Respiratory failure in neuromuscular diseases

B. D. W. HARRISON[1], J. V. COLLINS, K. G. E. BROWN,
and T. J. H. CLARK

Guy's Hospital, London S.E.1

A series is reported of five patients with acute respiratory failure complicating neuromuscular diseases, three of whom required assisted ventilation. Initially the arterial carbon dioxide tension fell to levels below the normal range in all the patients and this change reflects alveolar hyperventilation which is probably produced by a combination of fear, small airway collapse, and reflex tachypnoea. It is only late in the development of respiratory weakness that alveolar ventilation falls and carbon dioxide tension rises to normal and then elevated levels. Several factors contribute to the reduction in arterial oxygen tension, including airway collapse and infection, and it is important to try to prevent these by correct posture, vibration, and passive deep breathing. We think that objective measurements of respiratory function are essential in the management of these patients and that the most valuable are serial measurements of vital capacity and carbon dioxide tension and the least helpful is the arterial oxygen tension. Assisted ventilation will probably be required if the vital capacity falls below 30% of that predicted for the patient or if the carbon dioxide tension rises from low to normal levels as vital capacity is falling.

The development of effective vaccines against poliomyelitis and their widespread use has brought about a dramatic reduction in the incidence of paralytic poliomyelitis and its most serious acute and often fatal complication, respiratory failure (Walley, 1959; Plum, 1952). At the present time neuromuscular respiratory failure is more often encountered as a complication of acute polyneuritis, myasthenia gravis, or acute demyelinating disease. Respiratory failure is generally monitored by measurements of arterial blood gas tensions but in respiratory failure resulting from neuromuscular diseases we believe that this practice may be inadequate as the following reports demonstrate.

PATIENTS AND METHODS

The case histories of five patients with neuro-muscular diseases are presented: two patients with acute polyneuritis and one patient with demyelinating disease affecting the brain stem required assisted ventilation. One patient with acute polyneuritis and one with myasthenia gravis developed respiratory failure but did not require assisted ventilation. A summary of the important clinical details of the patients is given in the Table, and their arterial carbon dioxide tensions are shown in Figure 1.

[1]Present address: Medical Unit, Westminster Hospital, London S.W.1

TABLE
SUMMARY OF CASE HISTORIES

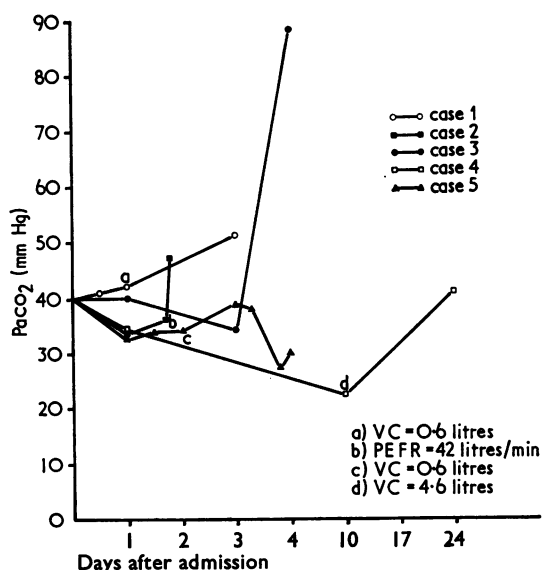| Case	Sex	Age	Diagnosis	Bulbar Palsy	Chest Infection	Vital Capacity (l.)		Assisted Ventilation
						On Admission	Lowest Recorded	
1	F	35	Acute polyneuritis	No	Yes	2·5	0·6	Yes (21 days)
2	F	29	Acute polyneuritis	Yes	No	N.M.	N.M.	Yes (31 days)
3	M	30	Demyelinating disease	No	Yes	N.M.	N.M.	Yes (42 days)
4	M	47	Acute polyneuritis	Yes	No	5·4	4·0	No
5	F	31	Myasthenia gravis	No	Yes	0·5	0·5	No

N.M. = not measured.

FIG. 1.   *Changes observed in PaCO₂ following admission to the intensive care ward. Cases 1, 2 and 3 required assisted ventilation.*

Measurements of vital capacity (VC) were made with a simple bellows spirometer or water-canister spirometer. Peak expiratory flow rates (PEFR) were measured with a Wright's peak flow meter (paediatric model). Arterial blood samples were obtained by brachial or radial artery puncture and gas tensions and pH were measured using a Radiometer A.M.I. machine.

