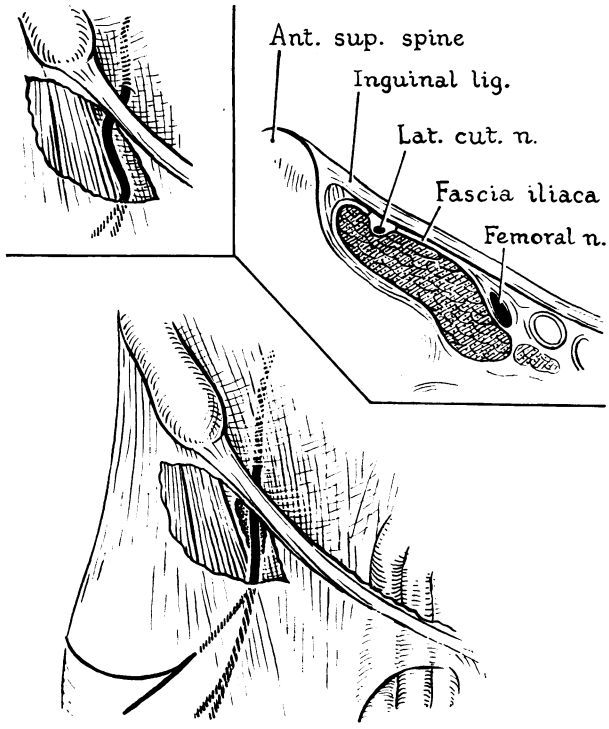

Fig. 8.—The operative treatment of meralgia paresthetica Type II.

ous exploration of the area on one occasion, with no improvement in symptoms. The results of muscle and nerve section in her case have been most gratifying.

Orthopedic surgeons have recognized the syndrome of pain in the distribution of the lateral cutaneous nerve of the thigh accompanying L4-5 or L5-S1 disc herniation; it was thought to be due to abnormal communications of the L1-L2 root complex with L4, L5 and S1. It seems more reasonable to assume that the spasm of the paravertebral musculature and consequent forward tilt of the pelvis is sufficient to cause a bowstring deformation of the lateral cutaneous nerve of the thigh and produce pain in its distribution.

SUMMARY

The subject of meralgia paresthetica is reviewed. The symptom complex can be divided into Types I, II, III, or IV, on the basis of the type of anatomical variant present. Meralgia paresthetica is not a rare disease, and it may be completely incapacitating. The conservative and operative treatments of this lesion are discussed.

I would like to thank Miss Janet Seaton for the excellent illustrations and her unfailing interest in the graphic reproduction of word pictures.

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VANILLIC DIETHYLAMIDE* IN THE MANAGEMENT OF ACUTE RESPIRATORY INSUFFICIENCY: A PRELIMINARY REPORT†

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THE occurrence of six cases of acute respiratory failure in the short span of a month at the Queen Mary Veterans' Hospital has prompted us to review our management of these cases. Our interest was further stimulated by the fact that we have been using a new respiratory stimulant, vanillic diethylamide,[1-3] in the treatment of patients with chronic respiratory disease. These six cases, therefore, furnished some basis for a preliminary evaluation of this compound in acute respiratory failure as well as for a review of other methods of treatment of this emergency.

Treatment of acute respiratory failure with hypoxemia, hypercapnia and acidosis, in the form in which it occurs in chronic lung disease such as obstructive emphysema, involves the management of factors such as respiratory infection, airway obstruction, heart failure and respiratory centre depression, all of which may combine to precipitate the alveolar hypoventilation which underlies the disorder. The liberal use of antibiotics and bronchodilators, digitalis, diuretics and occasionally adrenal steroids may be indicated in the therapeutic program, but may by themselves prove to be inadequate. Previous reports[4, 5] have demonstrated that the removal of tracheal secretions by tracheotomy and the maintenance of adequate ventilation by mechanical respirators are of paramount importance and may be life-saving when other measures have failed. Such reports have mentioned, but perhaps at times without sufficient stress, the meticulous and constant supervision and care which are necessary when these measures are added to the therapeutic regimen. Even with very careful supervision a significant number of patients with emphysema, amounting to some 30% according to published reports, do not survive these acute episodes.[5] This points up the difficulty of management of these cases, even when all the known factors, including ventilation, are well controlled.

Since respiratory centre depression is one of the factors involved, as well as total cerebral depression, it seemed worth while to study the effects of a respiratory centre stimulant and analeptic in addition to those of other measures in the manage-

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ment of these cases. The use of respiratory centre stimulants is not new. Nikethamide, alpha-lobeline and other drugs have been employed in the past to stimulate respiration.[6] Their effects have, however, been so widespread over the whole central nervous system or on other parts of the body such as the heart and circulation in general that they have fallen into disuse in many centres as therapeutic agents for this particular syndrome. Since vanillic diethylamide is thought to have a more selective effect on the respiratory centre than other compounds and since it has been reported to have a greater margin of therapeutic safety, it was felt that its administration to patients with acute respiratory failure could be of value.

During the month between February 21 and March 24, 1961, six cases of respiratory acidosis in patients with emphysema were seen at the Queen Mary Veterans' Hospital, and case reports of these six will be presented. Various combinations of the aforementioned modes of therapy were utilized in these patients, as well as vanillic diethylamide.

The basis of therapy in all except one of the patients was early tracheotomy with insertion of a cuffed Jackson tube through which frequent aspiration of sections was carried out and mechanical assistance to ventilation applied using either a pressure-cycled machine of the Bird type or a volume-cycled apparatus of the Engström type. A 40% mixture of oxygen and air was usually used with the respirator. In addition, a nebulized bronchodilator, usually isoproterenol, was given at hourly intervals during the acute stages, together with intravenous aminophylline either as a continuous infusion or intermittently. Large doses of penicillin, four or more million units daily, were used, frequently together with chloramphenicol. Digitalis and diuretics were administered when signs of heart failure were present. Oral feeding was avoided, in general, during the acute stages, and hydration and nutrition were maintained by intravenous administration of fluids and electrolytes or by Levin tube feedings. An attempt was made to avoid respiratory centre depression by the administration of sedatives, but these were used on two occasions for specific indications. Vanillic diethylamide in the intravenous form was given either as a continuous infusion in varying concentrations and at varying rates depending on the state of consciousness of the patient or in intermittent, moderately rapid injections. When the intravenous route appeared to be no longer necessary, the oral route was sometimes substituted in a dose of 40-60 mg. four times daily.

Besides observation of the clinical condition, especially the state of consciousness, the patient's course was followed by measurement of pH, pCO_2 and the standard bicarbonate of arterial blood on an Astrup pH meter. Determinations of oxygen saturation were made in some cases both with a Waters Conley ear oximeter and the Van Slyke apparatus.

CASE REPORTS

CASE 1.—A.G.M., a 50-year-old male clerical worker, gave a history of chronic cough dating back to 1948, with shortness of breath on exertion. In August 1960, increased dyspnea, of which he was complaining, was thought to be part of a hyperventilation syndrome, and re-breathing into a paper bag was recommended. In January 1961, management of a severe psychoneurotic disorder necessitated giving him a light job at a domiciliary care hospital; sedatives and tranquillizers were also part of his treatment. On February 1, 1961, he was hospitalized with a fever of 101° F. and increased dyspnea. Examination of his chest revealed bilateral basal inspiratory rales, though a chest radiograph was normal. His dyspnea became progressively worse and by February 20, 1961, he was described as being in "status asthmaticus". He was given morphine, 1/6 grain intravenously, aminophylline, antibiotics and oxygen by mask, as well as intravenous hydrocortisone. On the morning of February 21, 1961, with his state of consciousness already impaired, he was given 2 grains of sodium amobarbital intravenously and lapsed into coma.

