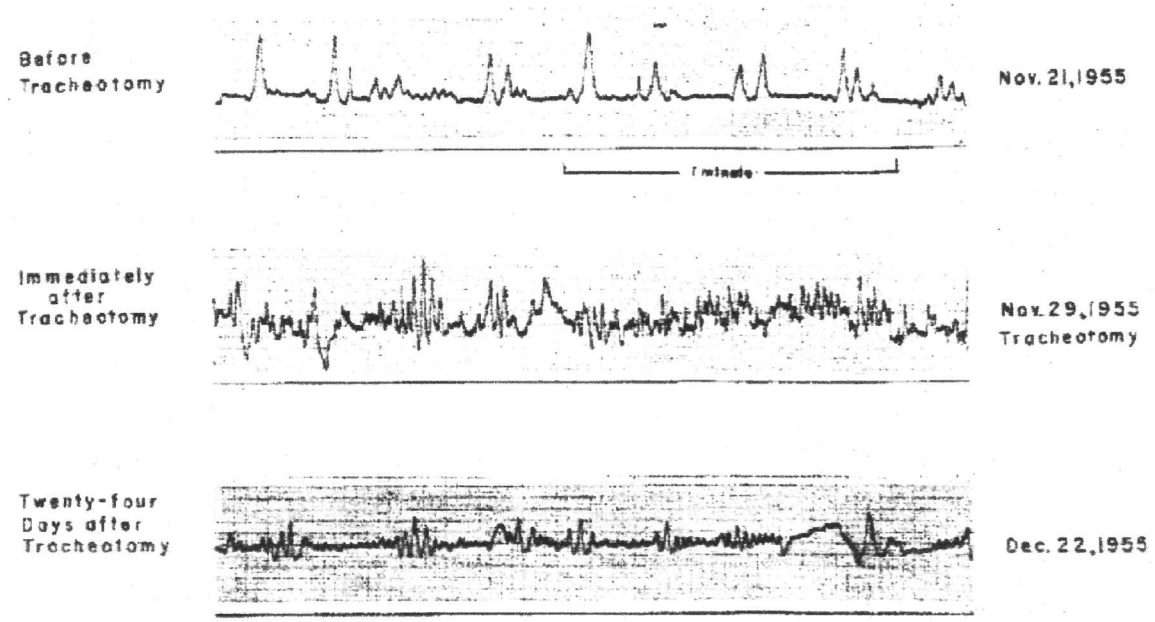

Fig. 6.—Pneumograms before and after replacement of tracheotomy in F. L. The respiratory irregularity failed to improve after the creation of an unobstructed airway.

Ventilatory Response to Carbon Dioxide Following Poliomyelitis

After the reduced ventilatory response to carbon dioxide was observed in the two patients described above, CO_2 response curves and the ventilatory response to oxygen were determined on a group of 16 additional patients convalescing from poliomyelitis. The patients were divided into three groups. All had required respirators during acute poliomyelitis and were studied several months after the end of acute disease. Group A had Stage || or Stage ||| centrogenic respiratory failure during acute poliomyelitis but had shown good to excellent recovery at the time of study. Vital capacity and maximal breathing capacity values were over 50% of the predicted normal. Group B had both bulbar and spinal paralysis during acute poliomyelitis. At the time of the study, moderate to sever residual spinal respiratory paralysis remained, with the VC or MBC less than 50% of the predicted normal. Group C had no evidence of central respiratory, with a defects or cranial nerve paralysis during acute illness; the patients suffered moderate to severe residual paralysis of the diaphragm and intercostal' muscles, with an MBC or VC of less than 50% of the predicted normal. Only E. T. still required artificial respiration.

TABLE 2.—*Ventilatory and Blood Gas Data*

	A. Patient F. L.	
	Before Tracheotomy	After Tracheotomy
Percentage predicted VC	42.8 (1.8 L.)	42.8
Percentage predicted MBC	13.9 (15.5 L./min.)	31.5 (35 L./min.)
PA_{CO_2}, awake, mm. Hg	70	45.5
PA_{CO_2}, with hyperventilation, mm. Hg	--	26
P_{aCO_2}, asleep, mm. Hg	71.5	55
Art. O_2 saturation	94.3%	96.4%
Arterial pH	7.39	7.40
Minute ventilation, air *	2.979 L.	4.97 L.
Minute ventilation, oxygen	2.14 L.	3.63 L.
	B. Patient A. W.	
	During Tracheobronchitis	Recovered
Percentage predicted VC	32.3 (1.4 L.)	48.6 (2.2 L.)
Percentage predicted MBC	34 (48.5 L./min.)	52 (73.5 L./min.)
PA_{CO_2}, awake, mm. Hg	55.5	43.1
PA_{CO_2}, with hyperventilation, mm. Hg	--	35
PA_{CO_2}, asleep, mm. Hg	59.5	59.6
Arterial pH		7.40
Minute alveolar ventilation, air	--	5.10 L.
Minute alveolar ventilation, oxygen	--	3.9 L.