CASE HISTORIES

CASE 1   A 35-year-old school mistress presented with a one-week history of ascending muscular weakness and paraesthesiae in the feet and hands. On examination there was weakness of all four limbs, most marked peripherally, absent tendon reflexes, and no objective sensory loss. The cerebrospinal fluid contained protein, 120 mg/100 ml, and no cells. A diagnosis of acute polyneuritis was made. During the next two weeks the muscular weakness increased until only minimal power of hip and shoulder adduction and some spinal movement remained. The facial and bulbar muscles were unaffected and she showed no respiratory difficulty. Vital capacity measured twice daily remained above 2 litres (predicted normal 3 litres) and arterial blood gas tensions were normal (pH 7·38, PCO_2 41 mmHg and PO_2 96 mmHg) breathing air. Her condition remained unchanged until four months after admission, when she developed a chest infection with sputum, fever, tachycardia, and tachypnoea. She was unable to cough effectively and there was clinical and radiological evidence of left basal pneumonia. Her vital capacity was 0·6 litre (20% predicted) and breathing air her arterial PCO_2 was 42 mmHg and PO_2 52 mmHg. She was bronchoscoped and a tracheostomy was performed to facilitate bronchial suction. She was given oxygen by M/C mask, but two days later while breathing oxygen the arterial PCO_2 was 51 mmHg and PO_2 68 mmHg. Intermittent positive pressure respiration (IPPR) was begun with a volume-cycled respirator and was continuous for nine days. After a further 12 days she was independent of the respirator.

Two years after her original admission she has had no further respiratory difficulties and has a vital capacity of 2·4 litres. However, she has made very little further recovery, she still has a tracheostomy and, apart from slight finger movement, has shown no increase in muscle power.

CASE 2   A 29-year-old housewife presented with a three-day history of weakness in the limbs associated with backache and dysphagia. On examination she had a partial left facial palsy, bulbar palsy, generalized muscle weakness, absent tendon and plantar reflexes, and impairment of all sensory modalities below the seventh cervical segment. Her respiratory rate was 40 per minute and her voice was inaudible. There was no clinical or radiological evidence of chest infection. The cerebrospinal fluid contained protein 120 mg/100 ml, and no cells. A diagnosis of acute polyneuritis was made. The arterial blood showed pH 7·49, PCO_2 33·5 mmHg, and PO_2 66 mmHg while she was breathing air.

She was nursed with the foot of the bed elevated and was given oxygen by 35% ventimask and her respiratory rate fell to 35/min with an arterial PCO_2 of 36 mmHg and PEFR of 42 litres/minute. Nineteen hours after admission, her pulse rate was 140/min in atrial fibrillation, and her respiratory rate had risen to 40/minute. There was no evidence of chest infection, but arterial blood now showed pH 7·33, PCO_2 47 mmHg, and PO_2 56 mmHg (breathing oxygen via nasal catheters). IPPR was begun via an endotracheal tube using a pressure-cycled respirator and 4 hours later a tracheostomy was performed. IPPR was continuous for three days and then she was gradually weaned from the respirator, becoming completely independent of it 31 days after IPPR had been started. She was discharged from hospital three months after admission and, although weak, was able to walk unassisted and had regained full sensory function.

CASE 3   A 30-year-old man, a broadcasting producer, presented with an eight-month history of a left homonymous hemianopia, numbness of the right arm and leg for two weeks, and frequency and urgency of micturition. On examination there was a left homonymous hemianopia, spastic weakness of the right arm and leg, and right-sided hypoaesthesia.

The cerebrospinal fluid contained protein, 75 mg/100 ml, and 5 lymphocytes/100 ml. A diagnosis of acute demyelinating disease was made. Arterial blood gases were normal (pH 7·37, Pco_2 40 mmHg, Po_2 92 mmHg breathing air).

On the day after admission he developed a flaccid paraplegia and a day later he developed a chest infection with fever, tachycardia, and tachypnoea. Arterial blood showed Pco_2 34 mmHg and Po_2 58 mmHg (breathing air). He was treated with antibiotics and oxygen via nasal catheters but the next day he became cyanosed and the arterial blood showed Pco_2 88 mmHg and Po_2 48 mmHg. IPPR was started via an endotracheal tube using a pressure-cycled respirator and six hours later a tracheostomy was performed. He required IPPR for six weeks and his recovery was complicated by repeated respiratory infections. He was discharged three months after admission, able to walk with the aid of sticks, but he had suffered some permanent loss of higher cerebral function.

