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Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

PART I: PATHOPHYSIOLOGY

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Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

PART I: PATHOPHYSIOLOGY

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PART II: *Treatment* will be published as the November issue.

and the severity and nature of the precipitating illness. For example, Jessen *et al.* have recently correlated 1-year survivals after respiratory failure with prior physical status: there was 60% survival in those capable of some work, with a 10% survival in those severely disabled (1).

It is often impossible to *predict* which patients will survive. Additionally, it is generally accepted that early diagnosis and appropriate therapy may restore such individuals to their preexisting levels of health. Thus, a pessimistic attitude is *unwarranted,* and it becomes *mandatory* to rapidly establish and maintain the support appropriate for all patients precipitated into acute respiratory failure. This key medical emergency therefore demands:

1. An awareness of the often subtle precipitating features, the reversible aspects and the complicated clinical course.
2. A reasonable understanding of the pathophysiologic processes leading to acute respiratory failure.
3. Practical diagnostic standards of acute respiratory failure.
4. Therapeutic intervention based on the above, founded on the established pharmacology of pertinent drugs and the effectiveness of mechanical devices.

This presentation will emphasize these considerations in patients with chronic bronchitis and chronic pulmonary emphysema. The principles apply as well to other obstructive lung diseases or other conditions leading to acute respiratory failure (2). The reader is referred to a recent review of status asthmaticus by our group (3).

Definition of Respiratory Failure

In the normal human lung, a remarkable series of integrated functions provide for the proper gas exchange commensurate with cellular metabolic requirements. Thoracic mechanical activity provides the energy to transfer over 300 liters of oxygen from the air to blood and to eliminate 240 liters of carbon dioxide every 24 hours. This requires a homogeneous gas distribution to 350 million alveoli, effective alveolar ventilation ($\dot{V}_A$), normal diffusion, adequate alveolar capillary perfusion ($\dot{Q}_C$) (flow, volume and distribution) as well as the appropriate matching of ventilation to perfusion ($\dot{V}A/\dot{Q}C$).

The clinical diagnosis of obstructive lung disease rests on a complete evaluation of the historical, physical, cytologic, radiologic and physiologic findings. Pulmonary function tests, which assist in the diagnosis and which assess the extent of the disease and functional reserve, are often of limited value in acute respiratory failure because of limited patient co-operation and technical factors. In addition, the forced expiratory volume (FEV) and indices of airway resistance are relatively insensitive to early changes in the small airways. Nevertheless, when baseline spirometry and arterial blood gas (and pH) are available prior to or following an episode of decompensation, they may be useful guides to pulmonary functional reserve and prognosis. For example, in a recent cooperative Veterans Administration study, a mortality rate of 26% was observed at 4 years when the $FEV_{1.0}$ (see footnotes to Table 1) was > 1.49 liters, with only 11% survival at 4 years, when the $FEV_{1.0}$ was < 0.5 liters (3). In general, a falling $FEV_{1.0}$ is related to a rising P_aCO_2. However, this relationship is not necessarily linear, is limited by the accuracy of available methods, is not observed in all patients, and may depend on the state of respiratory center sensitivity (5).

It may seem merely clinically convenient to measure the arterial tensions of oxygen ($Pa{O_2}$), carbon dioxide ($Pa{CO_2}$) and arterial pH (pH_a) as indicators of respiratory function. The arterial blood does, in fact, *reflect* the *net* effect of all processes leading to proper or improper gas exchange, even though these important parameters are not delineated. The exact level of blood gases at which respiratory failure exists is *arbitrary,* and the individual tolerances are variable. Any definition, however, should be relative to the adverse physiologic and cellular metabolic effects of hypoxia, hypercapnia and acidosis. Based on available information, tissue hypoxic damage occurs when the $Pa{O_2}$ is approximately 30 mm. Hg (arterial saturation 50%) (6). When the $Pa{O_2}$ falls below 65 mm. Hg, the decrease in O_2 content delivered to the tissues must be met by a higher cardiac output, increased hemoglobin concentration and greater tissue oxygen extraction. Hypercapnia per se is less dangerous and is so only when body buffers become limited and the pH_a acutely approaches values less than 7.20–7.25. A patient with a chronic hypercapnia of 45 mm. Hg and a near normal pH_a may be *clinically well.* Yet, this arterial Pa_{CO_2} value does reflect a minor *degree* of alveolar ventilatory failure [alveolar ventilation ($\dot{V}_A$)].

$$\dot{V}_A = K \times \frac{\dot{V}_{CO_2}\ \text{(carbon dioxide excretion per unit time)}}{P_{ACO_2}\ \text{(alveolar carbon dioxide tension)}}$$

Since carbon dioxide production is usually constant, and assuming that alveolar P_{CO_2} approximates the arterial Pa_{CO_2}, then "effective" $\dot{V}_A$ is inversely proportional to Pa_{CO_2}. Thus, if the normal Pa_{CO_2} is 40 mm. Hg, a value of 45 mm. Hg must reflect a proportionate decrease in effective alveolar ventilation.