On admission to the Queen Mary Veterans' Hospital at 4.00 p.m. on February 21, 1961, he was found comatose, markedly cyanotic and breathing rapidly, shallowly and ineffectively. His temperature was 101° F., blood pressure 90/45 mm. Hg and pulse rate 124/min. Some jugular venous distension was noted, and on auscultation of the chest there were diffuse expiratory rhonchi and basal inspiratory rales. The liver edge was palpated four fingerbreadths subcostally, but there was no peripheral edema. The conjunctivae were suffused and chemotic.

A tracheotomy was performed immediately with insertion of a cuffed Jackson tube, and he was started on a pressure-cycled mechanical respirator, and frequent suctioning of the tracheobronchial secretions was instituted. He remained comatose and cyanotic, and arterial blood gas studies at 7.00 p.m. revealed a pH of 7.08, a pCO_2 of 122 mm. Hg and a standard bicarbonate of 32 mM./l. His therapeutic regimen was at this point augmented by antibiotics in large doses, intravenous aminophylline in a continuous infusion and nebulized isoproterenol at hourly intervals. Also a continuous infusion of vanillic diethylamide was started in a concentration of 1 g. per 200 c.c., run in at 30 drops per minute. On this combined therapy, the patient became at least partially rousable, and a repeat arterial pCO_2 at 11.00 p.m. (see Fig. 1) showed a significant drop. By 9.00 a.m. the next morning he had received 3 g. of vanillic diethylamide in the above fashion but was still comatose. A further 100 mg. of the drug was injected rapidly by the intravenous route at this time. There was an immediate increase in frequency and depth of respiration, and within a minute the patient was restored to consciousness and was able to answer questions rationally. A repeat determination of arterial pCO_2 revealed a marked drop to 62 mm. Hg and a return of arterial pH to within normal limits. He relapsed to a somewhat drowsy state during the day and was given a series of moderately rapid intravenous injections of 100 mg. of vanillic diethylamide at approximately hourly intervals. By the third day he was normally alert and remained so thereafter. A rise in arterial pCO_2 accompanied by a marked rise of bicarbonate observed on the third day of treatment was possibly a response to temporary interruption of bronchodilators and respirator therapy or to tracheobron-

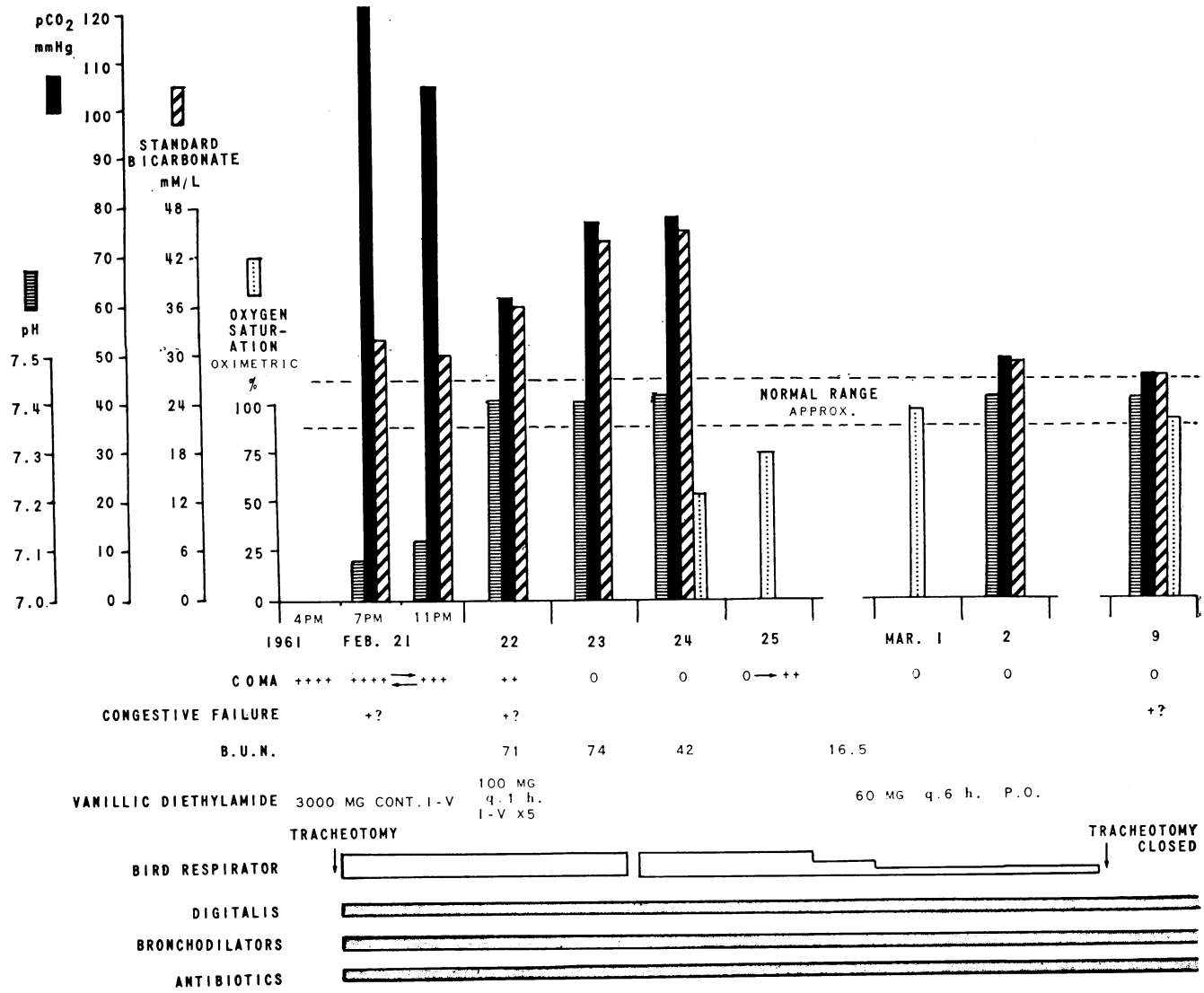

Fig. 1.—Case 1. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. Note the extremely high pCO_2 and low pH values at the outset. The effect of vanillic diethylamide as an adjunct to other therapy is indicated by the shift of abnormal values to normal while it was being used and by the rise in pCO_2 when its use was discontinued on February 23, 1961.

chial obstruction due to the accumulation of tracheal secretions. Subsequently the pCO_2 and bicarbonate levels dropped gradually toward normal levels concomitantly with a rise in oxygen saturation (determined by an ear oximeter while the patient was no longer using the respirator) to normal levels.

Admission laboratory studies revealed a hemoglobin value of 12.5 g. %, a hematocrit of 40% and a leukocyte count of 20,200 per c.mm. The blood urea nitrogen (BUN) level was elevated on admission to 71 mg. % and the serum potassium to 6.25 mEq./l.; the chloride value was 94.1 mEq./l. These abnormalities later disappeared. An electrocardiogram revealed auricular tachycardia, and chest radiographs were reported as showing hyperaeration, flat diaphragms and a prominent left hilar shadow.

It was found possible to discontinue respirator therapy and close the tracheal stoma on the 16th day of therapy. At this time the patient still complained of some dyspnea and was seen to be mildly cyanotic. The anteroposterior diameter of his chest was increased. Expansion was reduced and he had diffuse rhonchi on forced expiration, hyperresonance and poor air entry, with a few inspiratory rales at the lung bases posteriorly. This clinical picture and the results of pulmonary function tests which showed reduced vital capacity, increased residual and functional residual volumes, reduced expiratory flow rates and a markedly reduced diffusing capacity for carbon monoxide suggested the diagnosis of emphysema.