* Alveolar ventilation could not be calculated accurately because of respiratory irregularity.

Patients with overwhelming residual paralysis showing either a MBC or a VC of less than 25% were not included in either Group B or Group C. This exclusion was made in order to prevent, as much as possible, factors of restricted chest motion and fatigue from affecting the CO_2 response. At the time of study no patient was systemically ill, and no patient had parenchymal disease of the lungs.

Figure 8 and Table 3 show the ventilatory response to inhaled carbon dioxide of healthy adults studied in this laboratory, as well as the responses of the three groups convalescing from poliomyelitis. In the normal subjects a mean rise in PA_{CO_2} of 1.67 mm Hg (range 1.5-2.0 mm Hg) was required to double the ventilation over resting levels. This corresponds closely with Peabody's [14] and Tenney's [15] findings for normals. In Group A, a mean rise in PA_{CO_2} of 1.88±0.37 mm Hg resulted in doubling the ventilation. Only H. W's values fell significantly outside the normal range. In Group B, a mean rise in PA_{CO_2} of 12±1.70 mm Hg was required to double the ventilation. No patient in Group B fell within the normal range. In Group C, a mean rise in PA_{CO_2} of 5.14±1.36 mm Hg was required to double the ventilation over resting levels. Although the rise in PA_{CO_2} associated with doubling ventilation over resting levels was usually less marked in this group than among patients in Group B, only two patients in Group C had responses which were within the normal range.

