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Disease-a-Month

Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

PART II: TREATMENT

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Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

PART II: TREATMENT

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THE PROPER MANAGEMENT of respiratory failure necessitates a *total* support of the patient while effective measures are being instituted to reverse the acute pathophysiologic processes. This entire approach is best accomplished in a respiratory care unit, whereby the concentration of talent will be most effective. If such facilities are not available, the minimum demand is for 24-hour nursing care in conjunction with medical, surgical, inhalation therapy and laboratory support. A patent airway must be established to allow for correction of hypoxemia and improvement in ventilation. Control of infection, secretions, acid-base and electrolyte disorders, and management of polycythemia and cor pulmonale will also be important therapeutic considerations. We firmly emphasize that these guidelines *must* be suited to individual circumstances and patients. One should always avert and be on the alert for complications, since these are significant factors influencing survival.

For orientation in the subsequent therapeutic discussion, it may be advantageous to classify the clinical features of respiratory failure into (1) mild, (2) moderate and (3) severe phases. Patients with mild involvement (phase 1) are usually alert and cooperative with an effective cough, generally tolerate low-flow oxygen administration, can utilize assisting ventilators and manifest stable or improving arterial blood gases with conservative, yet intensive, management. Phase 2 patients may be drowsy or agitated, raise secretions poorly, resist or employ mechanical ventilators inefficiently or ineffectively, and show deterioration of arterial blood gases and pH despite controlled low-flow oxygen and additional therapeutic measures. At this stage, all conservative efforts should be further intensified, and supportive, effective, artificial ventilation may be indicated. Here, frequent clinical and physiologic monitoring is mandatory to identify or abort phase 3. This final phase is often characterized by extreme agitation or by gross stupor, coma or

apnea. The rapid establishment of an airway and ventilatory support, in conjunction with all other means, is then necessary.

The Airway

In all phases of acute respiratory failure, it is essential that a patent airway be established immediately and maintained constantly. Certain patients will be capable of maintaining a clear airway; others may require endotracheal intubation or tracheostomy. Airway support is particularly mandatory in obtunded, poorly cooperative patients who fail to respond to supportive measures including nasotracheal suction, physical therapy, transtracheal catheterization or therapeutic bronchoscopy. Endotracheal intubation and tracheostomy are indicated: (1) to establish and maintain a patent airway, (2) to permit aerosol therapy and mechanical removal of copious and/or tenacious secretions, (3) to provide a route for continuous ventilation, (4) to prevent aspiration of gastric contents or upper respiratory tract secretions, (5) for acute upper airway obstruction and (6) cardiorespiratory arrest.

Endotracheal Intubation

Endotracheal intubation is currently the preferred initial choice for an artificial airway. With meticulous care, endotracheal intubation can be maintained for 2–4 days, or up to a week if necessary. This averts the complications of a tracheostomy and often allows for a more rapid recovery and a briefer hospitalization. Both oral and nasal endotracheal tubes are available, but we prefer an oral tube because its larger diameter facilitates suctioning and decreases resistance to air flow. In alert patients, intubation is preceded by topical anesthesia; thereafter, the requirement for sedation or further local anesthesia is usually minimal. An oral tube with an internal diameter of less than 10 mm. will minimize vocal cord damage, and is positioned proximal to the carina to prevent unilateral main stem intubation. Proper securement will avoid accidental displacement, and free mobility of connections will minimize *mechanical stress* on adjacent tissues. An oral bite

block prevents proximal tube collapse. The balloon cuff is inflated just sufficiently to eliminate air leaks and is deflated for one minute every hour; both steps will minimize tracheal necrosis. Deflation must be *preceded* by careful suctioning of both oropharynx and trachea to avoid the aspiration of oral or gastric materials. Since the upper airway is bypassed, *constant* supplemental humidification is essential in preventing mucosal injury, ciliary dysfunction and thickening of secretions. Similarly, because tussive forces are limited by intubation, frequent suctioning with a long (20-inch), sterile, soft rubber, curved-tip catheter with a single side hole is recommended. Selective intubation of the main-stem bronchi is facilitated by the curved tip and contralateral rotation of the head. Following cuff deflation and catheter insertion, gentle suction is activated for 5–10 seconds with the catheter rotated during withdrawal. Repeated traumatic "ramming" movements are to be avoided. Prior to suctioning, the patient must be adequately oxygenated, unless a double-lumen oxygen suction catheter is used. Aseptic technic is mandatory, with sterile gloves, catheters and rinsing solutions employed only *once*.

The avoidable complications of endotracheal intubation include unilateral intubation, tube obstruction by secretions or slipped cuff, accidental dislodgment, acute laryngeal edema, vocal cord damage and tracheal ulceration, infection and stenosis.

Tracheostomy

Tracheostomy is required with upper airway obstruction where endotracheal intubation is not technically feasible or when the endotracheal tube must be replaced (after 2–4 days). In any event, the tracheostomy, besides providing a ventilatory route, permits more effective removal of tracheobronchial secretions. It is generally recommended that all tracheostomies be performed in the operating room, over an indwelling endotracheal tube and with adequate ventilation. Bedside surgery is to be avoided, and emergency tracheostomy is to be discouraged, because of its attendant hazards. Tracheostomy and endotracheal tube care are similar, particularly with respect to inflation and deflation of the cuff, suctioning, sterile manage-

ment and proper humidification of the inspired air. The largest, comfortable silver or plastic cannula with an evenly inflatable cuff is selected. A Rusch tube, with a double cuff for alternate inflation, may be used to minimize tracheal necrosis and prevent aspiration. It is important, for subsequent respiratory care, that the tracheostomy be placed high (2d, 3d or 4th tracheal ring) and the tube tip situated well above the carina. The wound is loosely closed, dressed with dry sterile gauze, and the tube secured firmly. With double-walled cannulas, cleansing of the inner tube about three to four times daily is recommended. The tracheostomy tube itself requires replacement only every 7–10 days unless compromised by encrusted secretions or a malfunctioning cuff. Wound or tracheal infections may require antibiotic therapy.

Tracheostomy complications occur during the operative and maintenance periods. Operative complications include apnea, hemorrhage, pneumothorax, subcutaneous emphysema, air embolism, damage to the contiguous structures and cardiac arrhythmias or arrest associated with uncorrected hypoxemia. These are minimized by elective tracheostomy and careful surgical technic. Meticulous tracheostomy care is required thereafter to prevent tracheitis, wound infection, tube obstruction or displacement, tracheal perforation and mediastinal emphysema. Late complications include tracheal or glottic stenosis, tracheomalacia, persistent fistula formation and esophageal injury.

Removal of the tracheostomy tube is considered when the patient is capable of maintaining adequate alveolar ventilation (acceptable Pao_2 and $Paco_2$), has a vital capacity of 30–40% of predicted, has an effective cough and is free of significant dyspnea. Prior to permanent removal, the use of a fenestrated tracheostomy tube for a few days may facilitate patient adaptation. Following removal, the wound is dressed with dry, sterile gauze, and spontaneous closure can be expected in several days. Because of depressed pharyngeal reflexes during this period, aspiration following oral feeding is a hazard. For further details on this subject the reader is referred to the text by Safar (1).

Secretions

One of the most significant, reversible factors in precipitating, accentuating or perpetuating acute respiratory failure is obstructing airway secretions. The presence and physical properties of sputum contribute to airway obstruction and ineffective gas exchange as well as place a greater demand on the cough mechanism; the latter, in itself, may be destructive and fatiguing. Thus, sputum mobilization and reversal of its inciting factors are mandatory. The causes of excessive or adverse secretions should be promptly identified to permit appropriate therapy. They include infection, allergy, dehydration, chemical irritants, dry inspired gases (e.g., anesthesia) and anticholinergic drugs. Usually, there are adequate clinical indications (i.e., cough, rhonchi) that secretions are a major problem. Occasionally, however, the patient may present without gross findings, particularly if there is stupor, or if dehydration with widespread bronchiolar inspissation has occurred. Thus adverse secretions must be suspected in any individual with known bronchopulmonary disease in acute respiratory failure.

Normal Secretions

About 5–10 ml. of mucus is produced each day by the submucosal glands and epithelial goblet cells (2). Ciliated epithelial cells propel this mucus blanket toward the pharynx at a rate of approximately 10–20 mm. per minute. Additionally, macrophages (histiocytes) containing phagocytic debris and foreign materials are mobilized from the periphery of the airways. Normal and abnormal secretions exhibit both viscous and elastic properties (3). A *viscous* liquid *flows* when force is applied (the ratio of applied force to flow rate is the viscosity); an *elastic* substance *deforms* when a force is applied to it. When a cough effort is exerted sputum first deforms and then flows; the rate of flow is *not* proportional to the applied force, since sputum is a "non-Newtonian" liquid. (Water, for example, is a Newtonian liquid). The other major properties of sputum are adhesiveness (surface-to-surface interaction) and surface tension. Alterations of these physical characteristics or of ciliary function can occur because of infection,

changes in inspired oxygen concentration, air pollutants or dehydration. *The cough reflex is then the key mechanism in secretion mobilization.* In the acute respiratory failure of obstructive pulmonary disease, cough velocities are often ineffective because of mechanical factors, central nervous system depression and dynamic airway collapse with undue effort. Under these circumstances, supportive measures are necessary in augmenting a defective cough and promoting sputum clearance.

Pathologic Secretions

Sputum is an excessive and altered bronchopulmonary secretion which signifies a pathologic process and often assists us to diagnose the nature of the events. It is a complex heterogenous substance, varying with different disorders, and our knowledge of it is still fragmentary. There are two basic sputum types, each requiring its own type of management. *Mucoid sputum* is white or opalescent, gelatinous and adhesive, due to the fibrillar structure of mucopolysaccharide and mucoprotein gels. Based on clinical observations, it appears that the more water this gel-sputum contains, the less viscid it becomes; alternatively, acid pH, altered ionic or electrolyte environment and changes in component sugars may favor increased viscosity and possibly adhesiveness. Noninfected mucoid sputum may be quite troublesome because of its viscous and adhesive properties, and because it cannot be altered by antibiotics (Fig. 1). N-acetylcysteine, by reducing disulfide bonds in mucopolysaccharide chains, tends to lower viscosity and thereby facilitates removal. Finally, it should be emphasized that mucoid sputum may be associated with significant infection.

On the other hand, *purulent sputum* (often yellow to thick green) usually contains tightly interwoven fibers of deoxyribonucleic acid (DNA) from necrotic parenchymal and inflammatory cell nuclei. Large volumes of such material, with increased viscous and adhesive properties, can be generated by any infectious process. Deoxyribonuclease or proteolytic enzymes promote the enzymatic degradation of DNA, thereby assisting the removal of lodged, inspissated material. Additionally, antibiotics will abort the infectious processes contributing to these sputum characteristics.

FIG. 1.—Mucoid sputum. Note how the specimen adheres to the side of the test tube (adhesiveness) while internal viscosity is manifest by its tendency to remain as a bolus. The reader is advised to envision this sputum in the airways.

Cytologic examination may more clearly reflect pathologic pulmonary changes and clarify dynamic alterations during the period of therapy. A fresh drop of sputum is mixed with a small drop of dilute, buffered aqueous crystal violet solution (0.02 to 0.06% crystal violet in 1/15 M Sørenson's buffer* at pH 7.0) and examined. Since large, flat squamous cells indi-

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*Preparation of Sørenson's buffer (place constituents in separate containers and in refrigerator):

a. 9.02 Gm. of KH_2PO_4 is diluted in 1 liter of distilled H_2O.

b. 9.47 Gm. of Na_2HPO_4 is diluted in 1 liter of distilled H_2O.