There are two major mechanisms responsible for impaired gas exchange in the obstructive lung diseases. The first, ventilation-perfusion imbalance, initially produces hypoxemia, and carbon dioxide retention develops as a consequence of advancing disease. Generalized or global alveolar hypoventilation is the second process and results in hypoxemia and hypercapnia together. In many instances, both mechanisms coexist (see section on physiology).

Patients with obstructive lung disease manifest a *spectrum* of abnormalities ranging from mild hypoxemia alone to severe hypoxemia with hypercapnia and respiratory acidosis. The onset of these alterations may be acute, subacute or chronic in nature. Despite certain limitations, and in the clinical context, a useful but arbitrary definition of acute respiratory failure is an arterial oxygen tension less than 60 mm. Hg (while breathing room air), and an arterial carbon dioxide tension greater than 50 mm. Hg (with appropriate pH_a change). If these findings progress acutely, we specify *acute respiratory failure.* Where the arterial blood gas and pH changes develop slowly, a stable state of *chronic respiratory failure* is present; it is important to recognize that a patient in this state is potentially subject to *superimposed,* acute respiratory failure. Early in airway obstructive disease, only minor changes in the arterial blood gases and pH may exist, because of the pulmonary reserve and the augmented respiratory work. *Respiratory insufficiency* is present when the arterial oxygen tension is mildly reduced; *exercise* intensifies this reduction and/or causes

TABLE 1.—CLASSIFICATION OF SEVERITY OF RESPIRATORY DISEASE

THE SEVERITY OF THE DISEASE	PERTINENT FINDINGS
Respiratory Impairment	Asymptomatic or mild symptoms.
	Objective evidence of airway obstruction: increased Ra, normal or mildly reduced FVC, $FEV_{1.0}$ and MBC* to 70% of predicted. Pa_{O_2} normal or reduced to 65–80 mm. Hg Pa_{CO_2} normal or decreased.
	Arterial pH normal, or mild respiratory alkalosis.
Respiratory Insufficiency	Moderate symptoms, physical limitation and exertional dyspnea. Spirometric data: FVC, $FEV_{1.0}$ and MBC to 50% of predicted.
	Pa_{O_2} 50–65 mm. Hg Pa_{CO_2} 40–50 mm. Hg, intensified with exercise. Arterial pH 7.32–7.40.
Respiratory Failure	Advanced symptoms, dyspnea at rest.
	Spirometric findings: FVC, $FEV_{1.0}$ and MBC $< 50\%$ predicted. $Pa_{O_2} < 50$ mm. Hg, $Pa_{CO_2} > 50$ mm. Hg and pH < 7.32.
	May be acute or chronic.

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*FVC = forced vital capacity.
$FEV_{1.0}$ = per cent of total forced expiratory volume expired in 1 second.
MBC = maximum breathing capacity.
Ra = airway resistance.
See Table 2 for normal values and other definitions.

hypercapnia (Table 1). Finally, even though a significant reduction in pulmonary function exists, blood gas alterations must be present to establish the diagnosis and extent of respiratory failure (Table 2). Table 3 presents a general classification of the disorders that may lead to respiratory failure. Figure 1 outlines a pathophysiologic sequence.

The Key Event: Precipitating Factors

Life-threatening respiratory failure must be *considered* in any patient with chronic obstructive lung disease who manifests a gradual or sudden increase in the severity of his symp-