Comment.—This case illustrates the kind of care necessary in the treatment of patients with pulmonary emphysema who may be on the verge of acute respiratory insufficiency. The two factors which apparently caused this patient to enter a state of CO_2 narcosis were the respiratory infection and the ill-advised use of sedatives, especially the intravenous sodium amobarbital, at a time when his consciousness was already impaired.

The institution of tracheotomy and assisted ventilation undoubtedly did much towards lowering his

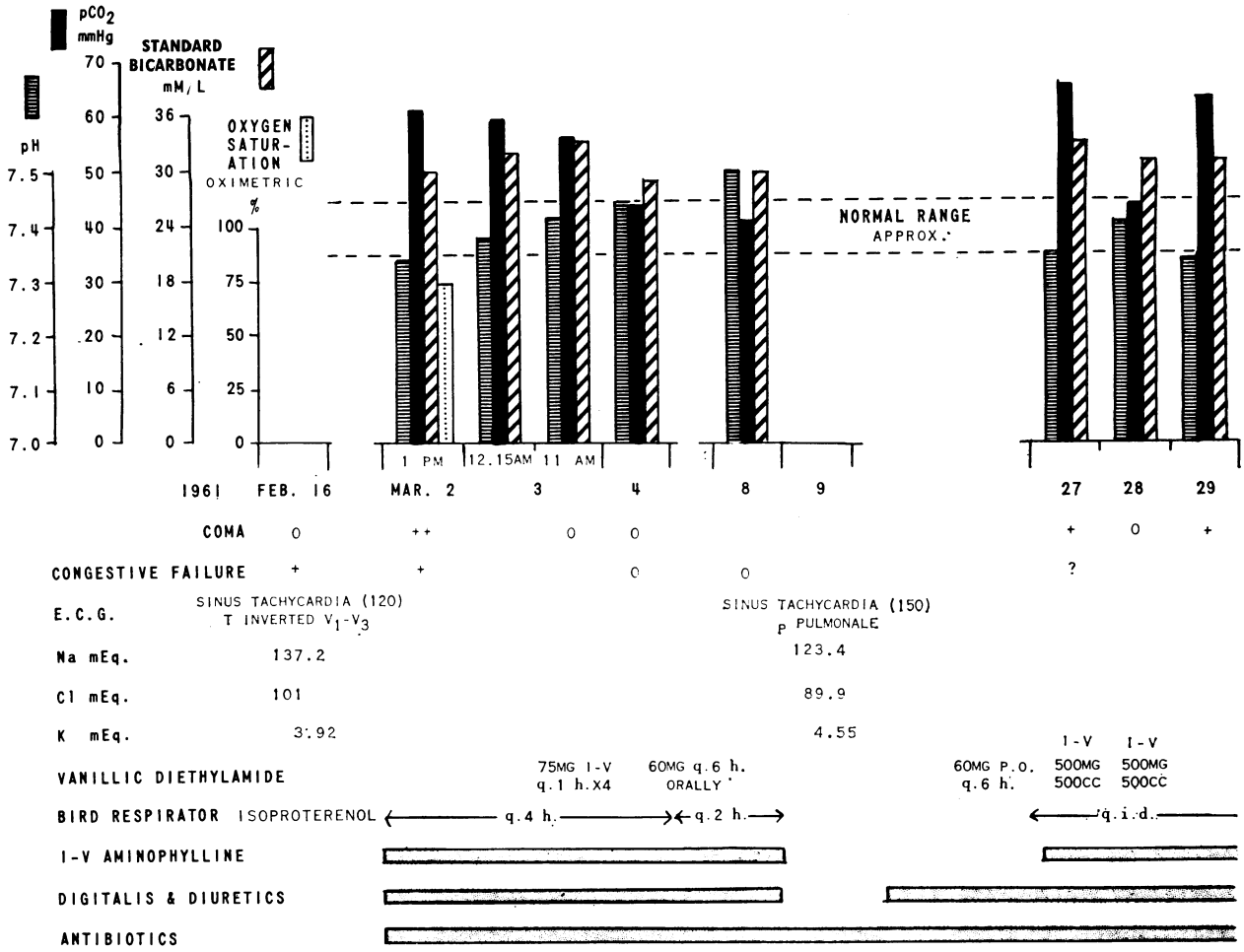

Fig. 2.—Case 2. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart shows how the abnormal values can be corrected by adequate multiple therapy and how they can revert to abnormal values when therapeutic efforts are lessened or discontinued.

pCO_2 values from the high level of 122 mm. Hg. The intravenous drip of vanillic diethylamide apparently contributed to this improvement. The dramatic response to the rapid intravenous injection of a further 100 mg. at 9:00 a.m. was probably due to the fact that the patient was fairly close to the level of consciousness at this time. Although the injection undoubtedly stimulated respiration greatly, as evidence by the patient's chest movements, the return to consciousness in such a short time was probably due to a general analeptic effect rather than an effect solely on the respiratory centre.

CASE 2.—D.B.J., a 68-year-old retired carpenter, was admitted to the Queen Mary Veterans' Hospital on February 12, 1961, complaining of severe shortness of breath and cough. There had been repeated admissions to hospital since he stopped work in 1955, for exacerbations of chronic bronchitis and emphysema, and he gave a history of cough and paroxysmal wheezing dyspnea since 1917.

On examination he was acutely dyspneic and cyanotic. He had clubbed fingers; his chest was barrel-shaped, moved poorly and was hyperresonant to percussion. There were diffuse expiratory rhonchi on auscultation. Some signs of right-sided heart failure were present. His hemoglobin value was 17.1 g. %, hematocrit 54%, and leukocyte count 18,700 per c.mm. Sputum culture revealed a heavy growth of *H. influenzae*. An electrocardiogram showed auricular fibrillation. The chest roentgenogram revealed low flat diaphragms, honeycombing at both bases suggesting bronchiectasis, and prominent hilar shadows.

After digitalization and administration of diuretics there was some transient improvement. He became less breathless, and sinus rhythm was seen to be restored on a subsequent electrocardiogram. On February 24, 1961, the patient developed a fever of 101° F., and a repeat chest radiograph revealed an infiltration in the right mid-lung field. The patient was placed on antibiotics and intravenous aminophylline was given, but the fever persisted, and on March 2, 1961, he was noted to be extremely drowsy, markedly cyanotic and tachypneic. There was a suggestion of flapping tremor, and mild ankle edema was noted. The oxygen saturation (oximetric) value was 74%; arterial blood pH, 7.34; pCO_2, 61 mm. Hg, and standard bicarbonate 30 mM/l. More intensive antibiotic therapy was instituted and he was given diuretics, a continuous intravenous infusion of aminophylline and nebulized isoproterenol delivered by means of the Bird respirator at four-hour intervals. In addition, meprobamate, which he had been receiving, was discontinued. With this program there

was some clinical improvement, in terms of increased alertness, but a repeat arterial pCO_2 determination the next day showed little change. He was accordingly given a series of four intravenous injections of 75 mg. of vanillic diethylamide at hourly intervals. The next day his mental state was quite clear, and his arterial pCO_2 had fallen to 44 mm. Hg. His course subsequently was without incident until March 7, 1961, when, because of apparent clinical deterioration, he was given an extra dose of digitalis, and isoproterenol treatments, using the Bird respirator, were increased to two-hourly intervals. On March 8, 1961, he was found to be weak, dyspneic and ashen in colour, and his heart rate was 144/min. An ECG revealed sinus tachycardia and signs suggesting cor pulmonale; electrolyte studies revealed low sodium and chloride levels, and the arterial pCO_2 was found to be 41 mm. Hg with a pH of 7.5 and a standard bicarbonate concentration of 30 mM./l. Use of diuretics and the Bird respirator was stopped; digitalis was temporarily discontinued; he was given a diet without sodium restriction, and subsequently improved.