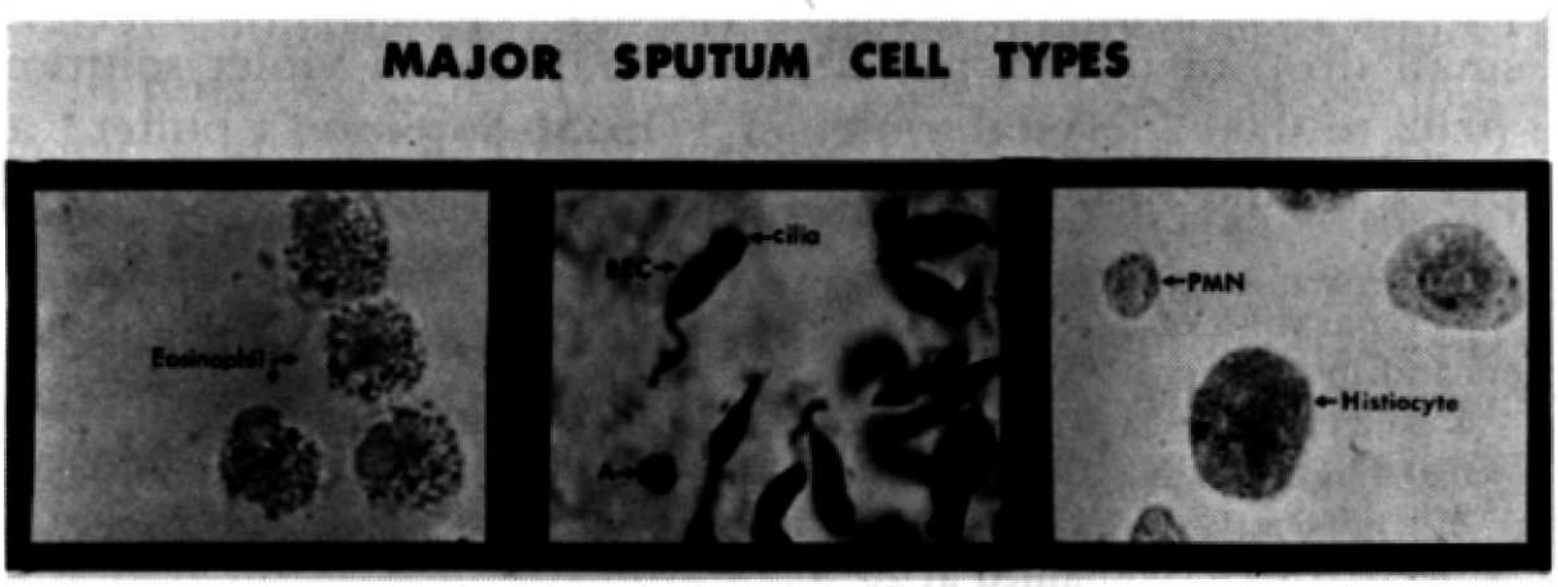
Mix 49.6 ml. of Na_2HPO_4 solution with 50.4 ml. of KH_2PO_4 solution. A pH of 6.8-7.0 is obtained at 20° C.

cate oropharyngeal contamination, only areas free of these cells should be selected for evaluation. Four major sputum cell types, as shown in Figure 2, can be distinguished; a differential cell count, similar to a blood examination can then be done.

In chronic bronchitis, the polymorphonuclear neutrophil comprises 70–90% of all sputum cells. Bronchial epithelial cells (BEC) constitute 5–20% of the total, and are frequently devoid of their ciliary border (in contrast to asthma). An appropriate cellular defense response to infection is a histiocyte count of at least 10–15%; a count less than 2% suggests an inadequate macrophage response (4). Eosinophils are usually rare (less than 1%), but may be elevated transiently during the recovery phase.

Bronchial asthma is characterized by a predominance of eosinophils, the presence of Creola bodies (clumps of BEC with intact cilia) and Charcot-Leyden crystals (4a). In asthmatic bronchitis, the predominant cellular features are bronchitic, with eosinophils comprising 3–25% of the total cells. In

FIG. 2.—Sputum cells as seen with crystal violet (outer panels) and Papanicolaou (inner panel) stains. The columnar bronchial epithelial cell (BEC) exhibits an ovoid, basally located nucleus, granular cytoplasm, a tapered base and a characteristic ciliated border. The polymorphonuclear neutrophil (PMN) is 10–15 μ in diameter, has a multilobed nucleus and a very pale cytoplasm containing small, variable granules, which, in a fresh preparation, demonstrate brownian movement. The main distinguishing feature of the eosinophil is the presence of larger, *uniform,* well-defined refractile cytoplasmic granules. The histiocyte is a larger cell (10-40 μ); it is uni- or multinucleated with variable cytoplasmic inclusions. Figures from oil immersion preparations, various magnifications. Cell A in the center panel is about 12 μ, the same size as a PMN neutrophil or eosinophil.



the clinical context, however, increases in eosinophils may reflect an asthmatic or allergic component.

The therapeutic approach to secretion mobilization is conveniently divided into (1) local measures, (2) inhalation therapy and (3) systemic agents. The procedures and medications that are least traumatic are preferable, but in severe cases more aggressive therapy is required.

LOCAL MEASURES.—The alert patient may mobilize his secretions with an effective cough, expectorant therapy and appropriate physical drainage with percussion (external vibration applied to the segment being drained. Nasotracheal suctioning may be added to stimulate an effective cough. This should be used with caution in asthmatics, in whom severe bronchospasm may result. The sterile insertion of a polyethylene catheter (#18 Bardic Intracath) through the cricothyroid membrane, with local anesthesia, is an effective supportive measure. The catheter tip is situated just above the carina, and 5 ml. of sterile normal saline solution are injected into the trachea rapidly. This will stimulate cough, and immediate aspiration through the catheter often provides an uncontaminated sputum specimen suitable for culture and microscopic examination. The catheter may be left in place for several days for local intratracheal therapy. Infrequent complications include subcutaneous and mediastinal emphysema, bleeding and infection at the puncture site (5).

Endobronchial lavage with suctioning is considered when widespread mucus plugs and voluminous or tenacious secretions fail to respond to the above measures. This is achieved by employing a bronchoscope or a Carlen's or selective Metras catheter. The latter two permit unilateral gas exchange with contralateral lung or segmental lavage. In all cases, oxygen must be provided. The repeated bronchoscopic instillation of small quantities (5–10 ml.) of warm, normal saline with the addition of Mucomyst or Dornavac is often effective in liquefying secretions and appears associated with limited toxicity. Total lung or segmental lavage in obstructive pulmonary disease, employing *large* quantities of saline (300 ml. or more), is controversial, although success has been reported in bronchial asthma. Significant improvement has occurred in only a few patients with bronchitis or emphysema (6). The

procedure is frequently associated with transient pulmonary infiltrates, inability to recover all the instilled fluid and a fall (5–15 mm. Hg) in the arterial oxygen tension. At present, bronchopulmonary lavage with small volumes appears relatively safe, but its effectiveness will depend on pathologic conditions and the talents of the endoscopist (7).

INHALATION THERAPY.—The rationale for water as a therapeutic agent is based on (1) the physiology of the respiratory humidification system and (2) its clinical effectiveness. *Humidification* is the addition of *molecular* water to the inspired air, while *nebulization* (aerosolization) is the suspension of liquid *particles* in a gas. The amount of molecular water required to fully saturate a gas increases with the temperature. Thus room air at 70°F., fully saturated with water, would be only 40% saturated at normal body temperature (98.6°F.). Temperature and humidity gradients exist in the airway, resulting in 100% saturation and warming of inspired air by the mucosa of the upper respiratory tract. Cold air is irritating to the epithelium. Furthermore, dry gases inhaled through an endotracheal or tracheostomy tube bypass these normal humidification mechanisms, forcing the lower airways (or wet intraluminal secretions) to contribute their water content to the onrushing air. Clearly this will impair ciliary function and cause secretions to thicken or become tenacious, and thereby difficult to mobilize. For these reasons any inspired gas must be humidified. This is particularly true for stored oxygen or anesthetic gases, which are absolutely dry. Since temperature is the major limiting factor in the volume of water vapor available for delivery to the airways, bedside humidifiers or ventilator mainstream humidifiers should be heated sufficiently to deliver the gases at body temperature; this is an efficient system for delivering warmed, highly humidified gases when the normal upper airway mechanisms have been bypassed. The usual, unheated bubble humidifier is of limited value, providing only 20% of the necessary bronchial humidification.

Conventional nebulizers utilize a high-velocity gas jet to convert a capillary column of liquid into suspended droplets within the gas. Baffling devices select smaller particles for delivery. Despite recent controversial data, in general, particle sizes between 0.5 and 3.0 μ in diameter drop out in the smaller

airways, larger droplets deposit in higher airways and trachea, while those less than 0.5 μ are exhaled. Additionally, the delivery site of any particle will depend on differences in regional air distribution and the presence of total regional obstruction beyond which no particle can penetrate. Furthermore, the volume of solution and the nature of the propelling device are factors influencing the net effectiveness or side effects of this treatment (8).

Nebulizers can be powered by compressed air, oxygen, hand-bulb or inert propellants. Large volumes of cold or heated water aerosols can be delivered from 300–500 ml. reservoir units which are driven by oxygen and/or compressed air. The heated unit is widely employed because of its effectiveness and relative ease of use, and it is administered periodically or continuously by mask, mouthpiece, face tent, tracheostomy collar or respirator. The solution being nebulized is preheated by an immersion probe and then delivered to the upper airway at body temperature. Simple liquefaction of secretions by *large* volumes of water or saline is the mainstay of treatment; *small volumes* of other therapeutic aerosols including pancreatic dornase, N-acetylcysteine, bronchodilators (notably isoproterenol) and occasionally antibiotics are added periodically. Slow, deep breathing, with periodic breath-holding, will achieve the most effective penetration and deposition of these substances. Nebulization therapy, particularly with mucolytic or proteolytic agents, must always be combined with active removal of secretions by encouraging cough, postural drainage, suctioning and other measures.

Through high-frequency vibration of a crystal-diaphragm apparatus, ultrasonic nebulizers generate water droplets of uniform particle size in high densities. Therapeutic, supersaturated fogs of water or normal saline are deposited over large areas of the tracheobronchial tree to facilitate the wetting of viscid secretions and surface mucosa. These devices deliver controllable volumes, usually delivering doses of 40–100 ml., four to six times a day for 30–45 minutes as tolerated. Water is often irritating, inducing cough, and limits patient tolerance, whereas physiologic or hypotonic saline is usually more acceptable, particularly with brief exposures. A mild increase in airway resistance has recently been observed in pa-

tients following inhalation of such ultrasonic fogs (9). Additionally, excessive volumes of aerosol may lead to water retention with decreased lung compliance and an increased alveolar-arterial oxygen gradient (10).

At present, two chemically active agents are in common use for nebulization or direct airway instillation to facilitate sputum mobilization. N-acetylcysteine (Mucomyst) is indicated where mucoid, sticky and/or viscid secretions and mucous plugs are present. Intratracheal instillation of 3–5 ml. of a 10% solution q.i.d. is suggested in the *acute* situation; proper positioning of the patient will direct the agent to regional areas. Nebulization of similar doses is continued during the remaining course of medication. A report of inactivation by oxygen has not been confirmed (11), but this product will attack rubber; plastic nebulizers and tubes are thus preferred. N-acetylcysteine should be used with caution in any individual with known bronchoreactivity since it may provoke severe bronchospasm; to prevent this, concomitant administration of 0.5 ml. (1:200) of isoproterenol is advisable in most patients.

Pancreatic dornase (Dornavac) depolymerizes the DNA of purulent secretions and thus decreases sputum viscosity. It may be administered by nebulization or endotracheal instillation (the latter route in acute situations) in doses of 50,000-100,000 U. in 2.0 ml. of saline q.i.d. It appears safe, and few side effects have been reported (12).

Many other sputum liquefiers have been used; the review of Lieberman (11) is suggested. Detergents such as tyloxapol (Alevaire) are generally no more effective than their water content (13); trypsin and chymotrypsin are often irritating, and their beneficial action must be weighed in any given case.

SYSTEMIC THERAPY.—Adequate hydration by the humidification of inspired air and by the oral or intravenous routes is a major step for adequate sputum mobilization. Potassium iodide and glyceryl guaiacolate (Robitussin) are expectorants which facilitate secretion clearance. Iodides have been given for many years on the empirical assumption that they increase the aqueous output of the respiratory tract (14). Sodium iodide, 1.0 Gm. per liter of fluid, is administered intravenously in the acutely ill patient. Oral saturated solution of potassium

iodide, 10 to 30 drops per day, may be substituted later. Side effects include skin rash, salivary gland enlargement, drug fever, rhinorrhea, angioedema, eosinophilia and sodium loading when given as sodium iodide. Glyceryl guaiacolate is for oral therapy only. Our double-blind crossover studies revealed a decrease in sputum adhesiveness, which correlated with a greater ease of expectoration (15). The daily dose is 300–600 mg. (15–30 ml. Robitussin) q.i.d. Side effects are usually limited to the gastrointestinal tract.

Other drugs used occasionally include antitussives to control an irritating nonproductive cough and atropine to reduce *true* bronchorrhea. To minimize respiratory depression, a nonnarcotic antitussive such as Theratuss (20–60 mg. q. 6h.) is preferred.

Infection

It is believed that viral and/or bacterial infections of the respiratory tract commonly exacerbate and perpetuate respiratory failure (16). Bronchial involvement is presumably more frequent, since a "true" pneumonic process is demonstrable in only about 10% of cases (17). Nevertheless, when bacterial infections are documented or implicated, prompt and vigorous treatment is imperative even though the exact organism is not immediately definable. *Gross purulence of the sputum is not necessarily an index of infection, nor is mucoid sputum necessarily noninfected.* Thus, a gram stain of the sputum, tracheobronchial washings or percutaneous transtracheal aspirate will aid in the initial identification of bacterial flora and act as a guide in antibiotic selection. The latter is modified, if necessary, once culture and sensitivity data are provided. Periodic re-evaluation of the sputum is necessary to detect changes in bacterial flora having clinical significance.

A "representative" sputum sample is substantiated by the crystal violet cytologic technic previously elaborated on. This same aliquot is then examined for bacterial constituents by the gram stain. At least twenty oil immersion fields are observed: (a) $>$ 100 organisms per field indicates infection, (b) 30–100 per field is highly suggestive and (c) $<$ 30 requires further clinical evaluation (4). It should be noted that the

bacteriologic examination of sputum may not entirely reflect the nature of the infectious-pathologic process (18). Furthermore, the mere presence of bacteria does not always correlate with phases of clinically significant infection. Nevertheless, while the distinction between infection and colonization may be difficult, antibiotics are presently indicated in many clinical episodes of respiratory failure.