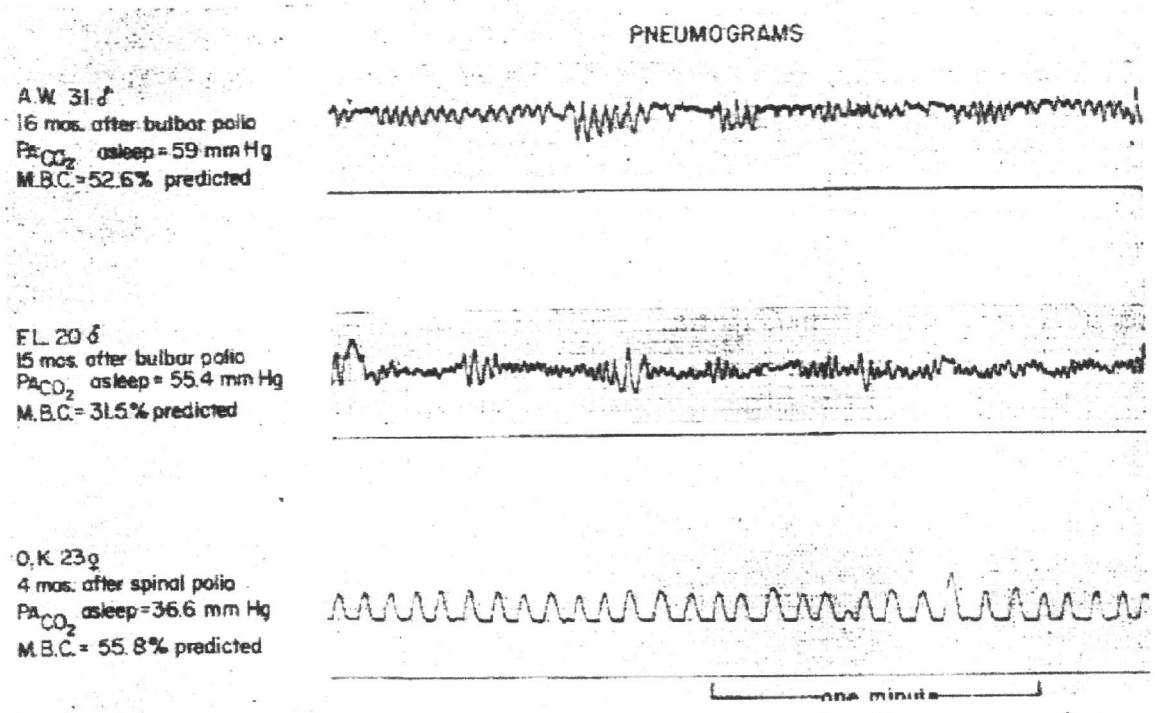

Fig. 7.—Pneumograms illustrating permanent irregularity in breathing patterns after poliomyelitis. A. W. and F. L. are reported on in the text. O. K. had spinal poliomyelitis without clinical signs of bulbar involvement. She had no respiratory irregularity during the acute phase or in convalescence. However, four months after the acute illness she had a reduced response to CO_2 as a respiratory stimulus (Fig. 8 and Table 3).

The ventilatory response to oxygen was determined in all patients in Group A, in three patients in Group B, and in six patients in Group C. The difference in response to oxygen between subjects in Group A and subjects in Group C was not significant, and no patient in these groups had the minute ventilation reduced more than 10.5% while breathing oxygen. Both A. W. and F. L. in Group B, however, showed a decrease in minute ventilation of more than 20% while breathing oxygen.

Review of the clinical data and ventilatory capacity of the subjects in Groups B and C who showed varying degrees of CO_2 responsiveness evinced no consistent differences in severity of acute illness, "encephalitic" symptoms, pulmonary complications, or other clinical findings. Within each group there was no correlation between the CO_2 response curves and the extent of ventilatory return. All the patients were able to hyperventilate voluntarily to levels considerably in excess of the minute volumes obtained by determining CO_2 responsiveness. The two patients with the lowest responsiveness, O. K., in Group C, and A. W., in Group B, had the highest MBC values of their respective groups.

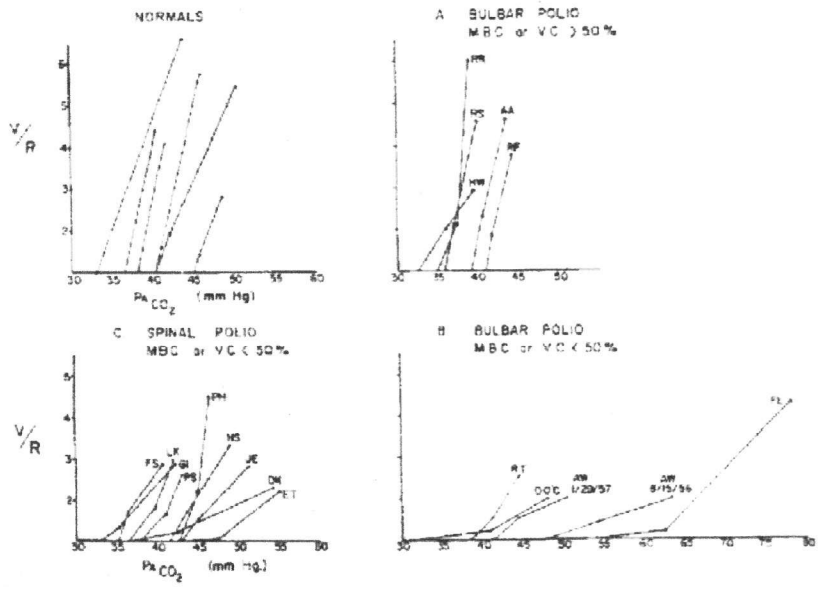

Fig. 8.—Carbon dioxide sensitivity following poliomyelitis. The ventilatory response to breathing increased concentrations of carbon dioxide. V/R= minute alveolar ventilation on CO_2 divided by resting minute alveolar ventilation.

Although CO_2 responsiveness could not be correlated with the return of ventilatory function, when one patient was compared with another, there was evidence that factors outside the nervous system affected the response to CO_2. Figure 9 illustrates the ventilatory response to CO_2 of R. W., a 25-year-old man, who had severe spinal poliomyelitis in 1946. He had not needed respiratory aid from 1947 until October, 1956, when he had severe bronchopneumonia, with marked carbon dioxide retention and respiratory acidosis. This required two weeks of treatment in a respirator for correction. On Nov. 20, one month after this illness, he doubled his ventilation only after a rise in PA CO_2 of 15 mm Hg. His MBC at this time was 30%; his VC 33%. Three months later his MBC had increased to 58% of the predicted normal level and his VC to 37%. He doubled his ventilation, with a rise in PA CO_2 of 4 mm Hg.