The improvement in this mild case of respiratory acidosis was short-lived, despite the administration of oral vanillic diethylamide in a dosage of 240 mg. daily. On March 27, 1961, he was again noted to be drowsy, and repeat arterial blood gas studies once more showed an elevated pCO_2 of 66 mm. Hg. It was observed, in addition, that his weight had increased by 11 lb. He was restarted on a diuretic and sodium restriction, as well as on nebulized isoproterenol delivered by the Bird respirator. In addition an infusion of 500 mg. of vanillic diethylamide combined with 7½ grains of aminophylline in 500 c.c. of 5% glucose in water was administered daily for two days. As can be seen in Fig. 2, some very brief improvement was obtained.

Comment.—This patient was recognized to be in acute respiratory insufficiency with hypercapnia due apparently to a combination of pneumonia and right heart failure. It is possible that the meprobamate which he had been receiving contributed to the acute respiratory failure. Measures to control these factors, together with increased mechanical ventilation and the respiratory stimulation of vanillic diethylamide, were sufficient to restore the arterial blood values to normal. It should be noted that in this relatively mild case tracheotomy was not necessary to reduce the respiratory dead space. Since the patient was sufficiently conscious to cough and expectorate, tracheostomy was also not necessary to remove excess tracheobronchial secretions.

It should also be noted that, in spite of oral therapy with vanillic diethylamide, increased cardiac decompensation caused him to revert to a hypercapnic state, which was again readily corrected by the use of a combination of intravenous therapy with the same drug, assisted respiration, diuretics and sodium restriction.

CASE 3.—J.A.R., a 63-year-old man, was admitted to the Queen Mary Veterans' Hospital on March 9, 1961, complaining of shortness of breath on exertion, orthopnea and a mild cough. He had a history of chronic cough since 1942, and previous episodes of confusion and sleepiness were recorded, once with a bout of lobar pneumonia. On examination he was noted to have distended external jugular veins, an increased anteroposterior diameter of the chest, with poor chest movement, and bilateral basal inspiratory rales. Marked edema of the lower extremities was also present.

His hemoglobin value was 12.9 g. % and hematocrit 43%. Chest radiographs were reported as showing cardiomegaly and pulmonary congestion. An electrocardiogram revealed right-axis deviation and clockwise rotation, and was considered characteristic of pulmonary disease with emphysema.

The patient was started on treatment for heart failure, and a bedtime sedative of 1½ grains of phenobarbital was also ordered. On the morning of March 13, 1961, he was reported to be confused and cyanotic, and at noon of the same day was found comatose and pulseless. Cyanosis was markedly increased and there were long periods of apnea. Intravenous injections of vanillic diethylamide and nikethamide, together with manual artificial respiration, improved his respiration, and further improvement resulted from the use of the Bird respirator applied with a mask, to the point where the patient returned to a confused state of consciousness. At this stage he was still cyanosed and unequal pupils were noted; the right pupil was dilated and nonreactive. Arterial blood gas studies revealed a pH of 7.20, pCO_2 of 66 mm. Hg and a standard bicarbonate value of 23 mM./l. A tracheotomy was performed, and the patient was continued on mechanical ventilation with the Bird respirator. Frequent suctioning of secretions was performed, and antibiotics and bronchodilators were given. By 10.00 p.m. the same evening a normal state of consciousness had been restored, and the pupillary inequality had disappeared; these changes were preceded by a drop in arterial pCO_2 to 52 mm. Hg.

On the second day of treatment there was a return of anisocoria and confusion, and a marked leak of air was noted through the mouth, all of which were associated with a rise in arterial pCO_2 to 60 mm. Hg (see Fig. 3). Re-inspection of the tracheotomy revealed that only the terminal portion of the Jackson tube was inserted into a largely intrathoracic trachea and that the rubber cuff was lying outside the trachea. Substitution of a long rubber endotracheal tube improved the patient's condition and the patient's subsequent course and recovery was uneventful. The tracheal stoma was closed and assisted respiration was discontinued on March 28, 1961.

Comment.—In this patient with emphysema the impetus to CO_2 narcosis was apparently provided by a combination of right heart failure, probable tracheobronchial infection and night-time sedation. Although some improvement was noted without the use of a tracheotomy, the accumulation of tracheobronchial secretions which could not be cleared by cough and expectoration made this procedure necessary.

The case does illustrate, however, the extreme care which must be exercised in watching such patients once the tracheotomy has been established.