CASE 4 A 47-year-old retired Royal Air Force N.C.O. presented with a 12-day history of increasing weakness, numbness, and pain in the legs and paraesthesiae of the hands. On examination there was weakness of all four limbs, most marked peripherally, absent tendon reflexes, and impairment of sensation below the tenth thoracic segment and in both arms below the elbows. The cerebrospinal fluid contained protein, 100 mg/100 ml, and no cells. A diagnosis of acute polyneuritis was made. His VC was 5·4 litres (predicted normal 5·3 litres) and arterial blood showed pH 7·44, Pco_2 34 mmHg and Po_2 56 mmHg (breathing air). Seven days later when his VC had fallen to 4 litres he developed dysphagia and difficulty with coughing and was found to have a diminished gag reflex. He was nursed with the foot of the bed elevated and after three days his bulbar symptoms improved. His VC was 4·6 litres and arterial Pco_2 22·5 and Po_2 51 mmHg (breathing air). His VC rose progressively to 5·1 litres over the next two weeks and his arterial blood showed Pco_2 41 mmHg and Po_2 95 mmHg (breathing air) on the 24th day of admission. He continued to improve and was discharged two months after his admission with some residual weakness and numbness in the legs. At no time during the admission did he show evidence of respiratory infection.

CASE 5 A 31-year-old housewife with a three-year history of myasthenia gravis developed a chest infection after influenza and presented with increasing weakness and difficulty in swallowing her pyridostigmine tablets unless they were crushed. On examination she was breathless and unable to lie flat and unable to cough. She was cyanosed, pyrexial, and had a sinus tachycardia of 130/min with signs of right basal pneumonia. She had generalized hypotonia and weakness with bilateral ptosis and in the absence of muscle fasciculation, colic, or bradycardia a diagnosis of myasthenic crisis was made. A
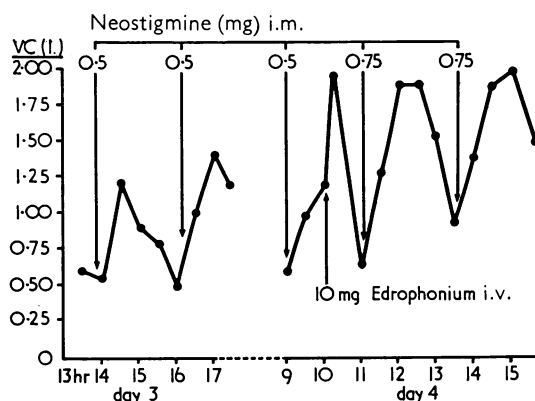

FIG. 2. *Case 5. Changes in vital capacity during treatment.*

chest radiograph confirmed the diagnosis of pneumonia and arterial blood showed pH 7·39, Pco_2 33 mmHg, and Po_2 52 mmHg (breathing 24% oxygen). She was treated with neostigmine, 0·5 mg intramuscularly three-hourly, oxytetracycline, oxygen by 24% ventimask and later by M/C mask, and physiotherapy. Repeated measurements of arterial gas tensions showed that the Pco_2 never rose above 39 mmHg. Frequent measurements of vital capacity were made and these showed an increase from 0·5 litre immediately before an injection of neostigmine to 1·4 litres 30 minutes after injection (Fig. 2). This figure also shows the result of an edrophonium (Tensilon) test carried out on the fourth day of admission. Edrophonium, 10 mg, was given intravenously 70 minutes after the last injection of neostigmine. One minute later the VC rose from 1·2 litres to 1·9 litres and her ability to maintain an upward gaze increased from 2 to 60 seconds. As a result of this test the dose of neostigmine was increased to 0·75 mg intramuscularly three-hourly, and on the fifth day oral pyridostigmine was reintroduced.

The pneumonia responded well to treatment and she made a rapid and full recovery. On the day of her discharge, nine days after admission, her $FEV_{1.0}$ was 1·7 litres, FVC 2·6 litres, and mixed venous Pco_2 37 mmHg.