TABLE 3.—*Ventilatory Response to Oxygen and Carbon Dioxide*

Name	Age	Sex	% Predicted MBC	% Predicted VC	PA_{CO_2} Values, Mm. Hg At V/R=1	At V/R=2	Difference	Minute Alveolar Volume, Liters Air	Oxygen	% Change
Group A										
A. A.	22	F	52	50	39.1	40.5	1.4	5.40	6.00	+11.1
R. F.	33	M	54	80	41	42.2	1.2	5.13	5.13	0.0
R. R.	31	M	120	110	35	37.3	2.3	4.49	5.12	+14.0
R. S.	37	M	65	76	35.7	36.7	1.0	4.85	4.55	— 6.2
H. W.	38	F	110	75	32.5	36	3.5	5.34	5.45	+ 2.1
					Mean difference ± S. E.		1.88±0.37		Mean change	+ 4.2%
Group B										
D. O'C.	30	M	39	45	31.3	47.7	16.2	8.24	--	--
R. T.	16	M	25	66	38.6	42.8	4.2	5.63	4.85	—13.9
A. W. 8/15/56	34	M	61	48	48.2	63.5	15.3	4.44	3.18	—28.4
A. W. 1/29/57	34	M	47	44	41.5	50.3	9.8	5.15	4.06	—21.2
F. L. 12/13/55	22	M	32	43	45.5	59.5	14	4.97 *	3.63 *	—27.0
F. L. 8/15/56	22	M	32	37	54.2	66.7	12.5	4.34 *	--	--
					Mean difference ± S. E.		12.0±1.79		Mean change	—22.6%
Group C										
F. S.	20	F	45	52	35.2	37.0	1.8	4.86	5.06	+ 4.2
L. K.	24	F	34	62	36.2	40.1	3.9	3.88	3.68	— 5.3
G. I.	30	F	52	49	33.2	37.8	4.6	4.94	5.05	+ 2.2
P. S.	22	F	29	20	37.8	41.8	4.0	5.83	5.41	— 7.2
P. H.	15	F	44	36	42.7	44.6	1.9	3.81	3.41	—10.5
H. S.	37	M	26	24	41.4	44.5	3.1	3.45	3.82	+10.7
J. E.	16	M	26	25	42.7	46.4	3.7	6.12	--	--
O. K.	25	F	62	47	36.6	50.0	13.4	5.77	--	--
E. T.	33	F	37	27	43.2	53.1	9.9	3.62	--	--
					Mean difference ± S. E.		5.14±1.36		Mean change	—1%

* Total minute ventilation.

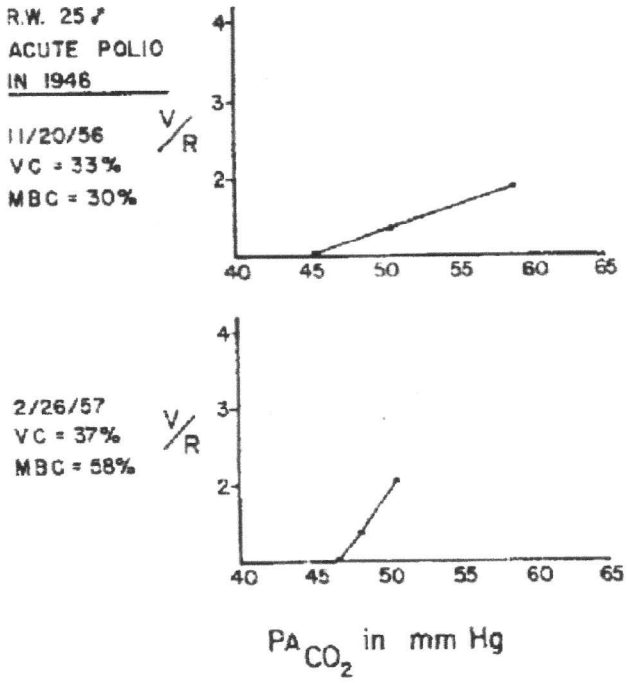

Fig. 9—Effect of an improved MBC on the ventilatory response to carbon dioxide.