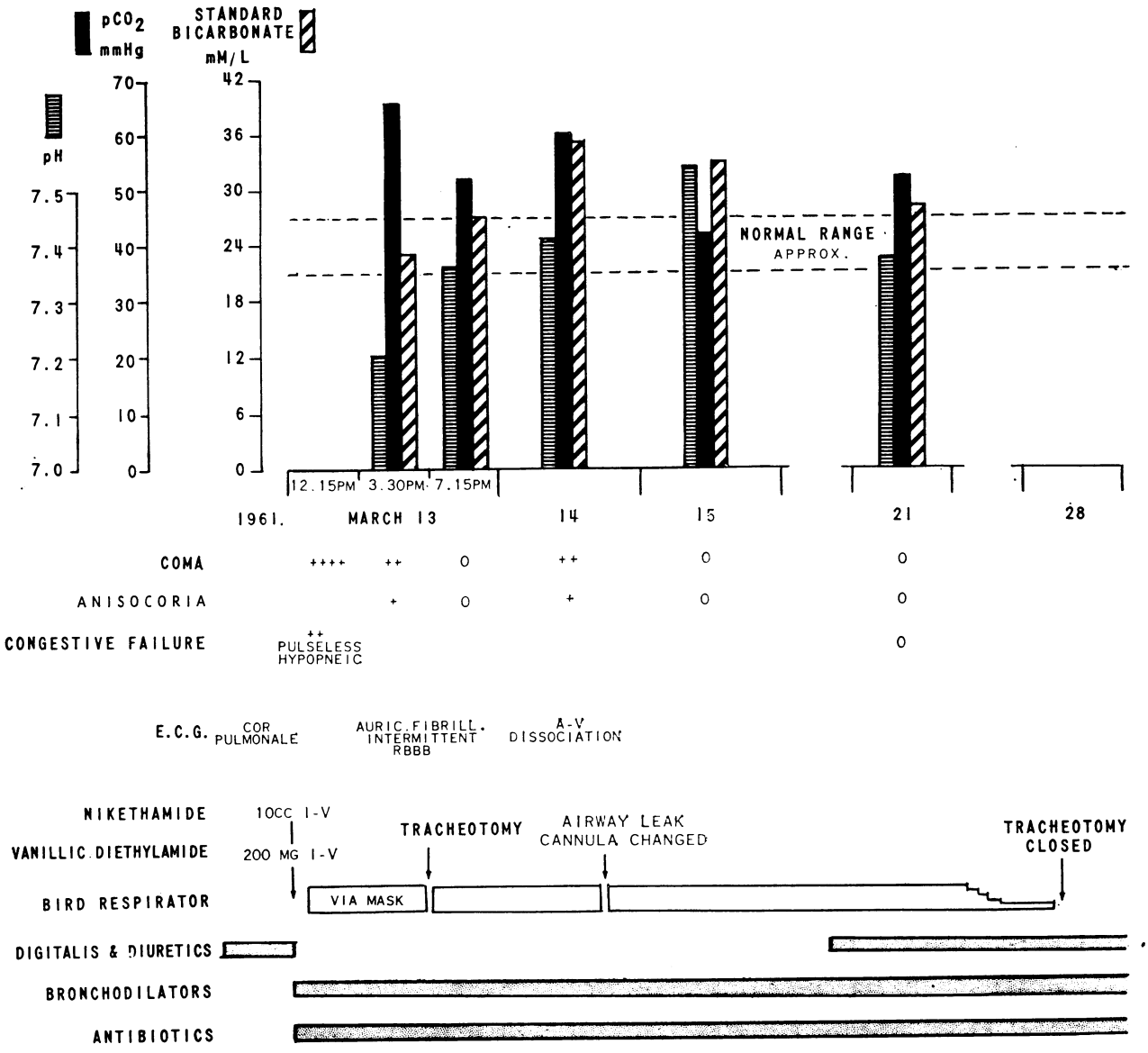

Fig. 3.—Case 3. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart indicates how rapidly a patient may sometimes come out of coma and how inefficient ventilation may tend to return the patient to this condition, as occurred on March 14, 1961.

A leak in the airway or obstruction in the tubes must be recognized and corrected immediately or they will nullify the whole procedure and cause a relapse.

CASE 4.—J.L.L., a retired clothing salesman, aged 71, had had previous admissions to hospital for management of symptoms of emphysema associated with cor pulmonale and congestive failure. He dated the onset of respiratory symptoms to 1951, but admitted to having had "a weak chest" since childhood, with frequent colds which went to his chest. During an admission dating from November 29 to December 23, 1960, arterial blood gas studies (Van Slyke) revealed an oxygen saturation of 89% and a CO_2 content of 39.45 volumes %.

He was readmitted to hospital on February 16, 1961, after a period without digitalis, in a state of severe dyspnea with signs of right-sided failure and radiological evidence of cardiomegaly. He was not cyanotic; his chest was hyperinflated and hyperresonant with little movement, poor air entry and no adventitious signs. The hemoglobin value was 17.1 g. % and hematocrit 52%. An ECG showed sinus tachycardia, p-pulmonale and right-axis deviation.

Administration of digitalis and diuretics as well as steroids and bronchodilators relieved the signs of heart failure but left him as severely dyspneic as before. On March 14, 1961, after one month in hospital, coincidentally with a rise in his temperature to 102° F., he lapsed into a confused drowsy state with increased dyspnea and inspiratory rales at the right lung base, suggesting the presence of pneumonia. The arterial pCO_2 was found to be 70 mm. Hg; pH, 7.38, and a standard bicarbonate 38 mM./l. The administration of aminophylline intravenously and an intravenous infusion of vanillic diethylamide containing 1000 mg. in 500 c.c. run in at 20 drops/min., with assistance to respiration provided by the Bird machine through

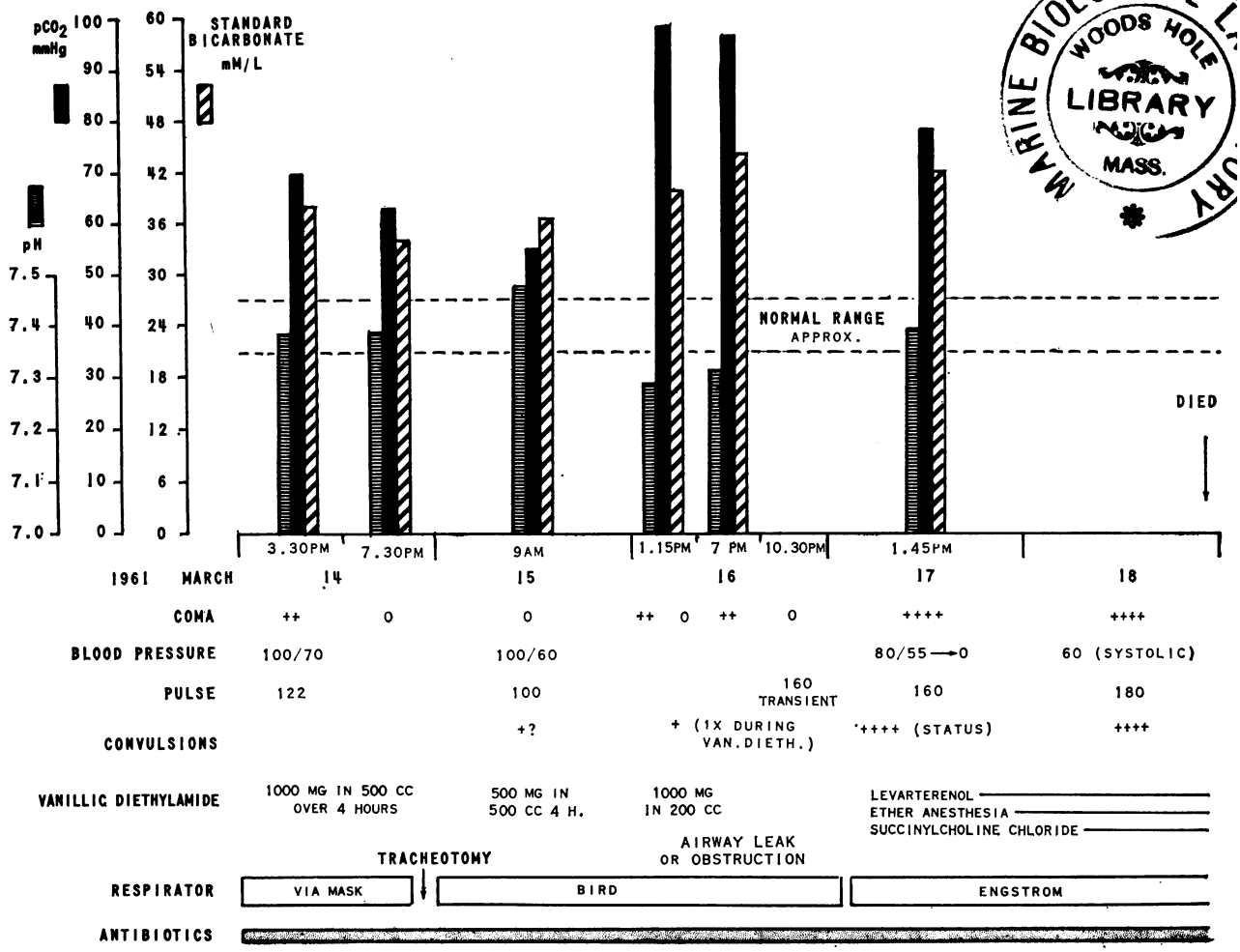

Fig. 4.—Case 4. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates the difficulties in management which may occur with some patients where irreversible brain damage due to anoxemia may occur. It is to be noted that the arterial pH had returned to normal but coma persisted.

a mask (which the patient tolerated poorly), resulted in a return to a normal state of consciousness and a drop in arterial pCO_2 to 63 mm. Hg. It was decided nevertheless to proceed with tracheotomy and mechanical ventilation with the Bird respirator applied through the tracheal stoma. Antibiotics and bronchodilators were also given. Despite the persistence of fever, on the second day of treatment he was normally alert and his pCO_2 had fallen to 55 mm. Hg. The next day, however, coincident with periods of leaking of air through the mouth (corrected by reinflating the rubber cuff), he became intermittently drowsy and confused again. Reassessment of the arterial blood gases revealed a pCO_2 of 98 mm. Hg, a drop in pH to 7.28, and a rise in the bicarbonate level to 41 mM./l. Intravenous vanillic diethylamide and reinflation of the cuff were only temporarily beneficial, and a recheck of the arterial pCO_2 value the same day showed no change. Furthermore, discontinuation of the respiratory stimulant was felt to be indicated, after a major seizure occurred followed by a period of tachycardia and marked hyperpnea.