The most common bacterial pathogens associated with exacerbations of bronchitis are *Haemophilus influenzae* and *Diplococcus pneumoniae; Neisseria* and other gram-negative organisms are occasionally observed. Staphylococci may cause serious bronchopneumonia, but in our experience these organisms only occasionally produce exacerbations of simple chronic bronchitis. Penicillin is the drug of choice for *D. pneumoniae;* 2–3 million units per day given parenterally will suffice. If *H. influenzae* is obvious or suspected (as it frequently is), then ampicillin (4 Gm. intravenously per day), high dose penicillin G (10–20 million units q.d.) alone or with streptomycin (0.5 Gm. b.i.d.) or oral tetracycline (2–4 Gm. q.d.) are effective choices. Alternatives include cephalothin (6–12 Gm. q.d., IV), while chloramphenicol is reserved for refractory, seriously ill patients because of the danger of bone marrow toxicity. Penicillin-resistant staphylococci should be treated with a penicillinase-resistant penicillin. The guidelines for clinical improvement include a reduction in sputum volume and purulence, lysis of fever, reduction in immature polymorphonuclear leukocytosis and improved gas exchange. Antibiotics are continued for 10–14 days as indicated; they are modified by changes in clinically significant bacterial flora or should be maintained until frank pneumonitis has substantially resolved.

Following several days of antibiotic administration, certain gram-negative bacteria, namely *Pseudomonas aeruginosa, Escherichia coli* and *Proteus* or *Klebsiella-Aerobacter* species may be isolated from the sputum, particularly from intubated patients. In some cases, they are a consequence of antibiotic usage permitting overgrowth of nonsusceptible organisms. Also implicated in their appearance is the use of adrenal corticosteroids, coexisting medical disorders, local trauma by indwelling airway or suction catheters, shock and anemia. In other cases, the sources of viable gram-negative bacteria

(*Pseudomonas,* flavobacterium, *Herellea,* etc.) are water reservoirs, mainstream nebulizers or connecting tubing; these organisms are aerosolized in great numbers, usually through the reservoir nebulizer (19). Recently, *Serratia marcescens* has been implicated in a hospital outbreak associated with ultrasonic nebulizers (20). To minimize these infectious complications, daily sterilization of the equipment with the use of 0.25% acetic acid, glutaraldehyde (Cidex) or ethylene oxide gas, more frequent changes of reservoir fluids and the avoidance of gross contamination are important. Nevertheless, we are dismayed by the rapidity by which such equipment becomes recontaminated.

When gram-negative bacteria are recovered in the sputum, treatment will be based on evidence of clinical deterioration and the features of the sputum, since cultural growth is not necessarily indicative of clinical infection. On the other hand, a pneumonia or septicemia caused by these organisms will necessitate immediate antibiotic therapy (Kanamycin, Polymyxin B, Gentamycin, etc.) with modification, if necessary, once identification and specific sensitivities are available. Failure to observe clinical improvement suggests that the antibiotic choice may be erroneous, that new organisms are present or that drug resistance has developed. A degree of caution is advisable when employing Kanamycin or Polymyxin B since respiratory paralysis has occasionally been reported with their use.

In the absence of demonstrable bacterial infection, certain viruses (for example, adenovirus and influenza A and B) may be contributory, precipitating or complicating factors. If *Mycoplasma pneumoniae* is identified by epidemiologic implication, antibody titer or culture, some benefit may occur with the early use of tetracycline or erythromycin. The role of this organism in infectious exacerbations of acute respiratory failure is not clear. Finally, the presence of tuberculosis or any fungal infection must always be considered.

Oxygen Therapy

Since hypoxemia is *always* present in acute respiratory failure and often of severe magnitude (20–40 mm. Hg), oxygen must be *provided* immediately and *maintained* throughout.

Arterial oxygen tensions below 20 mm. Hg for more than a few moments may cause death. Lesser degrees of hypoxemia result in numerous physiologic and metabolic derangements including hypoxic encephalopathy, increased airway resistance, pulmonary hypertension, maldistribution of pulmonary blood flow, cor pulmonale and left ventricular dysfunction. Earlier fears of respiratory center depression by removal of the hypoxic respiratory stimulus have been supplanted by the knowledge that physiologic oxygen tensions (60–90 mm. Hg) are *essential.* The distinction between arterial hypoxemia and tissue hypoxia must be stressed. The former arises from cardiopulmonary disorders. The latter is influenced by arterial oxygen tensions, cardiac output, distribution of systemic blood flow and hemoglobin content and oxyhemoglobin dissociation properties.

As Campbell has emphasized, the extent of hypoxemia in acute respiratory failure, *while breathing room air,* is generally associated with a $Paco_2$ no greater than 80–90 mm. Hg and an acidemia of not more than 56.0 nM. (H^+) per liter (pHa = 7.25) (21) . Thus, in the absence of respiratory depression by uncontrolled oxygen therapy, toxic acidemia is unlikely, and *death* is more likely to occur from severe *hypoxemia.* This is explained by the *reciprocal* relationships of alveolar gas; i.e., the rise in alveolar CO_2 tension approximates an equivalent fall in alveolar O_2 tension. Additionally, the alveolar-arterial oxygen gradient (normal 10–15 mm. Hg) is virtually always increased in patients with obstructive lung disease due to coexisting ventilation–perfusion inhomogeneity, and further reduces the arterial oxygen tension. Thus, when $Paco_2$ is greater than 90 mm. Hg, respiratory center depression from uncontrolled oxygen therapy should be highly *suspect;* levels $<$ 90 mm. Hg do not necessarily rule out this factor.

Since many patients can survive episodes of acute respiratory failure without intubation, and since mechanical ventilation by endotracheal or tracheostomy tube is associated with a high *morbidity* and *mortality,* controlled, low-concentration oxygen in conjunction with conservative medical management should be the *initial* therapy for the correction of hypoxemia and the management of acute respiratory failure. This concept of employing low concentrations of oxygen was originally de-

scribed by Barach some 30 years ago and popularized recently by Campbell. The rationale is the elevation of the arterial Pao_2 to acceptable physiologic levels, since at the steep portion of the hemoglobin association curve a *small rise* in oxygen tension (thus minimizing the danger of respiratory center depression) yields a significant increase in arterial O_2 saturation. For example, with an initial arterial Pao_2 of 20 mm. Hg (SaO_2* = 35%), an increase in the arterial O_2 tension to 40 mm. Hg would raise the arterial oxyhemoglobin saturation to 75% (at pH 7.40, 37°C.).

The two technics for controlled oxygen administration are (1) supplemental oxygen at low flow rates by any device and (2) special masks which deliver oxygen at predictable, relatively precise concentrations. In the former, oxygen is administered at flow rates of 1–3 liters per minute, usually by a nasal catheter or double-pronged nasal cannula. The inspired oxygen concentration depends on minute ventilation, accuracy of the oxygen flow regulator and, to some extent, mouth breathing. If the $Paco_2$ does not rise significantly (i.e., > 5–10 mm. Hg) over a several hour period, O_2 flow rates may be gradually increased as required. The second technic utilizes a series of disposable plastic Venturi masks (Ventimask) which fit over the nose and mouth and are designed to deliver either 24, 28 or 35% inspired oxygen. The masks operate on the Venturi principle whereby a stream of 100% oxygen (at 4–8 liters per minute) admixes with a fixed proportion of ambient air, and because the air/O_2 ratio is constant over a wide range of O_2 flow rates, a fixed inspired oxygen concentration is delivered. In general, the preferred method is to *initiate* the *lowest* concentration of oxygen (24%), and to increase this to 28 or 35% as required and/or tolerated by the patient. Small changes in minute ventilation and mouth or nose breathing will not alter the inspired O_2 tension. By these methods, in conjunction with all other medical measures, appropriate oxygen tensions and saturations can be achieved in a great many individuals (22). There are those, however, who exhibit unacceptable Pao_2 levels or respiratory depression for a given inspired oxygen concentration and, therefore, arterial blood

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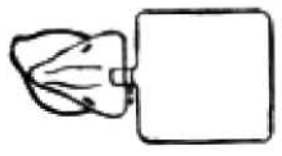
*SaO_2 = saturation of arterial hemoglobin with oxygen (in %).

TABLE 1.—METHODS OF OXYGEN ADMINISTRATION

EQUIPMENT TYPE	% OXYGEN	FLOW (L./MIN.)	COMMENTS
Nasal Catheter 	under 30	1-3	Comfortable. Higher flows provide up to 50% oxygen, but can cause respiratory depression, and drying of mucosa.
Nasal Cannula 	under 30	1-3	Comfortable. Higher flows provide up to 50% oxygen, but can cause respiratory depression, and drying of mucosa.
Venturi Masks 	24	4	Mask well-tolerated. Accurate concentrations delivered.
	28	4	
	35	8	
Face Tent 	30-55	4-8	Well-tolerated. Good for supplying extra humidity.
Mask without bag	35-45	6-8	Poorly-tolerated. Significant CO_2 rebreathing possible at low flows. Highest percentage requires tight mask and large bag.
	45-55	10	
	55-65	10-12	
Mask with bag 	40-50	6	
	50-60	8	
	90+	8-12	
IPPB Units (pressure-limited)	40-100	direct from supply	Oxygen per cent unpredictable.
Volume-limited Units	variable but predictable from simple tables		

gases should be monitored periodically; when indicated, other devices must be utilized to obtain physiologic oxygen tensions.

When *higher oxygen concentrations* are required, and ventilatory depression is not a problem, a number of semi-open or closed oxygen delivery systems may be employed (Table 1).

Inspired O_2 concentrations between 30 and 50% can be attained with oxygen flow rates of 5–8 liters per minute in semi-open systems including nasal catheters and cannulas, open-top face tents and loose face and tracheostomy masks. Non-rebreathing, closed systems, such as well-sealed rubber face masks and IPPB units, provide higher inspired oxygen concentrations (approaching 80–100%). Inspired oxygen tensions are determined by the oxygen concentration of the source gas and any dilution effect of air leaks and mixing systems.

Unfortunately, in some patients with chronic hypercapnia, oxygen therapy by any modality may *induce* respiratory center depression via the abolition of carotid and aortic chemoreceptor stimuli. While there are no firm criteria to delineate which patients will develop significant hypercapnia, this complication is usually associated with chronic hypercapnia greater than 50 mm. Hg, advanced hypoxemia or acidemia and a large increment in Pao_2 following oxygen treatment (23). Intermittent oxygen therapy should *not* be employed under these circumstances, since a severe rebound hypoxemia may occur. Thus, when oxygen cannot be adequately administered without this complication, or if refractory hypoxemia exists, it is the *responsibility* of the physician to provide adequate oxygen levels by appropriate ventilatory support with confirmation by arterial blood analysis (see section on ventilation).

Wall or tanked oxygen is completely *dry* and emerges at high pressures (ca. 50 lb./sq. inch) with appropriate reduction in pressure achieved by a rate-controllable flow meter. It is mandatory that oxygen be adequately humidified at all times to minimize drying of secretions or irritative bronchitis. The humidification of the inspired oxygen–air mixtures is achieved by a heated humidifier or a conventional or ultrasonic nebulizer.

Oxygen Toxicity

Oxygen is a *fundamental* therapeutic agent. Its potential toxicity must be recognized, however, and it must be administered cautiously, when indicated. In addition to respiratory depression, oxygen can be directly toxic to the tracheobronchial mucosa and the pulmonary parenchyma. Although exact

tolerance limits have not been defined, pulmonary oxygen toxicity occurs when the partial pressure of the inspired oxygen exceeds approximately 300 *mm. Hg* (24). The problem is complex; toxicity is enhanced by increasing oxygen partial pressures and by prolonging exposure; its onset is delayed by the presence of arterial hypoxemia or the intermittent breathing of ambient air. The precise mechanism(s) producing toxicity is unknown.

A fall in the vital capacity has been described as one of the earliest measurable parameters of pulmonary oxygen toxicity (25). With continued exposure, a chemical tracheobronchitis develops, characterized by substernal tightness or chest pain; adequate humidification of the inspired gas may relieve these symptoms. Significant retardation of tracheal mucus flow and ciliary action occurs when inspired oxygen is greater than 40% (26).

Parenchymal lesions, occurring with hyperbaric oxygenation or prolonged oxygenation with mechanical ventilators, have been associated with increasing respiratory distress, deteriorating pulmonary function and progressive difficulty in the weaning process. The early lesions are capillary congestion, interstitial edema, intra-alveolar fibrin deposition with hyaline membrane formation, alveolar edema and hemorrhage and atelectasis. Some studies show an impairment in surfactant production (27). Although the acute stage is reversible, a late *irreversible* stage, characterized by capillary proliferation and progressive fibrosis, can develop unless exposure to oxygen at *high* partial pressures is discontinued. An important clinical consideration is that *refractory* hypoxemia may have been produced by these mechanisms of oxygen toxicity.