Comment

These observations outline a progressive physiological abnormality in the control of respiration resulting from bulbar poliomyelitis. Respiratory rhythmicity is first impaired, but, in its early stages, dysrhythmia appears only during sleep, when afferent neural stimuli and the activity of the rostral reticular formation are markedly reduced. As the lesion progresses, loss of rhythm persists into waking hours, and increased neural activation by conscious effort or by auditory or painful stimuli is required to restore regularity. Impairment of chemosensitivity of the respiratory centers at this stage is strongly suggested by reduction in ventilation and induction of CO_2 retention by oxygen therapy.[16,17] Further progression of the disease produces a state in which an increasing amount of neural stimulation must be recruited to produce ventilatory efforts. Finally, reflex responsiveness of the respiratory center is lost, and sustained ventilation will not follow any stimulus. At any of the above stages of progressive failure, depressant drugs rapidly accelerate the deterioration of respiratory control.

There are two major theories of the neurogenesis of respiration. The first, summarized by Pitts,[18] views the medullary respiratory center as tonically active in inspiration, requiring periodic inhibition from a supramedullary "pneumotaxic center" to produce rhythmic breathing. The second theory, that of Hoff and Breckenridge,[19] views the medullary center as possessing intrinsic rhythmicity, with supramedullary and extramedullary impulses converging upon it to produce by summation the final respiratory act. If respiratory failure in bulbar poliomyelitis reflects progressive damage to-the medullary respiratory center, the findings strongly support, the view that rhythmicity is an inherent and extremely sensitive function of that center.

All available evidence indicates that central respiratory failure in poliomyelitis is medullary in origin. The medulla is the site of major pathological damage in patients suffering central failure.[4,20-22] Experimental physiological studies have demonstrated only in the medulla a dissociation in responsiveness to chemical and reflex stimuli, such as occurs in bulbar poliomyelitis.[23-25]

Indeed, the pattern of development of respiratory failure in bulbar poliomyelitis bears a close resemblance to the manner in which respiration deteriorates in the medullary animal who has suffered anoxia, drug depression, or trauma.[26,27] Finally, unpublished observations on humans in our own laboratory indicate that supramedullary brain stem lesions affecting respiration produce sustained hyperventilation or Cheyne-Stokes respiration rather than the breath-to-breath variations in respiratory rhythm with hyposensitivity to carbon dioxide that is seen in centrogenic respiratory failure in poliomyelitis.

Little elaboration of the clinical implications of observations made during acute poliomyelitis is necessary. Evidence presented in the clinical descriptions indicates that the changes observed in these patients could not be attributed to respiratory obstruction: Pharyngeal secretions were carefully removed in all patients before

recordings were made; some of the severest anomalies appeared in subjects who lacked swallowing paralysis, and establishment of tracheotomy with complete assurance of a clear airway failed to relieve the respiratory irregularity or to restore spontaneously adequate ventilation. Also, the respiratory defects could not have resulted from progressive involvement of spinal motoneurons serving diaphragm and intercostal muscles, since every patient demonstrated upon command the capacity for individual breaths, which, if rhythmically sustained, would have been adequate to maintain respiratory compensation.

One clinical phenomenon which was searched for was never observed. This was incoordination of the respiratory muscles themselves, resulting in expiratory and inspiratory groups contracting simultaneously. At times, retraction of the abdominal wall during inspiration gave the impression that active expiration was taking place, but fluoroscopic examination demonstrated diaphragmatic descent at this time and tidal volume showed no decrease. Wade[28] has emphasized how misleading abdominal movement may be in estimating the phase of diaphragmatic activity. He also reported inability to induce dissociation of inspiratory muscle groups. When respiratory rhythm was most markedly disturbed in poliomyelitis, the central respiratory discharge appeared to be either inspiratory or expiratory, and never a combination of the two. Incoordination of laryngeal activity with respiratory cycling was noted during both acute and convalescent poliomyelitis, but this could not be attributed to dysfunction of the respiratory center.