TABLE 2.—SELECTED PULMONARY FUNCTION TESTS AND NORMAL VALUES

TEST	SYMBOL	NORMAL VALUE (ADULTS)
	Lung Volumes (BTPS)	
Slow vital capacity	SVC	4.8 L.*
Residual volume	RV	1.2 L.*
Total lung capacity	TLC	6.0 L.*
Residual volume/total lung capacity	RV/TLC	<30%
	Ventilatory Performance and Airflow Parameters	
Forced vital capacity	FVC	4.8 L.*
Forced expiratory volume in 1 second		
as % predicted	$FEV_{1.0}$	>80%*
as % observed FVC	$FEV_{1.0}\%$	>75–80%
Forced expiratory volume in 3 seconds		
as % observed FVC	$FEV_{3.0}\%$	>95%
Maximum breathing capacity (maximum voluntary ventilation)	MBC (MVV)	>150 L./min.*
Maximal expiratory flow rate	MEFR	>300 L./min.*
Peak expiratory flow rate	PEFR	>350 L./min.
	Alveolar Gas	
Alveolar oxygen tension	P_{AO_2}	95–105 mm. Hg
Alveolar carbon dioxide tension	P_{ACO_2}	38–42 mm. Hg
Alveolar-arterial oxygen gradient	A-a O_2	5–15
	Gas Distribution	
Single breath N_2 test	SBN_2	<2.5% N_2 (between 750–1,250 ml. expired)
	Arterial Blood	
Arterial oxygen tension	P_{aO_2}	85–95 mm. Hg
Arterial carbon dioxide tension	P_{aCO_2}	38–42 mm. Hg
Oxygen saturation, rest	S_{aO_2}	95–98%
Arterial pH	pH_a	7.38–7.42
Hydrogen ion concentration (activity)	(H^+)	40.0 ± 2.0 nM./L.
Bicarbonate concentration	(HCO_3)	22–27 mM./L.
Oxygen content	C_{aO_2}	19.5 vols. %
Oxygen capacity	Cap	20.0 vols. %
	Ventilation/Ventilation—Perfusion†/Gas Exchange	
Alveolar ventilation	$\dot{V}_A$	4.0–7.5 L./min.
Physiologic dead space	V_D	100–200 ml.
Minute ventilation	$\dot{V}_E$	6.0–10.0 L./min.
Tidal volume	V_t	0.5–0.8 L./breath
Physiologic dead space/tidal volume ratio	V_D/V_t	<0.33
Venous admixture/cardiac output × 100	$\dot{Q}_S/\dot{Q}_T$	<2–4%
CO_2 evolution	$\dot{V}_{CO_2}$	200–240 ml./min.
O_2 consumption	$\dot{V}_{O_2}$	250–300 ml./min.
Respiratory quotient $\dot{V}_{CO_2}/\dot{V}_{O_2}$	R.Q.	0.8
Diffusion capacity of lung (STPD)		
for carbon monoxide	$D_{L_{CO}}$ (steady state)	15–20 ml./min./mm. Hg‡
for oxygen	$D_{L_{O_2}}$	>15 ml./min./mm. Hg
	Mechanics of Breathing	
Compliance of lungs	C_L	0.2 L./cm. H_2O
Total (lungs + thorax)	C_T	0.1 L./cm. H_2O
Airway resistance	R_a	1.5–2.5 cm. H_2O/L./sec. (Lung volume specified)
Work of breathing (rest)		0.5 kg. M./min.

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*Illustrative value only for a normal young male at rest. For specific predicted values, see references 26, 27. Observed normal values should be at least 80% of predicted.

†Approximate values for a normal male at rest.

‡See reference 28.

TABLE 3.—Disorders Leading to Respiratory Failure

I. *Generalized or global alveolar hypoventilation*
  - A. Respiratory center destruction or depression: cerebral trauma or ischemia, morphine, barbiturates, anesthesia, high flow uncontrolled oxygen, metabolic alkalosis, idiopathic.
  - B. Neuromuscular abnormalities: poliomyelitis, myasthenia gravis, Guillain-Barré syndrome, multiple sclerosis, muscular dystrophy, botulinus or tetanus toxins, drugs (curare, polymyxin, neomycin, etc.) or acute porphyria.
  - C. Skeletal or thoracic defects: spinal arthritis, kyphoscoliosis, thoracic surgery, rib fractures.

II. *Restrictive disorders with decreased distensibility of lung or reduced tissue mass with impaired gas exchange and diffusion*
  - A. Parenchymal: pulmonary fibrosis, granulomatosis, pneumoconiosis, edema, infiltrating tumor, atelectasis, pneumonia, pneumonectomy.
  - B. Extraparenchymal: pleural effusion, pneumothorax, fibrothorax, obesity, abdominal surgery, ascites.

III. *Pulmonary vascular diseases:* thromboembolism, vasculitis, vasoconstriction due to hypoxemia or acidosis, parenchymal destruction (emphysema).