Though his arterial pCO_2 was significantly lower the next day, his clinical condition had in fact deteriorated, a turn of events preceded by a period of cyanosis in the course of which it was found that the cuff of the tracheal cannula had slipped over the end of the cannula, obstructing the airway. Despite correction of this, the patient became increasingly drowsy, lapsing finally into a state of coma. Circulatory failure ensued, together with severe bronchospasm and generalized convulsions proceeding to status epilepticus. In spite of changing to an Engstrom respirator, and the use of intravenous hydrocortisone, ether anesthesia, intravenous succinylcholine chloride, diphenylhydantoin sodium, sodium phenobarbital (Luminal) and levarterenol, the patient died the next day, March 18, 1961.

At autopsy, marked emphysematous changes were found in the lungs associated with a marked degree of pulmonary congestion and edema, and right ventricular hypertrophy and dilatation; permission to examine the brain was not obtained. Details of the case are summarized in Fig. 4.

Comment.—In this patient hypercapnia was precipitated by a respiratory infection. The situation seemed to be moderately well controlled by the use of the measures initially instituted, since there was a return to consciousness and a drop in pCO_2. It is possible that, as in Case 2, these measures would have been sufficient had the patient been able to tolerate the oxygen mask. Since he had marked difficulties with this apparatus, a tracheotomy became necessary.

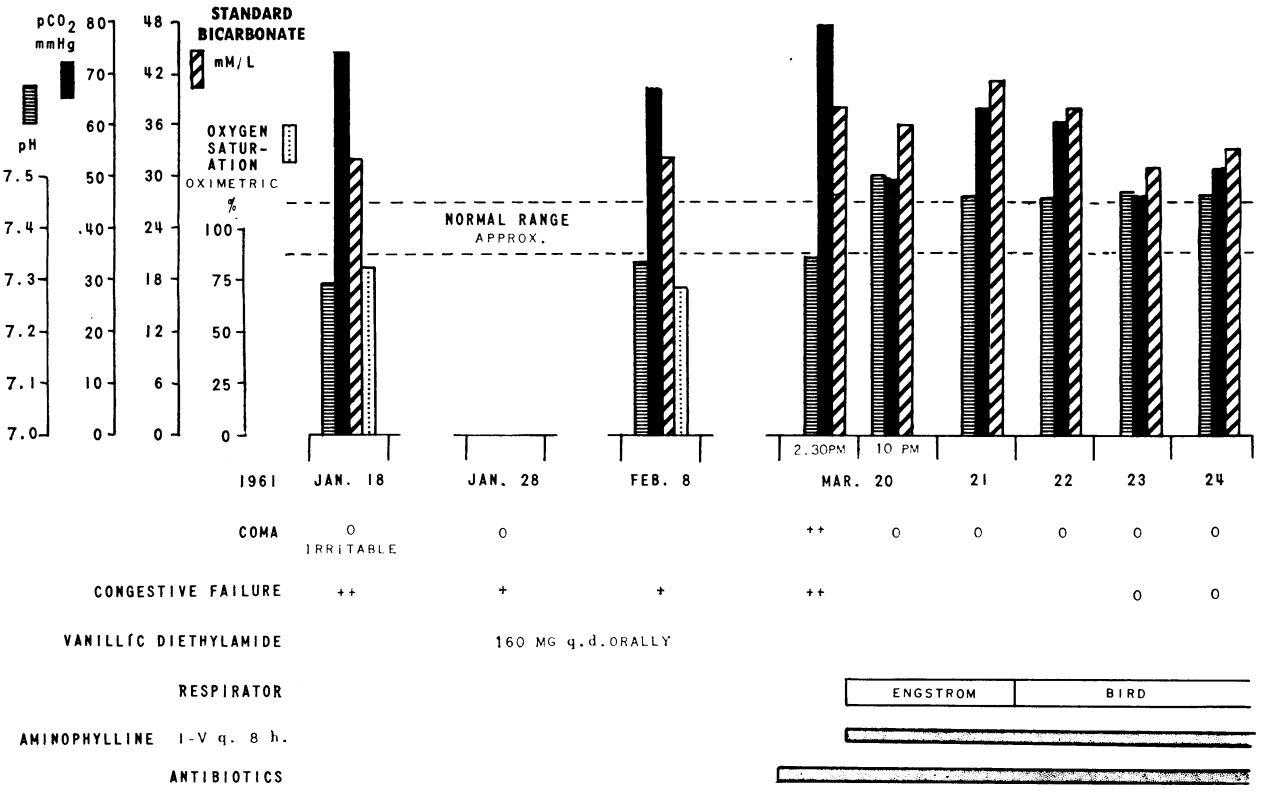

Fig. 5.—Case 5. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates the return to normal if satisfactory ventilation is established. It is possible that if continuous intravenous, instead of oral, vanillic diethylamide had been used, tracheotomy and ventilator therapy might have been avoided.

As in Case 3, the meticulous care necessary in watching for leaks in the airways is emphasized.

This patient also experienced convulsive seizures which were probably due to anoxemia. Since vanillic diethylamide may also cause cerebral irritation superimposed on that caused by the anoxemia, it was felt that this drug should be discontinued, which was done two days before his death. Further experience in its use may act as a guide in future cases of apparently irreversible cerebral changes due to anoxemia. The autopsy permission for examination of the brain was refused. This was unfortunate, since it might have helped in deciding what was the true cause of the failure to respond in this particular case. Since the convulsions had been present prior to the use of intravenous vanillic diethylamide and since the effect of this drug administered intravenously is very temporary, it is likely that the continued convulsions were due to either anoxemia or some other cerebral cause and not the drug itself.

CASE 5.—A.G., a 64-year-old man, had been diagnosed in previous admissions as having chronic bronchitis and emphysema with cor pulmonale and heart failure. He had a history of cough and wheezing dyspnea since his army service during World War I (1915). Arterial blood gas studies made on January 18, 1961, in the course of a prolonged admission to the Queen Mary Veterans' Hospital with congestive failure, revealed an oxygen saturation value of 81% and a CO_2 content of 54.2 vol. % (Van Slyke), with a pCO_2 of 74 mm. Hg, a pH of 7.29 and a standard bicarbonate of 32 mM./l. There was, at this time, no impairment of consciousness, though the patient was irritable. A 12-day trial of oral vanillic diethylamide in a dosage of 160 mg. daily produced little change in these values. The patient remained severely dyspneic and incapacitated despite treatment for heart failure and use of antibiotics and bronchodilators; he refused to go to a convalescent hospital for the remainder of the winter and was eventually released from the Queen Mary Veterans' Hospital on March 16, 1961.