The defects in respiratory regulation persisting after poliomyelitis were unexpected. The view is widely held that, if the patient survives poliomyelitis, central regulation of respiration will return to normal.[29] The impairment of respiratory rhythm, hypoventilation during sleep, depression of ventilation by oxygen, and low CO_2 responsiveness, shown by F. L. and A. W. strongly suggest that these patients have abnormally functioning respiratory centers. Less clear is the cause of the persistent defects observed in the larger number of subjects in Groups B and C. These defects were largely confined to reduced respiratory sensitivity to carbon dioxide without evidence of impaired respiratory rhythmicity or significant suppression of breathing by oxygen. Similar findings in a series of convalescent poliomyelitis patients with markedly reduced breathing capacity recently were presented by Linderholm and Werneman.[30] These authors noted that low CO_2 responsiveness was selective and did not apply to their entire low-vital-capacity, low-maximal-breathing-capacity group. The ventilatory response to exercise appeared normal in their low- CO_2-responsive cases, and ventilation during work was greater than during CO_2 inhalation. The percentage of low- CO_2-responsive cases among their patients with pure spinal paralysis was as high as the percentage among patients having bulbar pareses. The highest incidence of low-CO_2-responsive cases, however, was among patients showing "cerebral" symptoms during acute poliomyelitis. Linderholm and Werneman concluded that low responsiveness to CO_2 after poliomyelitis was due to persistent damage to the medullary chemoreceptors. They attributed little clinical importance to the

finding, save that it might create difficulties at times of future surgical intervention or anesthesia.

Permanent damage to chemoreceptive neurons in the respiratory center is an attractive explanation for the widespread finding of low CO_2 responsiveness after poliomyelitis. This explanation is supported by the observation that the indolent ventilatory responses to carbon dioxide were most prominent among patients who, clinically, had bulbar poliomyelitis. Permanent damage to central breathing mechanisms also would explain why impaired CO_2 sensitivity was not proportional to the reduction in the ventilatory ability when subjects within each group were compared. However, damage to the respiratory center is probably not the only cause of the impaired response to carbon dioxide during convalescence from poliomyelitis. Except in the case of H. W., low CO_2 responsiveness was never observed in convalescence among patients who had central respiratory failure unless they also suffered a significant restriction of MBC due to spinal paralysis. Isolated low responsiveness to CO_2 after poliomyelitis was nearly as frequent in patients who had had only spinal paralysis as it was in patients who also had suffered bulbar paralysis. The only common denominator to all patients who had a pronounced impairment in the ventilatory response to CO_2 was a restriction in the MBC or VC of 50% or more. At least part of the impaired sensitivity, therefore, may have been peripheral rather than central in origin. Peripheral mechanisms recently have been concluded to have such an effect in pulmonary emphysema. Cherniak and Snidal[31] demonstrated that low CO_2 response curves in emphysema are directly related to the reduction in the level of the MBC. If the MBC of emphysema patients was increased, so was the CO_2 responsiveness, in a manner similar to that if the MBC of a normal subject is reduced by artificial airway obstruction, CO_2 re-noted in the case of R. W., reported here. Furthermore, Cherniak demonstrated that responsiveness shows a proportionate decline. Restriction of MBC and VC in poliomyelitis is associated with a pronounced loss of chest-lung compliance.[32] Reduced compliance, of necessity, imposes an increase above the normal in the work- of breathing. Recent evidence[33] indicates that in emphysematous patients with restricted ventilation the increment in the work of breathing following CO_2 stimulation may be normal, although impaired pulmonary mechanics limits the ventilatory. response. Thus, "impaired CO_2 responsiveness following poliomyelitis in many instances may reflect merely an increase in the work requirements of breathing, and not any defect in the respiratory center.

Whatever its cause, reduced CO_2 responsiveness following poliomyelitis has important clinical implications. Emancipation from respiratory aid is an important goal during convalescence from poliomyelitis. The final, and usually the most difficult., step in the program of withdrawing respiratory aid is in enabling patients to sleep without artificial respiration. Extramedullary respiratory stimuli may be required to maintain respiratory homeostasis in the presence of low CO_2 responsiveness after poliomyelitis. Sleep eliminates many of these stimuli, producing the setting for respiratory decompensation to ensue. This was observed

in F. L. whenever artificial respiration was withdrawn at night. A. W. and R. W. developed the same problem during respiratory infections These findings indicate that there is a physiological basis for the claims of those convalescent poliomyelitis patients who state that they need artificial respiration in order to sleep, although they have what appears to he relatively good return of respiratory f unction. The findings also demonstrate that respiratory infections may induce insidious respiratory decompensation long after patients recovering from poliomyelitis have recovered apparently adequate ventilatory reserves.

Summary and Conclusions

Clinical, physiological, and pathological observations on the nature of central respiratory failure in anterior poliomyelitis are presented. Central respiratory disturbances were noted in 20 patients during acute illness and in at least 2 patients during late convalescence.