IV. *Obstructive airways disease:*
  - A. Upper airway disease: tumor, laryngeal obstruction.
  - B. Lower airway disease: acute and chronic bronchitis, pulmonary emphysema, bronchial asthma, bronchiectasis, bronchiolitis, cystic fibrosis.

toms or a change in physical signs. The acute precipitating event may appear to be insignificant, such as a simple viral or bacterial upper respiratory tract infection, and can upset any prior compensation, causing overt hypoxemia, hypercapnia, respiratory acidosis and cardiac failure—all of which may indicate a poor prognosis. Under these circumstances, acute and chronic factors will interact and result in the final common state of respiratory failure. This likelihood is clearly greater in patients with borderline function. The more normal the lung, the more severe and obvious may be the precipitating factors; the more severe the underlying chronic obstructive lung disease, the less dramatic may be the acute precipitating event.

Successful management focuses on this key concept; *acute*

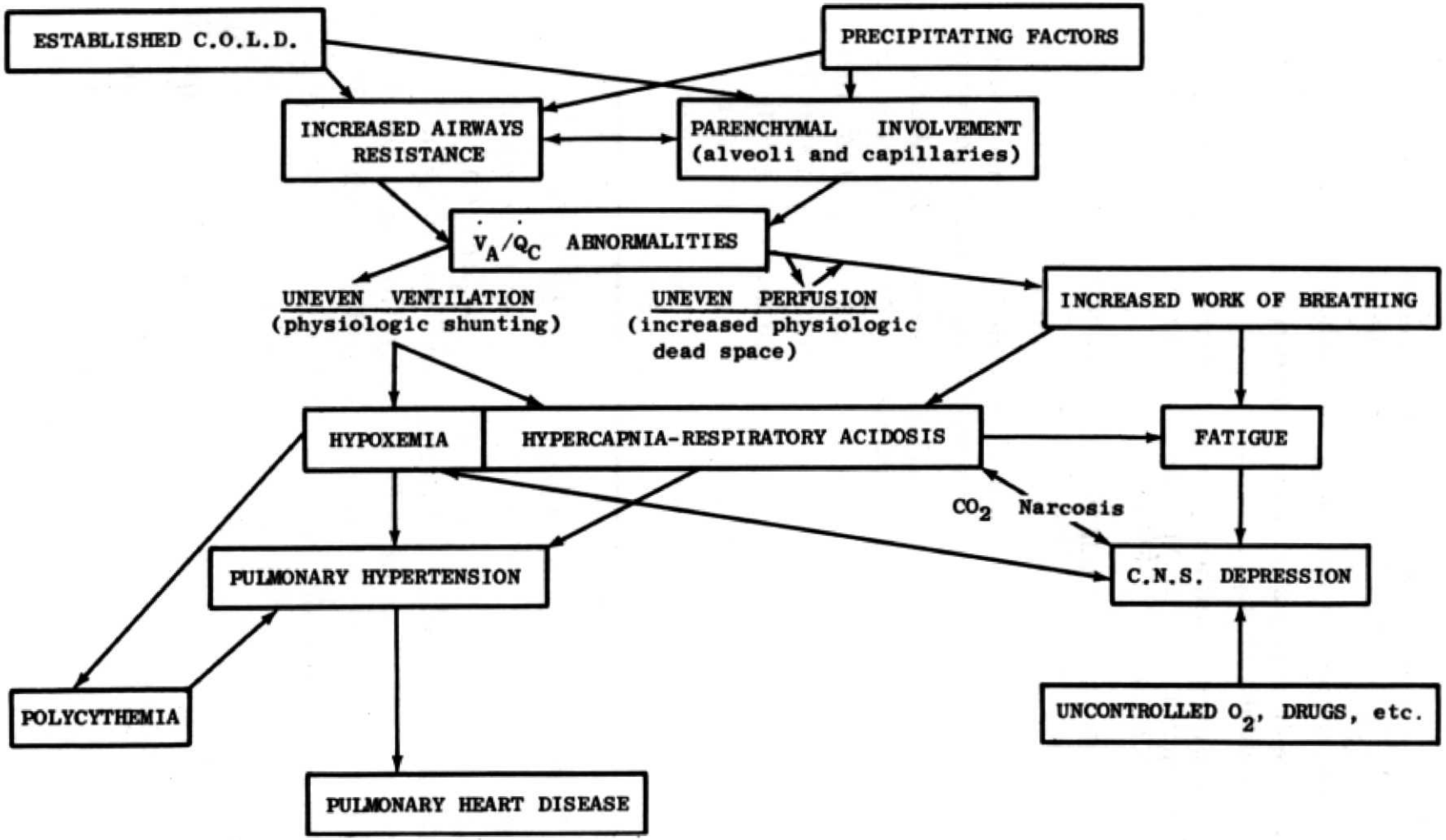

ESTABLISHED C.O.L.D.
PRECIPITATING FACTORS
INCREASED AIRWAYS RESISTANCE
PARENCHYMAL INVOLVEMENT (alveoli and capillaries)
$\dot{V}_A/\dot{Q}_C$ ABNORMALITIES
UNEVEN VENTILATION (physiologic shunting)
UNEVEN PERFUSION (increased physiologic dead space)
INCREASED WORK OF BREATHING
HYPOXEMIA
HYPERCAPNIA-RESPIRATORY ACIDOSIS
FATIGUE
CO_2 Narcosis
PULMONARY HYPERTENSION
C.N.S. DEPRESSION
POLYCYTHEMIA
UNCONTROLLED O_2, DRUGS, etc.
PULMONARY HEART DISEASE

FIG. 1.—Schematic sequence of the acute exacerbation in chronic obstructive lung disease (C.O.L.D.).

TABLE 4.—PRECIPITATING FACTORS

1. Infection: viral, bacterial, fungal, tuberculous–infections producing bronchial, bronchiolar or parenchymal disease
2. Allergic: extrinsic or intrinsic with bronchospasm, bronchial edema
3. Irritative or chemical: dust, fumes, smoke, air pollutants, cough, aspiration, respiratory burn
4. Drugs: oxygen, anesthesia, narcotics, sedatives, tranquilizers, atropine-like agents, Dornavac, Mucomyst, certain antibiotics (Polymyxin, Neomycin, Kanamycin
5. Cardiovascular: pulmonary emboli, pulmonary vascular thrombosis, cardiac failure, arrhythmias
6. Mechanical: abdominal distention, obesity, pneumothorax, pleural effusions, empyema, chest trauma, atelectasis, ascites, postoperative pain
7. Secretions: (mucoid or purulent), increased adhesiveness, viscosity, volume, dehydration and inspissation
8. Neuromuscular
9. Contributory factors
    - *a.* Hypermetabolic states (viz., fever)