He was readmitted three days later with a temperature of 102.4° F., drowsy, dyspneic and cyanosed, and complaining of being unable to cough up sputum. Signs of right-sided heart failure were present. He was treated by administration of digitalis, diuretics, antibiotics and bronchodilators, but his condition deteriorated. The next day, March 20, 1961, he was markedly drowsy, confused and had a flapping tremor of the hands. Arterial blood gas studies revealed a pCO_2 of 79 mm. Hg, a pH of 7.34 and a bicarbonate of 38 mM./l. A tracheotomy was performed without further delay, and the patient was started on the Engstrom respirator, intravenous aminophylline and antibiotics being continued. Rapid restoration of a normal state of consciousness, in this case, was associated with a more gradual lowering of arterial pCO_2 levels towards normal (see Fig. 5) and with persistence of muscle twitching and the flapping tremor despite normal or near normal levels of arterial pCO_2. During the first two days meperidine was required to sedate the patient, who was resisting the respirator. In addition, there was some initial difficulty with the airway; a leakage of air required correction by reinflation of

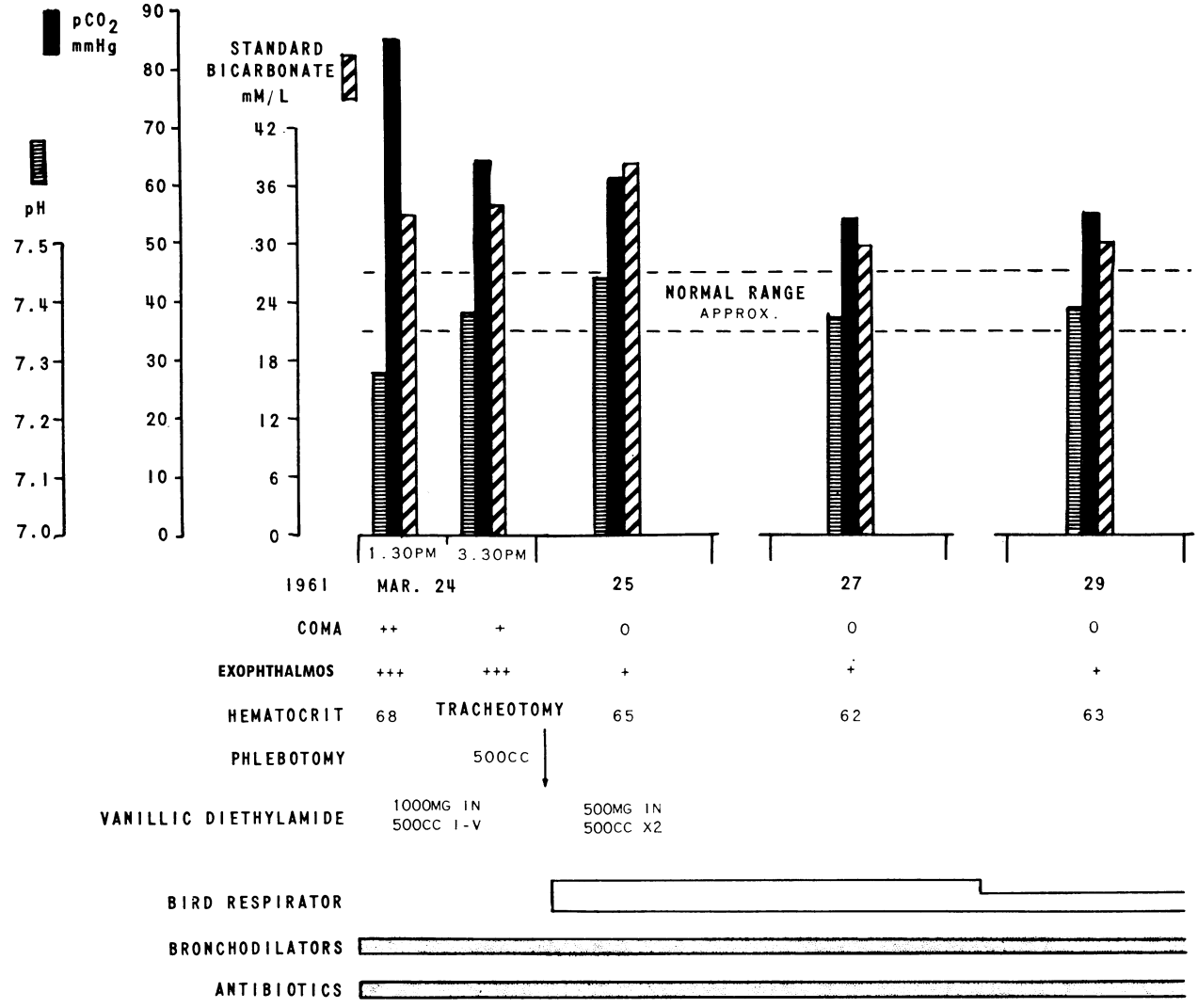

Fig. 6.—Case 6. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates a satisfactory return of blood values toward normal ranges with the continuation of therapeutic agents used.

the cuff, as well as by a change of tube. His clinical course was, however, unaffected by these factors, and it was possible by March 22, 1961, to substitute the Bird respirator for the Engstrom machine and by March 27, 1961, to begin gradual discontinuance of assisted respiration.

Comment.—This patient had shown little response to oral vanillic diethylamide used for his chronic symptoms. The contrast between this and the usual response to intravenous therapy with the same drug for acute cases may have been due to lack of absorption of the enteric-coated tablets which we were using at that time. It may also have been due to a difference in response between the chronic symptoms and the acute respiratory failure syndrome superimposed on chronic pulmonary disease.

As in some of the previous cases, an acute episode of hypercapnia was produced by a respiratory infection complicated by right heart failure.

Muscle twitchings and other signs of cerebral irritation were present in this patient, as were general restlessness and a tendency to "fight" the respirator. It has been noted in commenting on some of the previous cases that sedation may be one of the factors involved in precipitating CO_2 narcosis. In this particular case sedation was used, but it should be emphasized that this was done only when ventilation could be controlled mechanically in the sedated patient. When the patient is sedated the meticulous and constant care required in noting leaks or obstruction in the airways has to be redoubled.

CASE 6.—E.D., a 47-year-old taxi driver, was admitted to the Queen Mary Veterans' Hospital on March 24, 1961, complaining of increased dyspnea, cough and drowsiness. He had a history of chronic cough dating back to 1942, and had been hospitalized every year since 1957 for exacerbations of chronic bronchitis and emphysema. During an admission in 1958, he was found in a comatose state on one occasion in an oxygen tent and on another occasion after the administration of morphine. In the course of the latter admission, he was found to have exophthalmos, polycythemia and mild diabetes, but endocrine studies were negative.

Physical examination revealed an agitated and confused, obese man, markedly cyanotic and with pronounced exophthalmos and a flapping tremor. He was breathing rapidly and shallowly. Auscultation of his chest revealed bilateral basal inspiratory rales and diffuse, though not prominent, expiratory rhonchi. Some jugular venous distension was noted, but there were no other signs of heart failure. Hiccoughing was present. His rectal temperature was 101.2° F. His hemoglobin value was 20 g. % and hematocrit 68%. A portable chest radiograph revealed enlargement of the heart to the right, large bullae in the right apex, and fibrosis with pleural thickening in the right mid lung field. Some pulmonary congestion was also present. An ECG showed right-axis deviation with p-pulmonale. The arterial pCO_2 value at 1.30 p.m. was 85 mm. Hg; pH 7.28, and bicarbonate 35 mM./l.

Initial therapy included phlebotomy with removal of 500 c.c. of blood and an intravenous infusion containing 7½ grains of aminophylline and 1000 mg. of vanillic diethylamide run in at 20 drops per minute. A mercurial diuretic was also given, and antibiotics were started. Respirator therapy with a mask was attempted, but the patient resisted this. At 3:30 p.m. he appeared less cyanotic and agitated and the arterial pCO_2 was found to have dropped to 64 mm. Hg, with a rise in pH to 7.38. A tracheotomy was performed at this stage; mechanical assistance to ventilation by the Bird respirator and suctioning of tracheobronchial secretions were initiated.