DISCUSSION

EFFECTS OF RESPIRATORY MUSCLE WEAKNESS AND INCOORDINATION ON GAS EXCHANGE IN THE LUNGS Plum and Wolff (1951) have described the sequence of changes which occurs with increasing paresis of the respiratory muscles. They suggest that as the weakness increases the vital capacity is progressively reduced and subsequently the tidal volume is also reduced. With this fall in tidal volume the respiratory rate increases and minute ventilation is maintained but this pattern

of ventilation produces an increase in wasted (dead space) ventilation resulting in a fall in alveolar ventilation. These changes produce alveolar hypoxia and hypercapnia with corresponding changes in arterial oxygen and carbon dioxide tensions, and thus respiratory failure secondary to neuromuscular diseases is characterized by arterial hypoxaemia and hypercapnia. Crofton and Douglas (1969) and Sykes, McNicol, and Campbell (1969) have also described arterial hypercapnia as a characteristic finding in this situation. However, Dickinson, Wilson, and Graham (1953) found low arterial carbon dioxide tensions in the early stages of respiratory muscle involvement in patients with poliomyelitis, and in all our patients their illness was initially associated with hypocapnia and we found that hypercapnia occurred only at a later stage in neuromuscular respiratory failure (Fig. 1).

There are several factors which give rise to the sequence of changes in arterial blood gas tensions which we have observed in our patients. Respiratory failure in neuromuscular disorders may be peripheral, in which the lower motor neurones or motor units of the respiratory muscles are affected, or central when the respiratory centres in the medulla are affected (Plum, 1952). Weakness of the intercostal muscles and diaphragm reduces the vital capacity and impairs the ability to take occasional deep breaths. This weakness also reduces the linear velocity of air flow which can be achieved in the larger airways and this results in an ineffective cough. In patients with bulbar involvement the cough reflex is further impaired by failure to close the glottis, and these patients are in danger of inhaling nasopharyngeal secretions, food, and vomit. This group of patients also show incoordination and irregularity of respiration. Failure to take deep breaths and incoordination of respiratory movements may both contribute to collapse of small peripheral airways. The inability to cough, which in patients with bulbar palsy may be associated with aspiration from the nasopharynx, may lead to obstruction of larger airways with infection and collapse of the lung distal to the obstruction. Collapse of the lung from both these causes, with continued perfusion of unventilated or underventilated areas of lung, results in widening of the alveolar-arterial oxygen gradient and arterial hypoxaemia.

There are several possible explanations for the increase in respiratory rate which occurs in patients with respiratory muscle weakness. Fear probably plays some part (Bevan, 1969) and the

reduction in lung compliance resulting from airways collapse and infection will also cause tachypnoea. It is likely that the abnormal muscular effort produced by partial paralysis of respiratory muscles produces a distressing sensation and leads to reflex hyperventilation. A fall in arterial carbon dioxide tension has been observed in a normal subject given sufficient curare to paralyse the intercostal muscles and this was associated with unpleasant dyspnoea (Campbell et al., 1967). Reflex stimulation from receptors in the lung and chest wall (Guz et al., 1966) and arterial hypoxaemia acting through aortic and carotid body chemoreceptors (Comroe, 1965) may also be involved.

Initially this tachypnoea causes an increase in minute ventilation and although wasted ventilation rises there is also an increase in alveolar ventilation resulting in alvolar and arterial hypocapnia. This is shown by all our patients (Fig. 1). Later as tidal volume falls an increasing proportion of total ventilation is wasted in dead space ventilation and in consequence alveolar ventilation is reduced first to normal and then to low levels and this results in hypercapnia and further arterial hypoxaemia. This hypercapnia may be a late and dramatic event as it was in case 3 of our series. This pattern of change in pulmonary gas exchange and arterial oxygen and carbon dioxide tensions is similar to that which has been described in severe asthma by McFadden and Lyons (1968).

MANAGEMENT OF NEUROMUSCULAR RESPIRATORY IMPAIRMENT The aims of management of patients with neuromuscular diseases affecting the respiratory system are to prevent and treat infection and to ensure adequate respiration gas exchange.

Physiotherapy plays an extremely important part in the treatment of patients with neuromuscular diseases. In addition to passive movements of the paralysed limbs, chest physiotherapy with posturing and vibration are effective in helping the patient to expel bronchopulmonary secretions and this helps to maintain the patency of large and small airways. Patients with bulbar involvement who complain of dysphagia or are observed to choke when drinking should be nursed in the prone or head down position and can be successfully fed via a nasogastric tube (Hewer, Hilton, Crampton Smith, and Spalding, 1968).