    - *b.* Shock
    - *c.* Bacteremia
    - *d.* Metabolic acidosis

reversible precipitating factors must be defined and treated. These factors are listed in Table 4; the more significant provocations include respiratory center depression, heart failure, pulmonary emboli, bronchial or parenchymal infection, atelectasis, excessive or retained secretions and bronchospasm. Often many agents are operative and a specific delineation is not entirely possible. Nevertheless, while supportive measures are established to sustain life (i.e., oxygen therapy and appropriate ventilation), intensive treatment of the reversible processes is pursued until the patient is able to maintain adequate respiratory function on his own.

Clinical Considerations

Due to the complex nature of the basic pulmonary disease and the precipitating events, precise descriptions of the clinical picture are difficult. The clinical manifestations of chronic obstructive lung disease have been reviewed by the American Thoracic Society; however, certain significant practical information will be emphasized (7). The initial evaluation may clarify the historic features of the basic disease in assessing both its *nature* and *severity*. Details of the actual precipitating events may also be delineated; for example, the use of sedatives, recent infection with changes in sputum volume and/or ease of expectoration, symptoms of cardiac failure, changes in dyspnea (the severity of which may bear no relationship to blood gas changes) or physical tolerance, postoperative setting, or uncontrolled oxygen therapy. Patients are often confused, disoriented or comatose; while some are in obvious respiratory distress, others are too depressed to exhibit tachypnea or excessive respiratory work. The *absence* of wheezing may indicate markedly depressed ventilation or widespread airway obstruction. Careful examination of the chest may reveal pneumonia, pleural effusion, gross atelectasis or upper airway obstruction. Additionally, gross assessment of diaphragmatic function, regional distribution of air, and chest expansion is possible. Increased intracranial pressure with vascular dilation produces papilledema and ophthalmic vein distention in 10% of patients with hypercapnia; asterixis, tremors and altered reflexes are frequent. ***All*** pertinent cardiovascular, laboratory and radiologic data, and coexisting medical disorders must be considered in conjunction with the pulmonary findings in planning a comprehensive therapeutic approach.