Despite the dangers of oxygen toxicity, in patients with significant arterial hypoxemia, humidified oxygen *must* be provided with the minimum of hazardous exposure commensurate with tissue metabolic demands. In general, arterial PO_2 levels should not exceed 100 mm. Hg, but should be at least 60 mm. Hg to attain approximately a 90% arterial hemoglobin saturation (at pH 7.40). The inspired oxygen concentration should be the lowest necessary to achieve these tensions, and preferably less than 50%. An excellent review on oxygen therapy is recommended for further details on these topics (28).

Many pressure-cycled respirators may deliver 60–90% inspired oxygen concentrations while on the "40% oxygen" setting. This is promoted by dirty air filters, low flow-rate settings and high patient airway resistances. Oxygen toxicity often develops after 10 or more days of high inspired oxygen levels (29); pressure-cycled ventilators which are to be employed for these periods should be driven by an air compressor with a supplemental oxygen supply. Frequent measurements of the inspired oxygen concentration will be necessary. On the other hand, volume-cycled units are easily adjusted to provide fixed inspired oxygen concentrations by adjusting the oxygen inflow.

Ventilation

When significant ventilatory failure exists or develops despite supportive medical measures, effective ventilation *must be established.* The art of management often requires a decision under many variable conditions. Certainly, with correctable hypoxemia and mild respiratory acidosis, one may manage without ventilator intervention. When a patient is unable to effectively perform the respiratory work necessary for adequate gas exchange, artificial ventilation is warranted. Since the arterial $Paco_2$ reflects (1) tissue metabolic carbon dioxide production and (2) adequacy of alveolar ventilation, therapy is directed toward *reducing the work of breathing* by relief of airway obstruction or parenchymal disease, and by *improving alveolar gas exchange.* This often necessitates artificial mechanical support, which simultaneously facilitates the humidification of inspired gases, aerosol therapy and oxygen enrichment of the inspired air.

The following may be considered as relative guidelines for artificial ventilatory support when correlated with the *clinical situation* and when documented by the arterial blood gas and pH abnormalities of respiratory failure:

1. Advanced acute respiratory failure—i.e., $Paco_2 > 65$–70 mm. Hg, pH < 7.75, or inability of conservative medical management to *halt progressive* ventilatory failure.
2. States where *simple supportive measures* will clearly be ineffective—for example, severe drug overdose, widespread obstructing secretions or generalized pneumonia.

3. Inability to properly oxygenate the patient without suppression of the hypoxemic chemoreceptor stimulus and resultant *respiratory* depression.

4. Severe physical *exhaustion* from profound thoracic mechanical work in the context of arterial blood gas deterioration.

5. In the *pre-* or *postoperative* setting, particularly in individuals with previously established borderline pulmonary function.

6. In *agitated, confused* or *uncooperative* patients with hypoxemia and/or hypercapnia who cannot cooperate for conservative measures and/or who require sedation.

7. Acute cardiorespiratory arrest.

Artificial ventilation may be provided in numerous ways. In the acute, short-term situation, mouth-to-mouth respiration (in the absence of equipment) or manual compression of an anesthetic bag with mask (Ambu) may temporarily maintain alveolar ventilation. For long-term ventilation, however, a mechanical respirator is necessary.

Mechanical respirators are classified as (1) pressure-cycled, (2) volume-cycled or (3) external-body types. The two respirator types most commonly employed in the United States are the pressure-cycled (Bird, Bennett) and the volume-cycled (Emerson, Mörch, Engstrom, Air-Shields, Bennett Ohio) units.

Pressure-cycled devices operate on a pressure-limiting principle; that is, inspiration terminates when the pressure within the airway reaches a preset value, *irrespective* of the volume delivered. The respirator is activated by a slight negative inspiratory pressure, with an adjustable sensitivity setting. Expiration is passive. Periodic or continuous administration is possible, depending on the clinical needs and patient cooperation. In addition, most models provide automatic cycling (*controlled ventilation*) as well as patient-triggered operation *(assisted ventilation).* Several respirators have adjustable inspiratory flow rate controls permitting regulation of inspiratory/expiratory time. Their relatively low cost and durability, ease of operation and independence of electrical supply are desirable features. Their major disadvantages are (1) occasional inability to achieve high driving pressures, (2) inability of the ventilator to adapt to changes in tissue compliance and airway resistance, (3) frequent asynchronous operation creating patient exhaustion and persistent hypoventilation and (4)

inaccuracy in the inspired oxygen concentration (a 40% oxygen setting often delivers 60–90% oxygen) unless specifically supplied with a flow booster mixing cartridge. Successful ventilation with any pressure-cycled unit requires frequent monitoring of respiratory rate, measurement of expired tidal volume by a spirometer (Wright respirometer) and correlation with arterial blood gas and pH data. A negative pressure during expiration should not be employed in obstructive lung disease since it promotes bronchial collapse. Expiratory retard valves may be employed to permit greater respirator efficiency.

In contrast to pressure-cycled units, volume-cycled respirators deliver a preselected tidal volume at adjustable respiratory rates, irrespective of airway or tissue resistance. The final airway pressure is dependent on the tidal volume, inspiratory time and inflationary lung resistances. If the pressure to attain these fixed volumes increases, then secretions, atelectasis or changes in compliance may have developed. Except for the Bennett Ohio and Air-Shields models, these respirators cannot be triggered by the patient. Since constant volume breathing may lead to focal atelectasis and reduced lung compliance, desirable models incorporate an automatic sighing device for periodic hyperinflation. These units require both a safety valve to "bleed" excessive pressures and an air-tight system for normal function inasmuch as they are incapable of compensating for an air leak. The duration of inspiration and expiration is generally adjustable. A proper balance of the inspiratory/expiratory time ratio (1:2, 1:3) is necessary in obstructive lung disease to achieve adequate gas distribution and alveolar ventilation, while permitting adequate venous return and precluding air trapping. While such units basically operate with ambient air, oxygen may be added as required. Nomograms are available for regulating the inspired oxygen concentration (30) and determining the extent of error in measured expired gas volume occurring because of gas compression within the ventilator (31). It is important that all respirators possess a functioning humidification system.

External negative pressure ventilators (Drinker, Emerson) have had some success. They generally do not require masks or tubes, but are at a disadvantage if a tracheostomy tube is in place. Their use in obstructive lung disease is limited by

frequent inability to provide maximal ventilatory pressures, bulkiness, inaccessibility of the patient and a fixed inspiratory-expiratory respiratory cycle.

The selection of a respirator depends on its availability, cost, ease of operation and its acceptance by personnel. We have found the pressure-cycled devices adequate for most cases, provided constant monitoring and nursing care are available. They are adaptable to assisted or controlled approaches. Volume-cycled units are more expensive, but usually more powerful, and are quite dependable in delivering a given minute volume regardless of changes in airway resistance and lung compliance. With advanced airway obstruction or when used for controlled ventilation, such units are often preferable to pressure-cycled ventilators. A bag resuscitator should always be available at the *bedside* in the event of a technical failure.

In establishing the respirator, suggested initial relationships are a slow respiratory frequency (12–18 per minute), moderate tidal volumes (600–1,000 ml.) and an inspiratory/expiratory time-rate in the range of 1:2 or 1:3. Only cuffed endotracheal or tracheostomy tubes, inflated to a minimal leak, are used during continuous assisted or controlled ventilation. Minute ventilation nomograms established for normal individuals are often *invalid* in this patient population because of unpredictable increases and minute-to-minute variations in the physiologic dead space, and increases in carbon dioxide production. Thus the arterial $Paco_2$ and pH are the *key* measurements in assessing the *adequacy* of *artificial* ventilation. In addition, increased intrapulmonary shunting and abnormal ventilation to perfusion relationships can result in wide discrepancies between the inspired and arterial oxygen tension. Thus frequent arterial analysis will permit maintenance of a Pao_2 of 70–100 mm. Hg through proper control of the inspired O_2 concentration. Automatic or manual hyperinflation every 30 minutes at 30–50 cm. H_2O pressure for 5 seconds may prevent atelectasis. Finally, when the clinical pattern is stable, the tidal volume, or venous Pco_2 and pH can be followed as relative guides to effective ventilation with periodic confirmation by *arterial* blood analysis.

Assisted ventilation by IPPB (pressure-cycled respirator) can be administered intermittently or continuously. It is most

effective when the patient is either alert or stuporous, but capable of triggering and synchronizing with the respirator. *Continuous assisted ventilation* is the usual modality employed for intubated patients. Although the effects of *intermittent assisted ventilation* are transient, its use for 15–20 minutes in the alert individual may improve the arterial Pco_2 and pH for up to 2 hours, and therefore four to eight intermittent courses of therapy per day may be of supportive benefit (32). Clinical and physiologic improvement, when observed, is frequently due to improved gas distribution and alveolar ventilation, reduction in the work of breathing and the more effective delivery of aerosol agents.

On the other hand, *continuous assisted* ventilation with pressure-cycled units (IPPB) may *fail* or be *detrimental* in the management of acute respiratory failure. In a recent evaluation from this laboratory (33), the indications for controlled ventilation with IPPB were:

1. Failure of the patient to cooperate for assisted cycle because of stupor, agitation or refusal to accept, trigger and phase with the respirator.
2. Failure to reduce or prevent a rise in $Paco_2$ on *assisted* IPPB with progressive clinical deterioration.
3. Persistent tachypnea, physical exhaustion and obvious excessive work of breathing not alleviated by *assisted* IPPB.

In general, then, when *continuous assisted* ventilation fails, *controlled* ventilation employing pressure or volume-cycled respirators must be instituted. The goal of controlled ventilation is the elimination of patient respiratory control and effort and the institution of adequate artificial ventilation, thereby providing *time* for appropriate medical therapy. Once mechanical ventilation is established, the rate at which $Paco_2$ is reduced can be controlled and oxygenation can be improved.

Proper synchronization between the patient and the respirator is a *prerequisite* for successful controlled ventilation using pressure-limited units. Synchronization is of less importance with volume-cycled machines, since they deliver a preset volume regardless of the resistance encountered. With either type, however, failure of the patient to accept and follow the preset pattern of the respirator can lead to persistent hypoven-

tilation. Under these circumstances, elimination or reduction of patient-respirator incoordination is necessary.

Initially, controlled ventilation may be instituted by manual override or *automatic machine cycle.* Approximately 40–50% of patients will passively accept and coordinate with the respirator preset at a rate of 10–15 per minute. If this approach fails after 10–15 minutes, as judged by clinical deterioration and arterial blood analysis, short-term *100% oxygen* may be administered to depress ventilation in oxygen-sensitive individuals. This approach succeeds in only a small percentage of patients, but is advantageous because depressant drugs may be avoided. In any case, oxygen suppression should not be continued for more than 5–10 minutes, since progressive uncontrolled respiratory failure may be occurring. Finally, if the above measures fail to achieve synchronization, *drug suppression* is required. Morphine sulfate, meperidine (Demerol), barbiturates, diazepam (Valium) or curare-like agents may be selected. Initially 2–4 mg. of intravenous morphine sulfate is administered with an additional 2–5 mg. (up to 20 mg.) every 10–15 minutes until relaxation ensues. Succinylcholine (20–40 mg. IV) or D-tubocurarine (6–12 mg. IV, total dose not to exceed 25 mg.) will cause rapid partial or total paralysis. Once relaxation occurs, it is imperative that a preset automatic machine cycle be instituted *immediately.* These steps should permit an effective control cycle to be established and maintained in all patients, with additional drug doses required infrequently. In our experience, only 19% of patients with *far advanced complicated disease* could be managed by assisted IPPB. The remaining 81% required controlled ventilation (*employing IPPB*). Automatic machine cycle alone was effective in 41% of these instances, oxygen suppression in 18% and drug suppression (morphine sulfate and/or succinylcholine) in the remaining 41% (33).

We delineate two phases of controlled cycle: (1) a *"hyperventilation" period,* during which time severe arterial blood gas abnormalities are judiciously controlled, and (2) a *maintenance period,* where continuous supportive ventilation permits the treatment of reversible disease. During the hyperventilation phase (2–6 hours), gradual, controlled reductions in $Paco_2$ by 30–57 mm. Hg, improvements of pH by 0.09–0.17

units and adequate arterial oxygen tensions (> 70 mm. Hg) were observed in the above-cited study. These changes in effective gas exchange were associated with *slow* respiratory rates (16–20 per minute) and *increased* tidal volumes (from 67 to 211% over initial volumes) rather than gross increases in minute ventilation. The maintenance phase extended for an additional 12–30 hours before assisted ventilation could be resumed (33).

During artificial ventilation, appropriate management necessitates frequent and thorough monitoring by clinical, laboratory and roentgenographic parameters. In our experience, the constant attendance by a nurse will expedite not only physical care but will provide the contact and reassurance that many of these frightened patients need. Frequent changes in position (every 1–2 hours) will limit secretion stasis and aid in postural drainage. Flow charts are essential in serially recording pertinent data (Fig. 3) and should include the patient's daily weight, vital signs, electrolytes, intake and output, stool guaiac checks, respirator settings, minute volumes (respiratory frequency × tidal volume) and arterial blood gases. Proper management will require frequent arterial analysis and adjustment of the respirator to attain continually effective ventilation. A useful bedside technic is to compute effective compliance from tidal volume and peak ventilator positive pressure;

$$C_E = \frac{(\text{tidal volume})}{(\text{peak pressure})}.$$

Serial measurements are observed because a *fall* in effective compliance may indicate tube or airway obstruction as well as parenchymal "stiffness" due to pulmonary edema, pneumonia, atelectasis or ventilator oxygen toxicity. The alveolar-arterial oxygen tension gradient and the physiologic dead space volume/tidal volume ratio (V_D/V_T) are useful in interpreting certain pathophysiologic changes. A significant increase in the A-a PO_2 gradient (normal 10—15 mm. Hg at room air and 35 mm. Hg at 100% oxygen) at a constant inspired oxygen tension suggests, among other factors, an increased venous admixture. A rise in the dead space ventilation relative to minute ventilation ($\uparrow V_D/V_T$) compromises alveolar ventilation. An increased inspired oxygen concentration, larger minute volumes, or both, may then be necessary.