Even in the absence of bulbar involvement, when vital capacity is reduced to about three times the predicted tidal volume for the patient, effective coughing and deep breathing are no

longer possible, and Bendixen *et al.* (1965) have recommended that deep inspirations should be produced hourly by the use of a mask and bag-squeezing or a patient-triggered volume-cycled respirator. In the absence of bulbar involvement it is probably best for patients to be nursed sitting upright because diaphragmatic movement is restricted by the abdominal contents in the supine position and recent work has shown that recumbency may cause airtrapping and arterial hypoxaemia by promoting small airway closure (Leblanc, Ruff, and Milic-Emili, 1970). Case 5 was unable to lie flat on admission because of distressing dyspnoea.

Chest infection may contribute to respiratory failure as in cases 1, 3, and 5. This can be prevented by careful tracheobronchial toilet but this may require an early tracheostomy, especially in patients with bulbar involvement.

DETECTION OF RESPIRATORY FAILURE The clinical features of respiratory failure are notoriously unreliable (Campbell, 1965) and Plum (1952) has emphasized that some measurements of respiratory function are essential for the recognition and treatment of respiratory failure in neuromuscular diseases. The mixed venous carbon dioxide tension ($P\bar{v}_{CO_2}$) can be measured simply using the rebreathing method described by Campbell and Howell (1962). When there is paresis of the buccal muscles this technique can still be employed by using a face mask with the rebreathing bag. Regular measurements of carbon dioxide tension are of value in the management of these patients and a rise in carbon dioxide tension from low to normal levels is a warning that assisted ventilation may be required. Bendixen *et al.* (1965) recommend that the presence of hypercapnia is an indication for immediate assisted ventilation and cases 1, 2, and 3 support this view.

Arterial hypoxaemia in patients with neuromuscular diseases may be the result of several mechanisms and its detection is of limited value in the management of these patients. Two of the patients in our series (cases 4 and 5) demonstrate that arterial hypoxaemia may be present when respiratory function remains adequate, as judged by other criteria, and assisted ventilation is not needed. In case 4 the arterial oxygen tension was reduced to 51 mmHg on one occasion, although he never developed hypercapnia and his VC remained above 4·0 litres. Similarly, in case 5 arterial hypoxaemia developed without hypercapnia. In the remaining cases changes in the degree of arterial hypoxaemia did not closely mirror the deterioration in respiratory function which led to the need for assisted ventilation in each case.

One patient (case 4) was interesting in that his VC never fell below 4 litres but breathing air he had a big reduction in arterial oxygen tension (56 and 51 mmHg) with a wide alveolar-arterial oxygen gradient (51 and 57 mmHg) during his first 11 days in hospital. On the seventh day he developed signs of bulbar paresis and was nursed with the foot of the bed elevated and fed via a nasogastric tube for three days. He never developed any clinical or radiological signs of a chest infection and we conclude that his hypoxaemia resulted from small airway collapse and underventilation of some areas of the lung caused by incoordinated respiratory muscle action.

IMPORTANCE OF VITAL CAPACITY MEASUREMENT In the management of respiratory failure in poliomyelitis, Plum (1952), Walley (1959), and others have found that measurements of vital capacity are invaluable in detecting those patients who will need assisted ventilation. These measurements can be made at the bedside with a simple volume-recording spirometer. These authors found that in adults when the VC has fallen to 1·5 litres, oxygen should be given by nasal catheter or mask, and that when the VC is reduced to 1 litre or about 25% to 30% of the predicted normal value for the patient, assisted ventilation usually becomes necessary. Bendixen *et al.* (1965) have defined two critical levels of vital capacity, the first when the vital capacity is reduced to a volume equal to three times the predicted resting tidal volume for the patient when deep breathing and effective coughing are impaired, and the second when the vital capacity is equal to the predicted tidal volume, at which stage assisted ventilation is obligatory. Assisted ventilation was begun in case 1 when her VC had fallen to 0·6 litre which is 20% of her predicted value.

At rest in normal subjects diaphragmatic movement accounts for 75% to 80% of ventilation (Campbell, 1958), and it was observed during the epidemics of poliomyelitis in the 1950s that patients with respiratory difficulty associated with diaphragmatic paralysis had a worse prognosis and required assisted ventilation at an earlier stage, with reference to measurements of vital capacity, then those patients in whom the diaphragm was not affected. Zorab (1962) has shown that patients with ankylosing spondylitis may live for years with a rigid immobile thorax without developing respiratory failure because ade-

quate ventilation is maintained by diaphragmatic movement alone. In such a patient the development of paresis of one hemidiaphragm may prove fatal. Similarly, patients with neuromuscular diseases with ascending paralysis may rapidly develop respiratory failure if cervical segments and the diaphragm become affected.