As is commonly known, hypoxemic cyanosis is an unreliable clinical sign, since it depends on the level of reduced hemoglobin, blood flow, skin thickness and pigmentation; and significant arterial oxygen unsaturation ($Sa_{O_2} < 75\%$) can exist in its absence (8). Peripheral cyanosis alone suggests peripheral vascular stagnation with increased local O_2 extraction rather than pulmonary induced hypoxemia; this should be confirmed by arterial blood O_2 analysis. Dyspnea and hyperventilation, without cyanosis, may be observed in patients with salicylate poisoning, acute meningitis, metabolic acidosis, gram-negative septicemia, minor pulmonary embolization uremia and hepatic coma. This increased ventilation is a pulmonary re-

TABLE 5.—COMMON SIGNS AND SYMPTOMS OF HYPOXEMIA AND HYPERCAPNIA

HYPOXEMIA	HYPERCAPNIA (ACIDEMIA)
Judgment and personality changes	Headache, confusion
Confusion, stupor, coma	Dizziness
Insomnia, restlessness, seizures	Somnolence to coma
Headache	Papilledema, increased CSF pressure
Tachycardia, bradycardia	Focal twitching, asterixis
Cardiac arrhythmias	Diaphoresis
Hypertension (systemic or pulmonary)	Systemic hypertension. Pulmonary vascular hypertension. (secondary acidemia).
Hypotension	Hypotension (late)
Tachypnea, dyspnea	Cardiac failure
Cyanosis	

sponse to the underlying disease and its metabolic components, and respiratory failure per se is not present.

The major clinical manifestations of acute respiratory failure are reflected in the cardiovascular and central nervous systems, and are due to the metabolic and physiologic influences of tissue hypoxia, hypercapnia and respiratory acidosis (Table 5). The latter causes adrenal medullary catecholamine release. This may be compounded during severe hypoxemia or shock by a metabolic lactic acidosis (9). Hypercapnia exerts *circulatory effects* by activation of catecholamines and the sympathetic nervous system, and tachycardia and vasoconstriction with systemic hypertension are common, until severe acidosis leads to vasodilatation and circulatory collapse (10). The early chemoreceptor responses to hypoxemia (i.e., < 60 mm. Hg) produce tachycardia and increased cardiac output; selective vasoconstriction of the pulmonary vascular bed occurs through a direct, local action. Compensatory vasodilatation in the cerebral and coronary beds due to local hypoxia improves the capillary perfusion of these vital, aerobic organs. The important factors influencing cerebral aerobic metabolism are the cerebral oxygen consumption (normal 3.3 ml. 0_2/100 Gm. tissue/minute), the extent of tissue hypoxia, the duration of hypoxic exposure and the efficiency of compensatory cardiovascular mechanisms. Similarly, hypoxic pulmonary vasoconstriction, developing as a consequence of regional hypoxia, may serve initially to improve the matching of perfusion to ventilation in the alveolar-capillary bed. Progressive hypoxemia becomes depressant, however, and these adaptive mechanisms will eventually fail. Severe acidosis and hypoxemia in conjunction with sympathetic depletion may then result in cardiac failure, hypotension, arrhythmias and cardiac arrest. This is particularly evident in older patients presenting with obstructive lung disease and respiratory failure.

In the *central nervous system,* wide variations in response to hypoxia and hypercapnia are observed; in general, chronic exposures permit adaptation and greater tolerances. Kilburn has shown that the severity of stupor and coma varies with the speed of onset of acidosis and the defense of blood and spinal fluid pH, rather than the level of hypercapnia alone (11). Acute hypercapnia to 70 mm. Hg is frequently associated with coma, but many patients remain alert with carbon dioxide tensions of approximately 65 to 75 mm. Hg if this develops slowly, permitting pH defense. When cerebrospinal fluid pH falls below 7.25, disorientation, somnolence, hallucinations or coma often develop (12). Respiratory acidosis appears responsible for mental changes, twitching, asterixis and occasional focal neurologic signs, while carbon dioxide per se with a direct cerebral vasodilatating action produces the hypercapneic symptom of headache.

The effect of hypoxia on neuronal aerobic metabolism is critically important, but may prevail without obvious clinical findings. Normal individuals subject to acute hypoxemia reveal impaired motor function, poor judgment and mental abnormalities not apparent in the chronic hypoxemia of high altitudes. Although mild degrees of hypoxemia are associated with more subtle changes in judgment or mental and emotional status, severe hypoxemia, with arterial oxygen tensions between 20 and 30 mm. Hg, is generally associated with coma (13). This range is not necessarily incompatible with life or cerebral recovery if adaptive mechanisms are operative and if the actual duration of exposure is brief. Acute, superimposed hypoxemia during respiratory failure may develop accidentally through respirator failure or dislodgment, during protracted suctioning or by errors in oxygen administration.