Central respiratory failure in acute poliomyelitis evolves through three stages. Respiratory rhythmicity is first impaired during sleep. Dysrhythmic breathing then persists into wakefulness, and conscious drives must be recruited to maintain respiratory regularity and compensation. Impaired chemosensitivity to carbon dioxide is indicated by depression of ventilation while the patient is breathing oxygen. Finally, the respiratory response to chemical, as well as to reflex and other neural, stimuli shows progressive impairment, and artificial respiration is required to maintain respiratory homeostasis.

Depressant drugs accelerate markedly the deterioration of central respiratory control in acute poliomyelitis.

Pathological studies were performed on two patients. Both showed marked inflammatory changes and small areas of necrosis in the ventrolateral reticular formation of the medulla.

Irregular respiration during sleep persisted in two subjects for many months after acute poliomyelitis. These same patients also demonstrated carbon dioxide retention without dyspnea, an impaired ventilatory response to increased tensions of inspired carbon dioxide, and reduction in ventilation while . breathing 100Yo oxygen. These physiological abnormalities were attributed to permanent abnormalities in the functioning of the medullary respiratory center.

Seven out of nine convalescent subjects with spinal poliomyelitis having MBC or VC values of less than 50% of the predicted normal also demonstrated subnormal responsiveness to carbon dioxide as a respiraatory stimulus. It appears that in poliomyelitis, as in pulmonary emphysema, peripheral mechanisms restricting chest motion may contribute to an impaired ventilatory response to carbon dioxide.

The clinical and physiological findings in central respiratory failure in poliomyelitis support the theory that an intrinsic and sensitive function of the medullary respiratory center is to establish the rhythmicity of breathing.

Elizabeth McGowan and Charles. A. Donaldson gave technical assistance. Dr. James W. Stephens, of the University of Colorado Medical Center, placed the clinical observations and pathological material from his case at our disposal. Dr. Raymond F. Hain Director of the Laboratory of Neuropathology, assisted in the preparation and interpretation of the pathological material.

University of Washington School of Medicine (5).

REFERENCES

1. Wickman, I.: Studien über Poliomyelitis acuta, zugleich ein Beitrag zur Kenntnis der Myelitis acuta, Arb. path. Inst. Univ. Helsingfors 1:109, 1905.
2. Petrén, K., and Ehrenberg, L.: Études cliniques sur la poliomyélite aiguë, Nouv. inconog. Salpêtrière 22 :373; 546; 661, 1909.
3. Brown J. R., and Baker, A. B.: Poliomyelitis: I. Bulbar Poliomyelitis; A Neurophysiological Interpretation of the Clinicopathological Findings, J. Nerv. & Ment. Dis. 109:54-78 (Jan.) 1949.
4. Baker, A. B.; Matzkc, H. A., and Brown, J. R.: Poliomyelitis: I. Bulbar Poliomyelitis; a Study of Medullary Function Arch. Neurol. & Psychiat 63:257-281 (Feb.) 1950.
5. Wickman, I.: Acute Poliomyelitis (Heine- Médin's Disease), authorized English translation by W. J. M. A. Maloney, Nerv. & Ment. Dis. Monograph Series, No. 16, New York, Nervous & Mental Disease Publishing Company, 1913.
6. Barnhart, M.; Rhines, R.; McCarter, J. C., and Magoun H. W.: Distribution of Lesions of the Brain Stem in Poliomyelitis, Arch. Neurol. & Psychiat 59:368-377 (March) 1948.
7. Bodian, D.: Histopathologic Basis of Clinical Findings in Poliomyelitis, Am. J. Med. 6:563-578 (May) 1949.
8. Sarnoff, S. j.; Whittenberger, 1. L., and Affeldt, J. E.: Hypoventilation Syndrome in Bulbar Poliomyelitis, J. A. M. A. 147:30-34 (Sept. 1) 1951.
9. Baldwin, E. deF.; Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency: I. Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects, Medicine 27:243-278 (Sept.) 1948.
10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II: Methods, Baltimore, Williams & Wilkins Company, 1932.
11. Singer, R. B., and Hastings, A. B..: An Improved Clinical Method for the Estimation of Disturbances of the Acid-Base Balance of Human Blood, Medicine 27:223-242 (May) 1948.
12. Nielsen M.: Untersuchungen über die Atemregulation biem Menschen besonders mit Hinblick auf die Art des chemischen Reizes, Skandinav. Arch. physiol. (Supp. 10) 74:87-203, 1936.
13. Mangold, R.; Sokoloff, L.; Conner, E.; Kleinerman, j.; Therman, G. P-O., and Kety, S. S.: The Effects of Sleep and Lack of Sleep on the Cerebral Circulation and Metabolism of Normal Young Men, J. Clin. Invest. 34:1092-1100 (July) 1955.
14. Peabody, F. W.: Clinical Studies on the Respiration: 1 The Effect of Carbon Dioxide in the Inspired Air on Patients With Cardiac Disease, Arch. Int. Med. 16:846-864 (Nov.) 1915.
15. Tenney, S. M.: Ventilatory Response to Carbon Dioxide in Pulmonary Emphysema, J. Appl. Physiol. 6:477-484 (Feb.) 1954.
16. Shock, N. W., and Soley, M. H.: Effect of Breathing Pure Oxygen on Respiratory Volume in Humans, Proc. Soc. Exper. Biol. & Med. 44: 418-420 (Jme) 1940.
17. Dripps, R. D., Jr., and Comroe, J. H., Jr.: Clinical Significance of the Carotid and Aortic Bodies, Am. J. M. Sc. 208:681-694 (Nov.) 1944.
18. Pitts, R. F.: Organization of the Respiratory Center, Physiol. Rev. 26:609-630 (Oct) 1946.
19. Hoff, H. E., and Breckenridge, C. G.: Regulation of Respiration, in A Textbook of Physiology, Ed. 17, edited by J. F. Fulton Philadelphia, W. B. Samders Company, 1955, Chap. 43.