FLOW SHEET FOR CONTINUOUS (ASSISTED OR CONTROLLED) VENTILATION

TUFTS LUNG STATION
BOSTON CITY HOSPITAL
(BLOOD GAS LAB)

PATIENT: AGE: SEX: WARD: DIAGNOSIS:

TYPE OF VENILATION:
ASSISTED OR CONTROLLED

ORDERS: (1) SUCTION q_____ (2) INFLATE CUFF WITH _____cc. (3) DEFLATE CUFF_____MIN. PER_____ (4) OVERINFLATE q_____WITH____AIR PRESSURE

(5) TURN PATIENT q_____ (6) CHECK CUFF q_____ (7) REPLACE TRACH TUBE q_____ (8) MAINTAIN STERILE CONDITIONS

(9) AMINOPHYLLINE_____mgm/per_____, flow rate_____cc/(min.) (10) ADD TO NEBULIZER: (11) OTHER ORDERS:

ISUPREL 1:200_____cc. + _____cc. H_2Oq_____hr.

DORNAVAC_____units q_____hr.

MUCOMYST_____cc. q_____hr.

SALINE _____cc. q_____hr.

DATE TIME	VENTILATION						Blood Gas and Physiology Data								Clinical				R_x and Comments	I N T A K E	O U T P U T	Check List						Chemistries						
	Rate (min)	Pressure (cm)	TV (cc)	V/P	Vd/Vt	F_{IO_2}	P_aCO_2	pH	HCO_3	P_aO_2	S_aO_2	$A\text{-}aO_2$	V_{CO_2}	V_A	Wt	BP	P	T				W A T E R	C H A N G E	C U F F	D E F L A T E	S U C T I O N	T U B E	C L E A N E D	Hct	WBC	BUN	Na	K	Cl	CO_2

FIG. 3.—Sample work sheet and flow chart.

Following clinical improvement, controlled ventilation is terminated. Although patients on controlled ventilation can be weaned directly, we prefer to place them initially on *continuous* assisted ventilation and later *intermittent* assisted cycle. Weaning patients with chronic obstructive lung disease from ventilator support can be a slow and difficult process. It should be instituted as soon as clinically feasible. In general, a vital capacity at least 35% of predicted, a V_D/V_T ratio less than 0.6 and a Pao_2 of approximately 60 mm. Hg (while on supplemental oxygen) are necessary before respirator independence is feasible. Ventilation, in terms of arterial $Paco_2$ and pH, is restored to the approximate range existing in the prior chronic stable state. By gradually decreasing the respirator sensitivity, the work required to activate the ventilator is increased and the respiratory muscles are strengthened. The patient is then briefly removed from the respirator for 3–5 minutes every half hour. Depending on his tolerance, and confirmed with blood gas and pH samples, these intervals are increased gradually or rapidly until complete (or relatively complete) respirator independence is attained. Initially, a return to the ventilator during the evening is helpful, and humidified oxygen is provided while off the respirator. With end-stage pulmonary disease, weaning is usually impossible and long-term respirator support will be necessary.

Complications

Mechanical ventilation is associated with a number of complications. A common problem is *"iatrogenic" hypoventilation* caused by improper establishment of the respirator or failure to frequently monitor arterial blood gases. Tube obstruction, respirator failure, accidental dislodgment, aspiration, atelectasis and pneumothorax are other avoidable complications. Another problem, related to high mean airway pressures or a prolonged inspiratory phase, is systemic hypotension, usually transient, due to an impaired cardiac venous return. An increased central venous pressure and a reduction in urinary output may be noted. It is particularly hazardous if shock, hypotension or hypovolemia pre-exist and can be corrected by prolonging the expiratory phase and by lowering the peak

ventilator pressure. In some patients with severe airway obstruction, adequate ventilatory volumes requiring high respirator pressures can only be generated at the expense of a temporary reduction in venous return and cardiac output. The final respirator pressure will represent a compromise between circulatory and ventilatory needs at the given moment.

Too rapid reductions in $Paco_2$ (and resulting *alkalosis*) may cause neurologic dysfunction, circulatory collapse and occasionally death (34). Though this point is disputed (35), significant hypercapnia should not be corrected too rapidly and, in general, iatrogenic overventilation should cease at pH levels of 7.30–7.35. A critical reduction in cerebral blood flow as well as a shift of the oxyhemoglobin dissociation curve to the left are possible causative mechanisms of this syndrome.

Prolonged artificial ventilation has been associated with deteriorating pulmonary function in conjunction with characteristic pathologic abnormalities as discussed previously (see section on oxygen toxicity). More recently, another ventilator-related syndrome has been described. Deteriorating pulmonary function is attributed to *abnormal fluid retention* with weight gain. The chest film is compatible with pulmonary edema, and the main physiologic abnormalities include a decreased vital capacity and compliance with a rise in the alveolar-arterial O_2 gradient and V_D/V_T ratio. The speculated mechanisms include relative water overload, subclinical cardiac failure and an increased antidiuretic hormone release. Water restriction and diuretics are effective therapy (10).

Pulmonary superinfection is a frequent problem during artificial ventilation. Preventive measures include sterile, atraumatic technic during endotracheal and tracheostomy care or tracheal suctioning. Additionally, frequent sterilization of equipment, particularly tubing, valves and nebulizers, is mandatory. Sputum and tracheal aspirates should be cultured frequently. If pathogens are present, careful correlation with clinical, laboratory and x-ray parameters will clarify whether antibiotic therapy is required. *Nonspecific complications* noted during the course of controlled ventilation include acute myocardial infarction, cardiac arrhythmias, pulmonary emboli, gram-negative bacteremia, gastric dilatation, acute gastrointestinal hemorrhage and neurologic sequelae (33).

The level of arterial carbon dioxide tension is influenced by the rate of tissue carbon dioxide production and its alveolar clearance to the air:

$$Paco_2 = \frac{\dot{V}co_2 \text{ (tissue production)}}{\dot{V}_A \text{ (alveolar ventilation)}} \times k$$

During acute respiratory failure, a compromised alveolar ventilation produces rapid increases in carbon dioxide concentration throughout the body fluids; this effectively becomes hydrogen ion activity (H^+), i.e., respiratory acidemia,

$$CO_2 + H_2O \xrightarrow[\text{carbonic anhydrase}]{} H_2CO_3 \rightleftharpoons (H^+) + HCO_3$$

These relationships are described by the Henderson-Hasselbalch equation:

$$pHa = pK'a + \log \frac{(HCO_3)\,a}{(H_2CO_3)\,a}$$

where $(H_2CO_3)\,a = 0.03 \times Paco_2$ and where most of the plasma base is $NaHCO_3$. The final blood pH is dependent on the efficiency of many buffer systems including the bicarbonate-carbonic acid pair. Maintaining the relative ratio of

$$\frac{HCO_3}{H_2CO_3} \quad \frac{\text{(kidney)}}{\text{(lungs)}}$$

at approximately 20:1 is the role of body defense mechanisms, including chemical buffering systems. At rest, the normal individual eliminates about 12,500 mEq. of carbonic acid per day through the lungs, but only 50–100 mEq. of acid each day by the kidneys. The concentration of CO_2 (or H_2CO_3) and HCO_3 in the blood can be altered rapidly by changes in ventilation and much more slowly by the kidneys. Inasmuch as the amount of H_2CO_3 is small compared to HCO_3 (1:20), the concentration of H_2CO_3 and the ratio $\left(\frac{HCO_3}{H_2CO_3}\right)$ can be changed quickly by hyper- or hypoventilation. Thus,

intense, respiratory-induced acidemia can develop within brief periods placing demands on the buffering mechanisms.

The defense of pH during respiratory acidosis includes:

1. Blood buffers: hemoglobin, proteins, bicarbonate.
2. Tissue buffers.
3. Renal mechanisms: HCO_3 resorption, acid excretion.

The rise in plasma bicarbonate concentration is separable *temporally* into *acute and chronic phases.* The acute buffering is mediated by blood and tissue defenses and may be viewed as follows:

$$H_2CO_3 + ROH \longrightarrow R^+HCO_3 + H_2O$$

One complex aspect in the management of acute or chronic respiratory acidosis is the delineation of coexisting, complicating *metabolic* acid-base disturbances. Traditional nomograms (Singer and Hastings, Astrup), based on the in-vitro titration of whole blood with carbon dioxide, do not entirely delineate these factors for the *intact* organism. Thus recent studies by Schwartz and others employing the technic of "whole-body" titration curves, whereby the $Paco_2$ is varied and bicarbonate concentration or (H^+) a are measured at the steady state, have established the quantitative, physiologic response to acute hypercapnia or chronic "steady state" hypercapnia in man (36), (37).

The hydrogen-ion activity response to *acute* (< 12 hours) changes in $Paco_2$ is presented in Figure 4. It can be observed that despite the simultaneous generation of bicarbonate and the effect of blood and tissue buffers there is a relatively poor defense of the pH. In contrast, under the stimulus of *chronic* hypercapnia, the renal excretion of acid and the augmented generation of bicarbonate provide for a more effective defense of the *extracellular* pH than by the tissue mechanisms alone (Fig. 4). From such data, it appears that the hydrogen ion activity is *not fully* restored to those concentrations existing in the normocapnic state, despite what seems to be maximal renal compensation. In fact, it has been suggested by Robin *et al.* (38) that the regulatory mechanisms in chronic hypercapnia are not "geared" to maintain a normal *extracellular* pH, but that this compartment would be passively influenced by

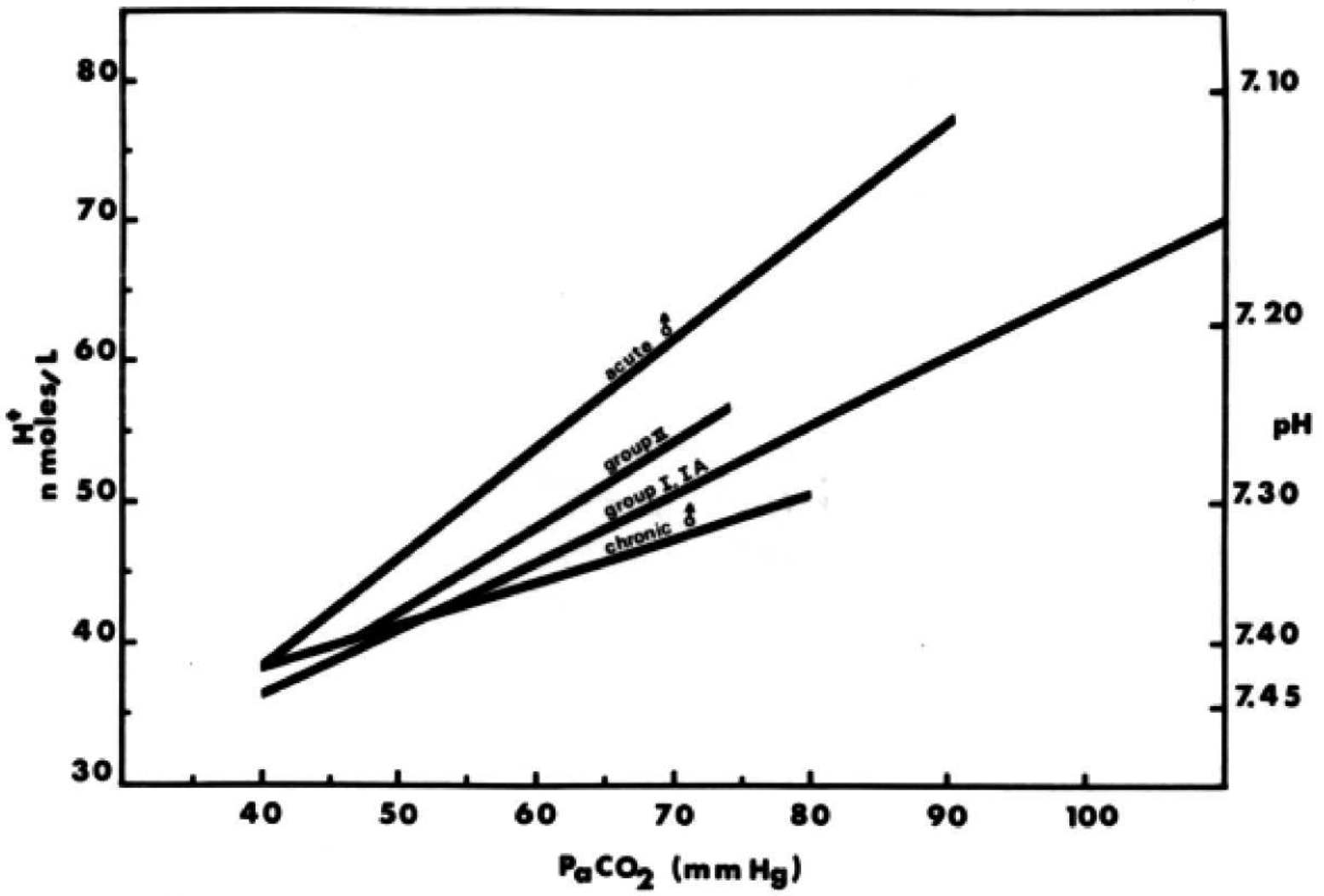


FIG. 4.—Relationship between hydrogen ion concentration and $Paco_2$ during acute hypercapnia in patients with chronic obstructive lung disease (C.O.L.D.). Acute carbon dioxide titration curve is based on the data of Brackett *et al.* (36); chronic line from the data of van Ypersele de Strihou *et al.* (37). Groups I and IA represent the response to acute hypercapnia occurring in C.O.L.D. where stable, chronic $Paco_2$-pH relationships are not defined (group I) and those in whom the stable, chronic $Paco_2$-pH data were known (IA). The duration of the acute CO_2 exposure for groups I and IA was 16–23 hours. Changes in pH to acute alveolar hypoventilation induced by 100% oxygen for 30 minutes in patients with chronic stable hypercapnia are shown by group II. Limits of reported observations are indicated by the lengths of the regression lines. Data suggest that uncomplicated acute hypercapnia *superimposed* on chronic hypercapnia in patients with C.O.L.D. limits the use of prediction bands established for stable state chronic hypercapnia or acute hypercapnia in normal man (39). See text.

the necessity for *intracellular* pH regulation. Such a viewpoint may explain the not infrequent observation of coexisting acidosis or alkalosis during chronic stable hypercapnia presumably unrelated to other specific medical complications.