Plum (1952) has shown that the ability of the patient to count aloud is of value in assessing respiratory function. The patient is asked to take a deep inspiration and count aloud at a rate of two digits per second until he is obliged to take another breath. Using this test he found that when an adult can count only to 20 his VC is reduced to approximately 2 litres, when he can reach only 15 the VC is approximately 1·5 litres, and so on. Although useful we do not think these tests replace the need for measurements of vital capacity which are simple and more accurate.

Case 5 was admitted in myasthenic crisis and the way in which an increase in vital capacity reflected improved muscle power is shown in Fig. 2. From these measurements of vital capacity the frequency of administration of neostigmine was determined. The effect of 10 mg edrophonium (Tensilon) on her vital capacity demonstrated that she required larger doses of neostigmine and these were therefore given. Although her VC fell to 0·5 litre, which was 15% of her predicted value, it was always increased after neostigmine and she never required assisted ventilation.

CONCLUSION

In neuromuscular diseases respiratory failure may pass unrecognized until a late stage and the type of respiratory failure that occurs resembles that observed in acute asthma with initially an arterial hypoxaemia associated with hypocapnia; carbon dioxide retention only occurs at a late stage when ventilatory capacity is severely reduced. Hypercapnia may develop rapidly and the clinical signs of hypoxaemia and hypercapnia are unreliable and are not a good guide to the need for assisted ventilation.

REFERENCES

Bendixen, H. H., Egbert, L. D., Hedley-Whyte, J., Laver, M. B., and Pontoppidan, H. (1965). *Respiratory Care.* C. V. Mosby, St. Louis.

Bevan, J. R. (1969). Polyneuropathy. *Lancet,* **1,** 1310.

Campbell, E. J. M. (1958). *The Respiratory Muscles and the Mechanics of Breathing.* Lloyd-Luke, London.

—— (1965). Respiratory failure. *Brit. med. J.,* **1,** 1451.

——, Freedman, S., Clark, T. J. H., Robson, J. G., and Norman, J. (1967). The effect of muscular paralysis induced by tubocurarine on the duration and sensation of breath-holding. *Clin. Sci.,* **32,** 425.

——, and Howell, J. B. L. (1962). Rebreathing method for measurement of mixed venous pCO_2. *Brit. med. J.,* **2,** 630.

Comroe, J. H. (1965). *The Physiology of Respiration.* Year Book Publishers, Chicago.

Crofton, J., and Douglas, A. (1969). *Respiratory Diseases.* Blackwell, Oxford.

Dickinson, D. G., Wilson, J. L., and Graham, B. D. (1953). Studies in respiratory insufficiency. 1. Carbon dioxide and oxygen studies in early respiratory paralysis in poliomyelitis. *Amer. J. Dis. Child.,* **86,** 265.

Guz, A., Noble, M. I. M., Widdicombe, J. G., Trenchard, D., Mushin, W. W., and Makey, A. R. (1966). The role of vagal and glossopharyngeal afferent nerves in respiratory sensation, control of breathing and arterial pressure regulation in conscious man. *Clin. Sci.,* **30,** 161.

Hewer, R. L., Hilton, P. J., Crampton Smith, A., and Spalding, J. M. K. (1968). Acute polyneuritis requiring artificial respiration. *Quart. J. Med.,* **37,** 479.

Leblanc, P., Ruff, F., and Milic-Emili, J. (1970). Effects of age and body position on 'airway closure' in man. *J. appl. Physiol.,* **28,** 448.

McFadden, E. R., and Lyons, H. A. (1968). Arterial-blood gas tension in asthma. *New Engl. J. Med.,* **278,** 1027.

Plum, F. (1952) *Monographs in Medicine,* Series 1 (edited by W. B. Bean), p. 225. Williams and Wilkins, Baltimore.

——, and Wolff, H. G. (1951). Observations on acute poliomyelitis with respiratory insufficiency. *J. Amer. med. Ass.,* **146,** 442.

Sykes, M. K., McNicol, M. W., and Campbell, E. J. M. (1969). *Respiratory Failure.* Blackwell, Oxford and Edinburgh.

Walley, R. V. (1959). Assessment of respiratory failure in poliomyelitis. *Brit. med. J.,* **2,** 82.

Zorab, P. A. (1962). The lungs in ankylosing spondylitis. *Quart. J. Med.,* **31,** 267.