Thus in the central nervous system, tissue hypoxia and acidosis may promote fatigue, headache, stupor, coma or death. Any resulting agitation or confusion often creates management difficulties and *commonly* results in the injudicious use of sedatives. Finally, since these symptoms or signs are quite nonspecific and may be common to many disease states, arterial blood analysis is needed to confirm their pulmonary origin.

Pathophysiology

The physiologic and biochemical alterations in acute respiratory failure are the result of the primary pulmonary disorder and the superimposed pathologic conditions. An understanding of the basic pathology and physiology of these diseases is a prerequisite for a rational therapeutic approach.

Chronic Bronchitis

Clinically, patients with "pure" chronic bronchitis manifest recurrent daily cough and expectoration of mucoid and/or purulent sputum for a minimum of 3 months per year, over 2 successive years, *exclusive* of other specific causes of productive cough such as bronchiectasis, tuberculosis and cystic fibrosis (7). Histologic examination of the bronchi reveals variable areas of inflammatory cell infiltration, with hypertrophy and hyperplasia of the mucus-secreting goblet cells and the submucosal glands. The ratio between submucosal gland thickness and "internal bronchial wall" thickness (Reid index) permits a rapid and quantitative assessment of the degree of histologic bronchitis present. Values greater than a normal of 0.26 relate well to histories of chronic cough and sputum production (14).

With exacerbation of the bronchitis, the hypersecretion of mucus may be accompanied by inflammatory cell infiltration, bronchial wall edema and damage or metaplasia of the epithelial cells. Also, impaired mucociliary activity has been demonstrated with aerosolized radio-tagged particles (15), and hypoxia is reported to inhibit tracheal mucus flow (16). *Haemophilus influenzae* and/or *Diplococcus pneumoniae* (the pathogens reported in 75% of cases) presumably initiate such inflammatory changes. With bacterial overgrowth and invasion, mucous hypersecretion and purulent sputum result in *intraluminal* airway obstruction by their volume as well as adhesive and viscous properties. This is often compounded by dehydration resulting in inspissation or plugging of the bronchioles. Bronchial wall glandular hyperplasia, inflammation with edema, vascular congestion and bronchospasm create added *luminal* resistances to air flow. Further irreversible destruction to the airways by ulceration, ischemia and necrosis leads eventually to bronchiolar fibrosis and stenosis. Additional dynamic expiratory airway obstruction will be considered subsequently. The severest damage appears when these processes are widespread and extend deep into the walls of bronchioles or even alveoli, whereas intraluminal infections may leave little residua. Bronchiolitis is a frequent necropsy finding and an important factor in respiratory failure and death. As a result of airway involvement, regional atelectasis, bronchopneumonia or air-trapping, abnormal ventilation-perfusion conditions will contribute to impaired gas exchange. It should be noted that bronchitis *alone,* in the absence of significant emphysema, may be lethal.

Pulmonary Emphysema

Pulmonary emphysema is a pathologic entity distinct from chronic bronchitis. Its onset is frequently insidious and symptoms arise usually after advanced involvement has transpired. While the accepted major clinical features are dyspnea, increased expiratory airway resistance and pulmonary hyperinflation, a definitive diagnosis requires morphologic confirmation. The prime defect is progressive destruction of alveolar walls and pulmonary capillary bed, creating abnormally enlarged air spaces and distortion of the lung architecture. The gas-exchanging surface area is thereby reduced. With destruction of respiratory bronchioles and with the distortion of alveolar collagen and