For the observed linear responses of (H^+) to both pure acute and chronic hypercapnia, 95% confidence bands have been created to facilitate the recognition of complicating metabolic acidosis or alkalosis (Fig. 5). The area included within the significance bands defines the relationships to pure hyper-

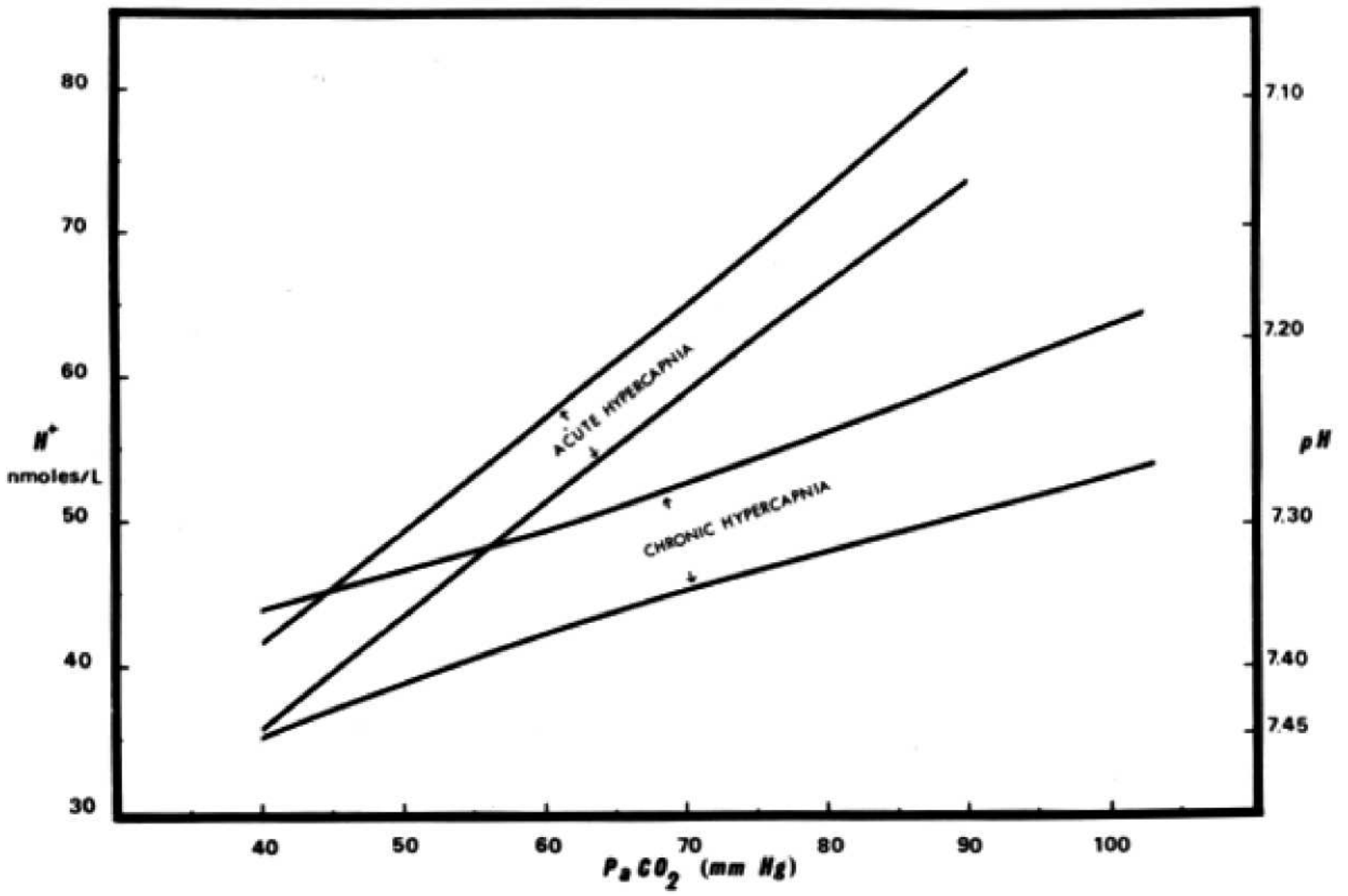


FIG. 5.—Confidence bands for acute hypercapnia in normal man and chronic hypercapnia in chronic obstructive lung disease based on $Paco_2$-hydrogen ion activity relationships (36, 37). In uncomplicated acute or chronic hypercapnia, there is a 95% probability that values of $Paco_2$-pH will fall within the respective band. Any values lying above the appropriate band indicate complicating metabolic acidosis; those falling below the respective band indicate complicating metabolic alkalosis. See text.

capnia, and any $Paco_2$ — (H^+) values situated outside these limits will indicate the existence of a mixed disturbance within a 95% probability. Values above either respective band indicate a coexisting metabolic *acidosis,* while those values below suggest a superimposed metabolic *alkalosis.*

In a strict sense, the recognition of a primary metabolic alkalosis with compensatory respiratory hypoventilation should be detectable by an alkaline pH or, in part, by reconstruction of the clinical events. The hypoventilation response will, of course, be limited by the progressive development of hypoxemia.

Finally, the cited significance-band analysis is subject to a pertinent limitation (39). This is the common clinical problem of a *dynamic, unsteady* state developing in patients with chronic obstructive lung disease and chronic hypercapnia who

manifest *superimposed acute* respiratory acidosis during an episode of superimposed acute respiratory failure. Here steady-state conditions do not necessarily exist and the in-vivo responses to dynamically fluctuating arterial carbon dioxide tensions (due to disease, therapeutic agents or mechanical ventilation) will create pH and HCO_3 relationships, *somewhere in between* the acute and chronic responses (Fig. 4). Based on our observations, the defense of the extracellular pH under these conditions is related not only to tissue buffers but is time-dependent on renal buffering mechanisms. As a result, there could exist infinite, "superimposed" CO_2-titration curves, varying from patient to patient, depending on the extent of CO_2 variation and buffering defense mechanisms. Thus the above-cited confidence prediction bands, established for pure acute hypercapnia in normal man or steady state chronic hypercapnia in man, are not necessarily valid for distinguishing complicating metabolic disorders (39). This concept is important clinically when pure respiratory acidosis must be distinguished from the multiple extrapulmonary metabolic disturbances that these patients are known to exhibit. In these circumstances, interpretation of the acid-base state by nomograms is limited, and reconstruction of clinical events and clinical judgment are necessary for clarification.

Other acid-base disturbances that the physician must be aware of during acute respiratory failure are:

1. Respiratory alkalosis. Endogenous or exogenous hyperventilation by mechanical respirator with uncovering of alkalosis from increased compensatory HCO_3 levels.

The consequences of this acute alkalosis include central nervous system findings, seizures, coma, hypotension, apnea and death. Additionally, the oxygen-dissociation curve is shifted to the left and release of oxygen to the tissues is impaired.

2. Metabolic alkalosis. From chloride or potassium depletion; commonly resulting from dietary restrictions, diuretics, steroids or chloruresis occurring during the development of respiratory acidosis.

3. Metabolic acidosis. Excess (H^+) formation, excess intake, reduced excretion.

The treatment of respiratory acidosis is *primarily* directed to controlling all causes of ventilatory failure. Improvement in

net alveolar ventilation with reduction in $Paco_2$ is the logical and acceptable method of dealing with excess hydrogen ion activity. When *severe* acidosis exists during acute respiratory failure (either pure respiratory or mixed metabolic) and while ventilatory support is being established, exogenous buffers or sodium bicarbonate may be administered; a pH less than 7.20 may be life-threatening, particularly with regard to fatal arrhythmias. With serial pH measurements to clarify an end point in the range of pH = 7.25–7.30 intravenous infusion of 90–135 mEq. of $NaHCO_3$ will temper the acidosis and permit time for supportive ventilatory measures to become effective. Although we prefer $NaHCO_3$, sodium-free THAM (tris [hydroxymethyl] aminomethane) can be employed where Na^+ restriction is mandatory; it, however, may depress respiration, causing further hypoxemia and acidosis in some patients.

Finally, since potassium or chloride depletion is common during the stage of acidosis (compounded by the use of corticosteroids, diuretics, gastric suctioning), the recovery phase is frequently associated with a persistent hypochloremia and/or hypokalemic alkalosis; this requires proper electrolyte replacement, particularly potassium chloride for the correction of hypokalemia and hypokalemic alkalosis (40).

Bronchodilators

While bronchodilator drugs are basic to the management of bronchial asthma, they may also be of significant benefit in the bronchitis-emphysema complex when reversible airway obstruction exists. In principle, they reduce airway obstruction, thereby improving gas distribution and alveolar ventilation, and in some measure diminishing excessive respiratory work. Simultaneously, the regional distribution of aerosolized medications to previously obstructed zones is enhanced. Since cardiovascular and other systemic side effects are common, their use necessitates a knowledge of their indications, mechanisms of action and potential complications.

Aminophylline

The therapeutic effects of aminophylline (81% theophylline, 14% ethylenediamine) are generally related to plasma

levels of its active component, theophylline. This xanthine derivative exhibits a marked bronchodilator action as seen clinically and documented by pulmonary function tests. It is important to realize that airway obstruction is not necessarily "fixed" in patients with chronic obstructive lung disease and that in some instances airway resistance and respiratory work can be reduced with bronchodilators (41). In the presence of pulmonary hypertension, aminophylline may cause dilatation of the pulmonary vascular bed, an increased cardiac index and reduced right ventricular end-diastolic pressure and work; heart failure may be further relieved by its diuretic action (14). In some cases, aminophylline increases minute and alveolar ventilation, and may partially restore respiratory center sensitivity to carbon dioxide (42).

In acute situations, 250–500 mg. intravenous aminophylline is administered *very slowly* over a 10–15-minute period, since cardiac arrest and fatalities have been associated with rapid intravenous injection (43). This is followed by the continuous infusion of 250–750 mg. aminophylline per liter of 5% D/W at 20 to 30 drops per minute. We prefer not to exceed 1.5–2.0 Gm. per day. Caution is necessary in hypotensive states, with cardiac irritability and in recent myocardial infarction. *The exact dosage should be tailored to the clinical situation* with regard to the patient's age and weight and possible side reactions. Relief is immediate and prolonged in some individuals, whereas others will require repeated or continuous infusion. Aminophylline, in similar doses, may be given rectally as a retention enema when the patient has improved sufficiently to omit the intravenous route. Oral preparations or rectal suppositories are not recommended except for maintenance therapy. Clinically significant reactions include nausea, vomiting, gastrointestinal distress, local tissue irritation, diaphoresis, tachycardia, arrhythmias, seizures, severe agitation, and rarely hypotension or shock and cardiac arrest. Allergic reactions have not been documented to date.

It has been demonstrated by Daly and Howard that arterial hypoxemia may be induced in *some* patients with stable chronic bronchitis following the intravenous administration of aminophylline (44). The physiologic explanation for this is either an increase in dead space ventilation ($\uparrow \dot{V}_D/\dot{V}_E$) and/or

an increase in pulmonary capillary blood flow to underventilated lung regions. However, these individuals usually show improvement in ventilatory function tests and subjective relief of dyspnea. The generally small reductions (2–10 mm. Hg) in arterial oxygen tensions are not a contraindication to the use of aminophylline or other bronchodilators. Their beneficial effects may be noteworthy, and any fall in Pao_2 is easily treated by enriching the inspired air with oxygen.