20. Thomas, A., and Lhermiitte, J.: Les lésions cérébrales et médullaires de la poliomyélite aiguë de l'adult, Rev. neurol. 1:1242-1250 (June) 1929.
21. Lherinitte, j.; P@ez, P., and,' Plichet, A.: Forine respiratoire ou asphyxique de la maladie de Heine-M@@ Bull. et m6m. Soc. m6d. h6p. Paris 48:76-92 (Feb.) 1932.
22. Finley, Y, H.: The Neuro,-Anatomy in Respiratory Failure, Arch. Neurol. & Psychiat. 26:754-783 (Oct.) 1931.
23. von Euler, C., and Söderberg, U.: Medullary Chemosensitive Receptors, J. Physiol. 118:545-554 (Dec.) 1952.
24. Comroe, J. H., Jr.: Effect of Direct Chemical and Electrical Stimulation of the Respiratory Center in the Cat, Am. J. Physiol. 139:490-498 (Aug.) 1943.
25. Winterstein, H.: Chemical Control of Pul- monary Ventilation: II. Hypoxia and Respiratory Acclimatizatior4 New England J. Med. 255:272- 278 (Aug. 9) 1956.
26. Breckenridge, C. G., and Hoff, H. E.: Ischemic and Anoxic Dissolution of the Supra- medullary Control of Respiration, Am. J. Physiol. 175:449-457 (Dec.) 1953.
27. Breckenridge, C. G., and Hoff, H. E.: Re-flex Respiration, Am. Physiol. 178:521-528 (Sept.) 1954.
28. Wade, 0. L.: Movements of the Thoracic Cage and Diaphragm in Respiration, T. Physiol. 124:193-212 (May28) 1954.
29. Lassen, H. C. A.: Management of Life- Threatening Poliomyelitis, translated from the Danish by Hans Andersen and others, Edinburgh, E. & S. Livingstone, Ltd., 1956.
30. Linderholm, H., and Wernerman H.: On Respiratory Regulation in Poliomyelitis Con-valescents, Acta med. scandinav. (Supp. 316) 154: 135-157, 1956.
31. Cherniack, R. M., and Snidal, D. P.: The Effect of Obstruction to Breathing on the Ventila- tory Response to C0s, J. Clin. Invest. 35:1286- 1290 (Nov.) 1956.
32. Ferris, B. G., Jr.; Mead, J.; Whittenberger, L., and Saxton, G. A., Jr.: Pulmonary Function in Convalescent Poliomyelitic Patients: II. Compliance of the Lungs and Thorax, New England Med. 247:390-393 (Sept. 11) 1952.
33. Fritts, H. W.; Fishman, A. P., and Cournand, A.: Factors Contributing to the Diminished, Ventilatory Response to CO_2 Of Patients with Obstructive Emphysema, Fed. Proc. 16:41-42 (March) 1957.