Postoperatively, to control intractable coughing, the patient was given 75 mg. of meperidine intramuscularly, with the result that he became unresponsive and developed shallow respirations (despite the automatic operation of the Bird respirator). Increasing the rate of the vanillic diethylamide infusion aroused him fairly quickly, after which a good deal of agitation was noted for a short period.

By the second day of treatment the patient was quite clear mentally, and an obvious decrease in the degree of exophthalmos was noted, though the level of arterial pCO_2 had not decreased significantly since the previous determination (see Fig. 6). Hiccoughing and some nausea and vomiting over the next several days proved to be difficult to control; intramuscular diphenhydramine was tried but was discontinued when drowsiness occurred. Another feature was a pocket of air opposite the superior mediastinum on the right side in chest roentgenograms subsequent to tracheotomy which suggested a pneumothorax but which, however, gradually became smaller. This might have been due to the tracheotomy. Melena also occurred, the cause of which has not as yet been determined.

His arterial pCO_2 levels showed a gradual drop towards normal and by March 30, 1961, he was symptom-free; gradual discontinuation of the respirator had been started.

TABLE I.

Case and patient	*Age*	*Sex*	*Diagnosis*	*Precipitating factors*	*Degree*[1] *of coma*	*Initial* pCO_2	*Initial pH*	*Chief form of therapy*	*Complications*	*Outcome*
1. A.G.M.	50	M	Chronic bronchitis and emphysema	Sedation and resp. infection	4+	122	7.08	Tracheostomy, mech. ventil., vanillic diethylamide	None	Recovery
2. D.B.J.	68	M	Chronic bronchitis and emphysema, bronchiectasis	Resp. infection; cong. ht. failure; sedation?	2+	61	7.34	Bronchodilators, antibiotics, vanillic diethylamide, diuretics	Electrolyte imbalance	Transient improvement
3. J.A.R.	63	M	Chronic bronchitis and emphysema	Cong. ht. failure; sedation?	4+	66[2]	7.20	Tracheostomy,* mech. ventil.	None	Recovery
4. J.L.L.	71	M	Emphysema	Resp. infection	2+	70	7.38	Tracheostomy, mech. ventil., vanillic diethylamide	Shock, status epilepticus	Death
5. A.G.	64	M	Chronic bronchitis and emphysema	Resp. infection, cong. ht. failure	2+	79	7.34	Tracheostomy,* mech. ventil.	None	Recovery
6. E.D.	47	M	Chronic bronchitis and emphysema, pulmonary fibrosis	Resp. infection, cong. ht. failure	2+	85	7.28	Tracheostomy, mech. ventil., vanillic diethylamide	Melena, pneumothorax	Recovery

[1]Degrees of coma: 0; + = dullness, mild drowsiness; 2 + = marked drowsiness, confusion; 3 + = stupor; 4 + = coma.

[2]After partial arousal from coma with therapy.

*Vanillic diethylamide was also used in these two patients (see charts) but was not considered one of the chief forms of therapy as the dosage used was small.

Comment.—Again, the role of infection and sedation in initiating CO_2 narcosis is noted. Another point worthy of note in this patient was the improvement initially with the use of a respiratory stimulant in addition to the other measures utilized. With an uncooperative patient, however, tracheotomy may become necessary, in spite of this improvement, in order to ventilate the lungs more satisfactorily and to remove tracheobronchial secretions.

The effect of sedation, even with tracheotomy and mechanical ventilation, may still be poor, unless ventilation is watched very carefully and increased either by adjusting or changing the type of apparatus used or, as was done in this case, by increasing the dose of respiratory stimulant.

It should also be noted that mechanical respirators may occasionally cause pneumothorax, a fact which should induce caution in the pressures used in patients with large blebs complicating their emphysema.

DISCUSSION

A summary of the clinical picture of acute respiratory failure, its therapy and the results obtained is given in Table I. As can be seen, five of the six patients survived. In the case of the patient who died, Case 4 (J.L.L.), the brain was unfortunately not examined at autopsy and a cerebrovascular accident cannot be excluded. However, the course of events seems to have been that a moderate degree of respiratory failure was considerably aggravated by recurrent leaking of air around the tracheal cannula (owing to deflation of the rubber cuff) as well as by obstruction of the cannula by the rubber cuff in one instance; and the irreversible terminal situation with status epilepticus and circulatory failure appears to have been due to the resulting hypercapnia and hypoxemia, possibly on the basis of cerebral arteriosclerosis. Hickam and Ross[7] have previously pointed out that difficulties may arise in maintaining a leak-proof airway with positive pressure respiration through a tracheal stoma; the same problem arose in two other patients in this group. Undoubtedly small leaks can be compensated for by increasing the ventilation, but the patients should be observed carefully for the cause of the leak, which should be corrected as speedily as possible.

The question arises as to whether Case 4 could have been managed more successfully without a tracheotomy, as was tried in Case 2. The patient's resistance to the mask made this procedure necessary. Certainly, in mild cases of respiratory acidosis the effects of a conservative therapeutic approach may be determined first, utilizing antibiotics, bronchodilators, continuous mechanical ventilation through a mask or even intermittently at frequent intervals, and respiratory stimulants. Mechanical ventilation through a tracheotomy is a much more reliable method of providing continuing assistance to respiration and is certainly indicated in the more severe degrees of respiratory acidosis, particularly when retained secretions are a factor. Difficulties with the airway must be anticipated and corrected as they arise, by a well-trained team of observers. The establishment of ventilation through a tracheotomy does not permit any relaxation of attention to these patients, even if a respirator delivering a constant minute volume is used. The administration of sedatives is necessary only in exceptional circumstances, since they eliminate an important guide in following the course of the illness, that is, the patient's state of consciousness.

With regard to the use of vanillic diethylamide for such patients, the capacity to produce hyperventilation with the intravenous form is suggested by the prompt lowering of arterial pCO_2 achieved without the concomitant use of a respirator at the start of treatment in Cases 4 and 6 and in Case 2 where the intermittent use of the Bird machine seemed by itself to have been ineffective. The agent may conceivably have played some part in improving ventilation in Case 1, but any such effect was obscured by the use of other modes of therapy at the same time. It did, however, rouse the patient very promptly to a state of consciousness. It is evident that its effect is not limited to the respiratory centre, and it has the capacity to induce convulsions and agitation, necessitating caution in dosage, particularly in patients with only mild degrees of central nervous system depression. The most satisfactory method of administration seems to have been as a continuous intravenous infusion varying in concentration from 1000 mg. in 200 c.c. to 500 mg. in 500 c.c. of fluid, infused at a rate between 20 and 40 drops per minute, depending, as has already been indicated, on the severity of the disturbance. Further experience with the agent appears necessary, but present experience suggests that it may prove to be a useful adjunctive mode of therapy in the treatment of acute respiratory failure in emphysema, particularly in the milder cases where the need for tracheotomy might thereby be obviated.

SUMMARY

Case reports have been presented of episodes of acute respiratory failure in six patients with emphysema. After treatment with a regimen which included tracheotomy with frequent aspiration of secretions, mechanical assistance to ventilation, bronchodilators, antibiotics and a recently introduced respiratory stimulant, vanillic diethylamide, one patient died and five patients recovered. Of the survivors, one showed only a transient period of improvement. Clinical and biochemical improvement was observed in some of the patients with the use of intravenous vanillic diethylamide. This drug may prove to be a useful adjunct to therapy in acute respiratory acidosis and perhaps an alternative to tracheotomy in the milder forms of this disorder.

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