Adrenergic Drugs

The mechanism of action of adrenergic drugs is the stimulation of specific (alpha and beta receptor) effector cell sites. Epinephrine is both an alpha and beta receptor stimulator while isoproterenol is a powerful, pure stimulant of beta receptors in the heart, peripheral vasculature, smooth muscles of bronchi and other organs. In the patient with acute respiratory failure, these agents may be beneficial in alleviating regional airway obstruction. Isoproterenol is best administered as an aerosol, since the parenteral route accentuates its side effects and toxic reactions (14).

The use of epinephrine is limited unless significant bronchoreactivity exists. Its therapeutic value is related to a bronchial decongestant and bronchodilatory action. Precautions are necessary in cardiac, hypertensive, hyperthyroid or cerebrovascular-risk patients. Arrhythmias can develop, particularly in those with significant hypoxemia or coexisting cardiac disease, and may cause unexpected death. The intravenous route is contraindicated since it may create a hypertensive crisis or cerebral hemorrhage (14). Aerosols of racemic epinephrine solution (2.25% Vaponefrin) are generated by hand-bulb, inert propellant, compressed air or oxygen, or side-arm ventilator nebulizers in doses of 0.2–0.5 ml. with 2.0 ml. saline. Epinephrine refractoriness has been reported in asthmatic patients as a result of repeated use (usually after 2–3 days), and is possibly related to a coexistent acidosis. Correction of pH may restore responsiveness (45).

An important property of isoproterenol (Isuprel) is its bronchodilator effect. Significant improvement of the $FEV_{1.0}\%$ after aerosolized isoproterenol may occur in patients

with chronic obstructive lung disease; the peak effect occurs approximately 30 minutes after inhalation, and the total duration of activity extends for several hours (46). Systemic absorption of isoproterenol may invoke its myocardial inotropic effect and improve the cardiac index (47). Additionally, active dilatation of the pulmonary arteries and veins decreases pulmonary vascular resistance and increases capillary conductance and volume (48). For nebulization, 0.5 ml. (or less) of a 1:200 solution is diluted to 2.0 ml. with saline or sterile water, and prescribed four to six times per day. The *smallest* dose affording relief is selected. Aerosol isoproterenol is administered by the same methods described for epinephrine. If required, the nebulizer of the respirator can be employed for those patients with an endotracheal or tracheostomy tube.

Precautions, as stated for epinephrine, should be observed. Side effects are attributed to excessive systemic absorption and include dizziness, sinus tachycardia, anxiety, angina pectoris and palpitations. The excessive use of adrenergic agents has been implicated as a cause of sudden death in asthmatic patients (49). They should be used cautiously, with electrocardiographic monitoring if administered repeatedly. Hypoxemia has been reported with the use of isoproterenol in patients with chronic bronchitis (50), presumably by mechanisms similar to those described for aminophylline; it is also corrected by the administration of oxygen. In some patients, isoproterenol or epinephrine can cause *hyperventilation* by central nervous system stimulation and a net increase in alveolar ventilation. Finally, since a few asthmatic patients apparently develop further airway obstruction following isoproterenol, this phenomenon should be considered in refractory cases (51).

Adrenal Corticosteroids

The beneficial therapeutic action of adrenal corticosteroids in acute respiratory failure associated with chronic obstructive lung disease has not been proved. While these steroids are accepted for use in bronchial asthma or asthmatic bronchitis, controlled studies (52) have shown no beneficial effects in pulmonary emphysema, presumably because of the characteristic irreversible structural changes. Yet, acute and chronic

bronchitis with hypersecretion of mucus, vascular congestion, inflammation and bronchial mucosal edema, as well as widespread bronchiolitis, provide a rationale for their use. Furthermore, adrenal corticosteroids will inhibit inflammatory responses, whether the inciting agent is chemical, immunologic or mechanical (14). In a recent uncontrolled study, with 4 mg. of betamethasone q.d. in stable chronic bronchitis, some improvement in the forced vital capacity, arterial O_2 tension and venous admixture effect was observed (53).

While conclusive evidence is lacking, exogenous adrenal corticosteroids may be considered: (1) when an asthmatic component is present, as ascertained by allergic or asthmatic history, sputum or blood eosinophilia (> 250 eosinophils/mm.^{3}), or established bronchoreactivity; (2) in the presence of high volumes of mucoid secretions; (3) in the presence of chronic steroid therapy or if relative adrenal insufficiency is suspect, and (4) *empirically,* if the patient is deteriorating and all other bronchodilator measures have failed, particularly if a prior response has been favorable.

An initial dose of 40 to 80 mg. of intravenous methylprednisolone (Solu-Medrol) or its equivalent is given immediately, followed by approximately 50–150 mg. over the subsequent 24 hours. Such doses and duration of administration are arbitrary and should be the least necessary to obtain a therapeutic result. A working laboratory guide to the biologic effectiveness of adrenal corticosteroids, if present, is eosinopenia; an effective dose should produce total eosinophil counts of 100/mm.^{3} or less, with larger numbers suggesting increased corticosteroid requirements. Following improvement, these drugs are tapered; specific recommendations for withdrawal have been reviewed by Thorn (54). ACTH has been employed to restimulate the adrenal cortex during this phase. If prolonged steroid therapy is necessary, the use of oral corticosteroids on alternate days, administered in the early morning, may reduce undesirable side effects, such as intensification of diabetes mellitus, hypokalemia, progressive osteoporosis, psychosis, fluid retention, hypertension, risk of infections, spread of a tuberculous process and other steroid stigmata. Since 25% of patients with obstructive lung disease have peptic ulceration, they may, consequently, be particularly at risk to develop

hemorrhage of the gastrointestinal tract on steroid therapy.

The use of supplemental potassium (liquid KCl), the regulation of sodium and water intake, adequate protein diet, antacid therapy, the monitoring of blood sugar and electrolytes and bone films will aid in management, particularly with chronic steroid therapy.

Until better data are available, we must emphasize that unless specific indications are present in the select case, the decision to employ exogenous adrenal corticosteroids is empirical, and careful observation is necessary thereafter.

Analeptics

The place for analeptics in the treatment of acute respiratory failure in airway obstructive disorders is controversial. The rationale for their use is a temporary improvement in mental alertness and alveolar ventilation. The ideal respiratory stimulant, yet to be provided, should produce maximum alveolar ventilation with minimum thoracic work and be free of significant central nervous system complications (e.g., seizures). The overlap of therapeutic and toxic levels, the variability of response, the transient effect of a single intravenous dose, the increased work of breathing during hyperventilation with a possible increased cost of dissipating CO_2, and the variable seizure threshold are all considerations in the use of respiratory stimulants (55). They do *not* supplant other, more basic, measures.

Acetazolamide (Diamox) and dichlorphenamide (Daranide) are carbonic anhydrase inhibitors; it is not known whether these agents act directly on the central nervous system or indirectly by the development of a metabolic acidosis. Results with these drugs have been disappointing, primarily because of their relative ineffectiveness (55).

Some xanthine derivatives, notably aminophylline, have a central stimulating action, and a 250 mg. intravenous dose of this drug will increase both minute and alveolar ventilation. Picrotoxin and related agents have a low stimulant/convulsant ratio and currently are not recommended.

Nikethamide (Coramine), vanillic acid diethylamide (Emivan) and doxapram hydrochloride (Dopram) are the more

common direct CNS stimulants available. After a single intravenous dose, a small transient increase in minute ventilation develops, peaking in a few minutes and rapidly decreasing to preinjection levels in 10–40 minutes. This results from increases in tidal volume, although it is occasionally related to a more rapid respiratory rate.

The rise in total ventilation may improve alveolar ventilation and consequently lead to an increased carbon dioxide excretion. Often, however, the ratio of $\dot{V}_A/\dot{V}_E$ does not improve, indicating no change in the efficiency of ventilation. Dulfano and Segal, employing nikethamide, observed an acute decrease in arterial P_{CO_2} in 13 of 15 chronic bronchitics with hypercapnia (56); other investigators have reported more variable results (55). Side effects suggesting or indicating an endpoint include severe tachycardia, hypertension, tremor, muscle twitching, psychic excitation, itching about the nose, vomiting, hallucinations and convulsions. Too rapid administration may cause apnea or other serious side reactions (57).

In selected circumstances, analeptics may be employed. Slow intravenous administration, careful clinical observation and physiologic monitoring are required. For example, initially we slowly inject 5–10 ml. of nikethamide directly intravenously; if indicated, this may be followed by an intravenous drip of 20 ml. in 300–400 ml. of 5% D/W over an extended period. The administration to seizure-prone and alcoholic patients requires great caution. These agents may be helpful when acute alveolar hypoventilation develops from sedatives, narcotics, oxygen administration or idiopathic respiratory arrest. These precarious situations may be of brief duration, and the temporary respiratory stimulation with analeptics may obviate more heroic measures. On rare occasions, the use of an analeptic may obviate a tracheostomy and mechanical ventilation; it may also be employed for transient stimulation while these measures are being instituted.

End-organ response is a key problem: inefficient respiratory work against high airway resistance, manifested by excessive oxygen uptake, is often an undesirable consequence of these drugs. Thus bronchodilators should be administered concurrently to reduce airway resistance, unless aminophylline is the

chosen analeptic. Concomitant oxygen administration will help alleviate any increased thoracic muscular oxygen requirement.

Sedatives

While sedatives may be of some value in the anxious patient without hypercapnia, they are not routinely recommended in acute respiratory failure. Many patients with acidemia in the range of pH 7.20 are poorly responsive or comatose and, in fact, narcotized. It must be appreciated that the concomitant decrease in breath sounds in such patients may indicate poor ventilation and significant lodging of secretions. The injudicious use of these drugs (morphine, meperidine, barbiturates, tranquilizers) is *frequently* the precipitating factor in this entity. When alveolar hypoventilation is present, sensitivity to even the smallest dose of tranquilizers or narcotics may exist. Any of these drugs may potentially depress the medullary control centers, and they should be generally avoided where chronic hypercapnia exists or during acute ventilatory failure (57). Additionally, by causing shallow respiration, they will inhibit the normal sighing phenomenon necessary to re-expand collapsed alveolar groups.

Under controlled conditions, however, with arterial blood gas monitoring, cautious sedation may be of benefit in the anxious or agitated patient. We have found chlordiazepoxide (Librium), Valium or meperidine useful for this purpose. Proper sedation is often necessary during the establishment and maintenance of intubation or mechanical respiration, particularly controlled ventilation (see section on ventilation). Finally, "cough syrup" preparations containing narcotics, or antihistamines and tranquilizers with potentially adverse anticholingic properties (producing dry, thick secretions), should be avoided.

Polycythemia

An increase in red blood cell mass associated with obstructive airway disease is a complex, but fundamental, response. The diagnosis is established by an increased red cell mass, employing the ^{51}Cr-labeled red cell technic; the hematocrit

alone is suggestive, but it is an unreliable test since the associated plasma volume is often variable (58). Dehydration, polycythemia rubra vera and other secondary polycythemias must be excluded. The hallmark of polycythemia secondary to lung disease is hypoxemia, with the arterial Po_2 usually less than 65 mm. Hg (59). Hypoxemia may also exist in the other polycythemias, but is seldom as severe ($Pao_2 > 65$ mm. Hg), with the obvious exception of cyanotic congenital heart disease. Unfortunately, overlaps in arterial oxygen tension do occur, and clinical judgment and confirmatory laboratory data are necessary.

The etiology of the polycythemia secondary to bronchitis and emphysema is not entirely clear. Arterial hypoxemia is probably a major factor, since the red cell mass increase is proportional to the decrease in arterial oxygen saturation (58). It is believed that tissue hypoxia stimulates erythropoiesis primarily through renal erythropoietin release. Previous studies of erythropoietin levels have revealed variable results, but newer methods may clarify this issue (60). In patients with a deficient response, severe infection, iron deficiency or undefined factors may be responsible.

The functional consequences of polycythemia are complex. An elevated hemoglobin concentration improves the oxygen-carrying capacity of the blood and may temper pulmonary-induced hypoxemia. On the other hand, a rising red cell concentration promotes red cell aggregation and therefore increases the blood viscosity. Additionally, acidosis creates internal rigidity of the red cells, and bronchopulmonary infection tends to increase their aggregation. These blood rheologic factors are particularly adverse where the red cell mass exceeds 60 vol.%. Thus during acute respiratory failure, as viscosity rises, peripheral vascular resistance increases, cardiac output may fall, flow through the microcirculation (alveolar capillary and tissue) is diminished and eventually tissue oxygen delivery declines, despite an elevated oxygen-carrying capacity.

Circulatory *improvement* has been observed in severe polycythemia following hemodilution. Similarly, it has been demonstrated that a *simultaneous* increase in both blood volume and red cell concentration (hematocrit) increases rather than diminishes cardiac output and tissue oxygen transport. The

presence of an expanded plasma volume, therefore, offsets the sludging effects of a high red cell concentration and to some extent is beneficial. On the other hand, this hypervolemia potentially contributes to pulmonary hypertension as well as to overt cardiac failure and various clinical symptoms; in these instances venesection is beneficial (61). While these concepts are didactically clear, the optimal clinical moment for a beneficial venesection is less precise.

Nevertheless, with an exceptionally high hematocrit (65–70 vol.%), judicious phlebotomy may limit adverse viscosity effects and volume overload in association with overt cardiac failure. We perform this slowly, 250–500 ml. at a time, while carefully observing the patient and his laboratory parameters until the hematocrit is 55–60 volumes per cent, providing volume depletion is not a consideration.

Cor Pulmonale

DEFINITION.—Cor pulmonale is a cardiopulmonary entity in which there is *hypertrophy* or *dilatation* of the right ventricle, with or without heart failure; it is the consequence of parenchymal and/or vascular disease of the lung with pulmonary hypertension as an essential factor in its evolution. The interplay of hypoxemia, pulmonary hypertension, hypervolemia and altered cardiovascular dynamics influences the development of the syndrome, but it is unclear why heart failure develops only in some patients. In urban America, the most common cause of this entity is acute and chronic obstructive pulmonary disease (62). Cor pulmonale has many facets, with its clinical course reflecting primarily the progression of the underlying pulmonary disorder. Considerable physiologic derangement may precede any clinical evidence of cardiac failure, however; this fact has important therapeutic significance.

PATHOLOGY.—A definitive diagnosis of cor pulmonale is made only at necropsy. Reliable pathologic guides to right ventricular hypertrophy include a right ventricular anterior wall thickness of 6 mm. or greater, a right ventricular wall weight of more than 75 Gm., and a reduced ratio of the weight of the left ventricle and interventricular septum to the right ventri-

cle (LV+S/RV) (63). Evidence of the primary pulmonary disease is also found; also, pulmonary arteriolar intimal thickening and muscularization are common, and significant reduction in the capillary bed may be present. The extent of anatomic emphysema does not necessarily correlate with the degree of right ventricular hypertrophy and/or dilatation (64).

Hemodynamics

Pulmonary hypertension, presenting an increased resistance to pulmonary blood flow, is the initial derangement leading to right ventricular hypertrophy. While there are multiple mechanisms contributing to this hypertension, the critical vessel radius and blood viscosity properties are undoubtedly the major limiting features. Factors responsible for the pulmonary hypertension include anatomic and functional considerations:

1. *Significant anatomic reduction* in the pulmonary vascular bed occurs when it has been at least 50% obliterated; lesser reductions appear less critical because of pulmonary vascular reserve capacity.
2. *Hypoxemia* and *acidemia* alone may cause reversible pulmonary vasoconstriction; a synergistic relationship exists between them, so that for a given arterial oxygen saturation a greater pulmonary artery pressure elevation occurs with concomitant acidosis (65).
3. *Pulmonary blood vessel compression* may result from elevated alveolar, intrathoracic (66) or perivascular interstitial pressures; the magnitude of the effect of these factors is unknown.
4. *Increased blood viscosity* (due to polycythemia) and *elevation of the total blood volume* (67) aggravate pulmonary hypertension and increase right ventricular work. Augmented pulmonary arterial blood flow does not seem to be a major factor in the genesis of pulmonary hypertension (68).

There is often an intervening period between the progression of lung disease and obvious hemodynamic deterioration. When cardiac failure is *absent* in chronic cor pulmonale, hypoxemia with *normocapnia* is usually present. A moderate pulmonary artery pressure elevation occurs, but the right ventricular end-diastolic pressure remains normal, and the variable (but usually normal) cardiac output increases appropriately with exercise. In contrast, when cardiac failure becomes *overt,* the arterial hypoxemia is more severe and respiratory

acidosis is usually manifest. The resting pulmonary artery pressure is elevated further, and the right ventricular end-diastolic pressure is now raised. A normal, but variable, resting cardiac output responds poorly to exercise. If low, the resting cardiac output may increase following treatment; a previously high cardiac output, however, may actually fall as the patient's heart failure improves (65).

Advanced hypoxemia is a direct myocardial depressant. Coronary vasodilatation, by increasing blood flow, compensates for most levels of hypoxemia; a *severely* reduced Pao_2 and/or concomitant coronary vascular disease can result in anaerobic myocardial metabolism, with lactic acid production. Concurrent acidemia further depresses the myocardium, resulting in even greater diminution of ventricular performance. Chronic hypoxemia may lead to myocardial dilatation, hypertrophy and possibly ultimately to myocardial fibrosis.

Diagnosis and Clinical Findings

Cor pulmonale is frequent and obvious in patients with chronic bronchitis (BB type), but is a late and ominous development in the course of relatively pure emphysema (PP type). Signs of right heart failure may dominate the clinical picture in these patients and overshadow the complaint of dyspnea, especially in the BB-type patient. Exacerbations of bronchitis (often with mild symptoms) frequently herald the development of heart failure. Cardiac examination may reveal a forceful systolic subxiphoid impulse, a loud pulmonic closure sound and wide splitting of the second sound. Additional findings are an early diastolic (Graham Steell) murmur of pulmonary valve regurgitation, a prominent jugular venous "a" wave, a systolic ejection click due to pulmonary hypertension and a right atrial fourth heart sound (S_4). Heart failure is associated with signs of venous hypertension, including distended neck veins, hepatomegaly, edema, ascites, ventricular gallop and a low parasternal holosystolic murmur accentuated on inspiration. The reader is referred elsewhere for details of radiographic and electrocardiographic findings (69, 70).

Left Ventricular Failure

Although associated left ventricular hypertrophy has occasionally been found at necropsy, classically, left ventricular failure has not been recognized as a significant component of cor pulmonale. In fact, postmortem studies have suggested a lesser incidence of myocardial infarction in patients with pulmonary emphysema, presumably due to augmented coronary collateral circulation (71). More recently, however, evidence has been accumulating to show that left ventricular involvement does occur in obstructive lung disease with cor pulmonale. Many of the signs of left ventricular failure may be masked by the underlying lung disease (72), but cardiac catheterization demonstrates elevations of the pulmonary wedge, left atrial and left ventricular end-diastolic pressures. The left ventricular failure probably results from multiple etiologic factors which include myocardial hypoxia, hypercapnia, acidosis, high output state, bronchopulmonary vascular anastomoses and right ventricular failure altering left ventricular function. Thus in some cases cor pulmonale can be viewed as a generalized cardiomyopathy, with severe left ventricular failure occasionally presenting as the dominant clinical pattern. How commonly this complication occurs is unknown, but its presence should be strongly suspected.

Prognosis and Complications

It should be emphasized that the long-term outlook for the patient with cor pulmonale depends largely on the course of his underlying pulmonary disease (73); several years of survival may occur after the initial episode of right ventricular failure if the exacerbations and/or progression of the pulmonary disease are limited (74). There seem to be some prognostic correlations with the degree of ventilatory function or blood gas abnormalities, the severity of the dypsnea, the occurrence of congestive heart failure, the development of weight loss and residence at an altitude greater than 4,000 feet above sea level (75). Still in all, not all factors influencing the rate of progression are known, and individual variability is significant; because of this, dogmatic pronouncements about life expectancy

in any single patient are unwarranted. The causes of death in cor pulmonale have received little attention, but the acute insult leading to ventilatory failure is undoubtedly critical; not infrequently, overwhelming infections, digitalis intoxication with cardiac arrhythmias, gastrointestinal hemorrhage, multiple pulmonary emboli or large pulmonary artery thromboses are implicated.

Treatment

Awareness that the pulmonary disease is the major pathophysiologic derangement in cor pulmonale dictates the basic therapeutic approach. The prime goals of treatment are reversal of hypoxemia, improvement in alveolar ventilation and acidemia with reduction in pulmonary hypertension. Particularly significant is the *reversible* pulmonary vascular obstruction that coexists with the anatomic destruction of the basic disease. Treatment of the cardiac failure with digitalization and diuretics, reduction in blood viscosity, control of life-threatening arrhythmias and support of adequate tissue perfusion are other major considerations. Since pulmonary embolism or thrombosis de novo are significant contributory features, they should be suspected in all cases and treated where indicated (76).

While digitalis is an established drug in the treatment of left ventricular congestive heart failure, its therapeutic value in cor pulmonale has been questioned (77). Theoretically, further augmentation of a normal or increased cardiac output by increasing pulmonary blood flow against a fixed pulmonary vascular resistance limits the rationale for its use; other considerations include total body potassium depletion related to chronic acidosis, hypoxemia and the high frequency of digitalis toxicity (73). Clearly, however, where pertinent atrial arrhythmias or accompanying left ventricular failure exist, digitalis may be beneficial. In any event, the *cautious* use of short-acting digitalis preparations is recommended, preferably after correction of the acidemia, and with continuous oxygenation and attention to electrolyte balance. Diuretics may be effective in the treatment of edema, hypervolemia and the restoration of sodium and water balance; fluid and sodium restrictions are enforced

when necessary. Central venous catheter monitoring may aid in these considerations. The adverse effect of severe polycythemia (hematocrit over 60%) on blood rheology and right ventricular work necessitates careful and discriminant venesection.

Complications

The course of acute respiratory failure is frequently stormy and marked by unsuspected complications and death. These may be related to the therapeutic hazards discussed in each preceding section. The mortality rate remains high (up to 60%), due primarily to the serious nature of the underlying disorder, the acute pathophysiologic insults, and the host of pulmonary and extrapulmonary complications that may occur during the patient's management. The presence of a complication must be seriously considered when the patient is not making satisfactory progress or suddenly deteriorates. The complications we have observed are listed in Table 2.

Prognosis

Information documenting the long-term prognosis of patients with chronic obstructive lung disease following an episode of acute respiratory failure is still incomplete. In some recent studies, the survival varied from 54% in 3 years (78) to only 20% over a 30-month period (79) to 10% in 5 years (80). In contrast, chronic survival data as reported by Burrows and Earle conclude that chronic obstructive lung disease is a slowly progressive disorder, relatively uninfluenced by conservative medical therapy, with a 47% over-all mortality during a 5-year period (81). Clearly all such observations must relate to the age and general medical status of the patient, degree of physiologic impairment, severity of recurrent episodes of ventilatory failure, extent of respiratory care, and the establishment of well-controlled groups for comparative data.

Over-all, certain factors are considered to adversely influence survival both for the acute and long-term phases. These include older age; early onset of disease; coexisting medical disorders with their therapeutic complications; significant reduction in vital capacity and airflow parameters; advanced

TABLE 2.—Complications during Acute Respiratory Failure in Chronic Obstructive Lung Disease

Acid-Base, Electrolyte Disturbances
Respiratory acidosis with metabolic alkalosis or metabolic acidosis (less common)
Hyponatremia, hypokalemia, hypochloremia

Cardiovascular
Pulmonary emboli, shock, myocardial infarction, heart failure
Arrhythmias, including digitalis toxicity, cardiac arrest

Central Nervous System
Personality change, psychosis
Cerebral vascular insufficiency, seizures, coma

Iatrogenic
Endotracheal tube: unilateral intubation, dislodgment, laryngeal edema
Tracheostomy: bleeding, necrosis, infection, tracheal stenosis
Suctioning: damage, stasis and accumulation of secretions
Ventilators: hyperventilation (alkalosis), hypoventilation, hypotension
Oxygen: toxicity or hypoxemia
Inhalation equipment: infection, overhydration and underhydration (also parenteral), failure to humidify the inspired air
Antibiotics: superinfection with Staphylococci, gram-negative organisms
Intravenous tubing: bacteremia

Common Drug-Related Manifestations
Bronchospasm: with N-acetylcysteine
Respiratory center depression: with narcotics, sedatives, uncontrolled O_2 administration
Hypotension or seizures: aminophylline or analeptics

Miscellaneous
Gastrointestinal bleeding, liver cell necrosis
Renal failure, oliguria
Aspiration pneumonia

hypoxemia, hypercapnia and respiratory acidemia reflecting progressive impairment of gas exchange; coexisting cor pulmonale; significant anemia; possibly advanced erythrocytosis; obesity; and advanced pulmonary emphysema often associated with appreciable weight loss. Asmundsson and Kilburn have recently observed a high death rate in the initial 30 months following the first episode of respiratory failure in patients whose follow-up care was considered not optimal. Mortality

thereafter approached the death rate for a male population at large of similar age (79). While the factors characterizing this higher risk period are unclear at present, particularly careful observation during this, as well as all other phases, may be rewarding.

On the other hand, a uniformly poor prognosis is not necessarily inevitable, and the long-term benefits of intensive pulmonary care and rehabilitation in patients with chronic obstructive lung disease, with or without intercurrent acute respiratory failure, are still to be delineated. The recent, short-term studies by Petty *et al.* (82, 83) suggest that continuous low-flow oxygen administration and a comprehensive pulmonary care program may delay functional deterioration in the chronic phase. In any case, total supportive care will provide symptomatic relief and significant improvement in exercise tolerance to many patients. Further follow-up studies should clarify the effects of therapeutic agents and mechanical aids on the natural course of chronic obstructive lung disease. Finally, we return to the concept that since absolute survival, for a *given* patient with acute respiratory failure, is undefinable at any period, a comprehensive and intensive therapeutic program as outlined in this monograph must be instituted immediately as the initial approach to this common medical problem.

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