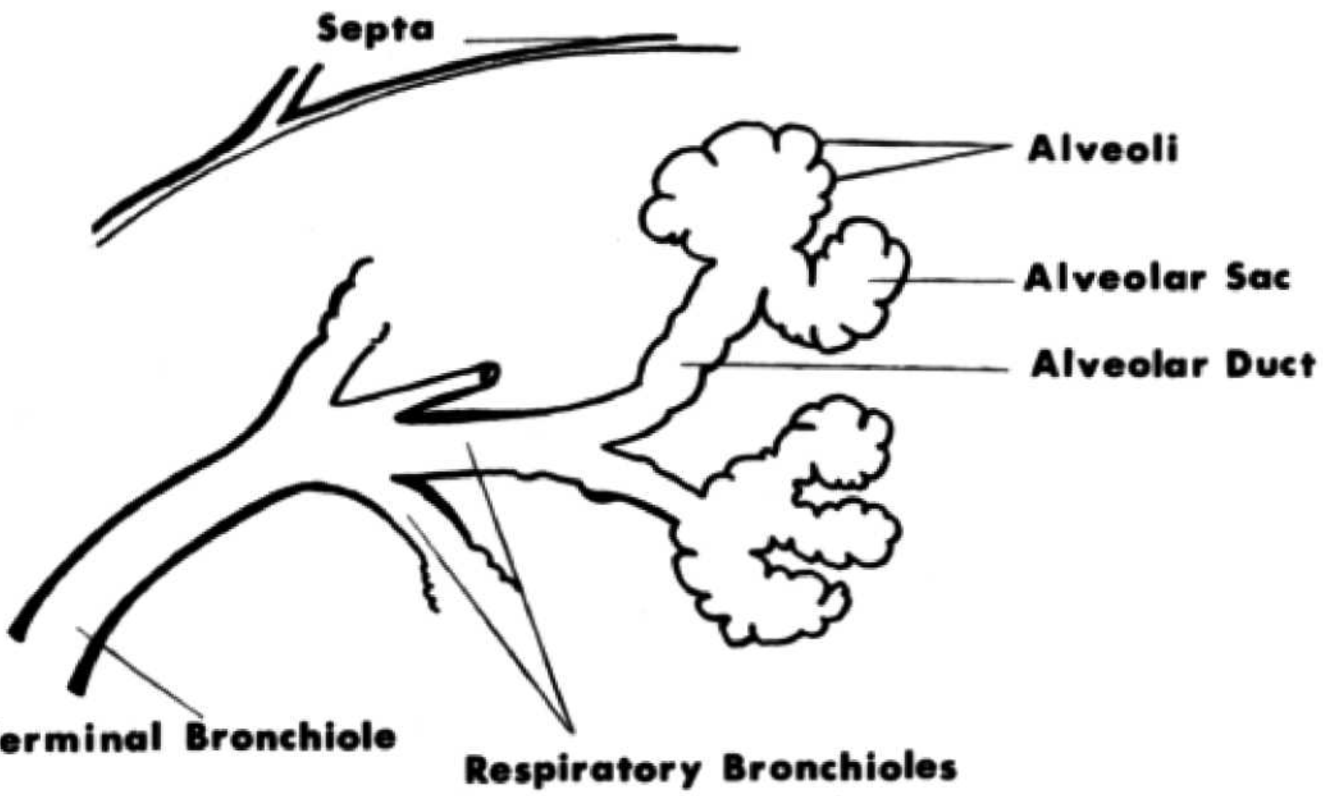


FIG. 2.—The secondary lobule of Miller is a pyramidal structure about 1–2 cm. in diameter and enclosed in a thin fibrous septa. This lobule contains from 5 to 10 terminal bronchioles. The latter are about 1 mm. in diameter, contain neither alveoli or alveolar sacs, nor cartilage or submucosal glands. Each such terminal bronchiole subdivides into three orders of smaller respiratory bronchioles. These are distinguished by the occasional presence of alveoli. The primary lobule arises from a single tertiary respiratory bronchiole and contains the alveolar ducts, atria and alveoli. The term *acinus* includes all the respiratory structures arising from a single terminal bronchiole.

elastic supporting structures, a reduction in the usual tractional forces on the bronchioles favors their expiratory collapse. These structural alterations influence airway resistance and lung compliance, favor maldistribution of ventilation and perfusion, and limit the forces necessary for an effective cough.

The secondary lobule (Fig. 2) is the smallest division of lung tissue bounded by fibrous septae. It consists of 5–10 terminal bronchioles, divisions of the peripheral respiratory bronchioles, atria and alveolae, and is the lung unit examined for the various types of emphysema. On gross pathologic sectioning, the distribution of such alveolar destruction is classified as:

1. *Centrilobular (centriacinar):* a patchy, centrally located lobular destruction with intervening normal parenchyma. The centrally placed respiratory bronchiole is most involved; acinar structures are spared until late.

2. *Panlobular (panacinar):* a generalized or diffuse involvement of respiratory bronchioles and alveoli within the

secondary lobule. Mixtures of panlobular and centrilobular types are common.

In addition, *retraction emphysema* arises by expansion of lung adjacent to a scarring process; local or generalized *blebs* and *bullae* (large, thin-walled cystic air spaces) may occur with either form of emphysema.

Centrilobular emphysema tends to involve the upper zones of both upper and lower lobes and is associated with inflammatory changes or fibrosis in the respiratory bronchiole. Increases in residual volume are generally less than in panlobular disease. Chronic bronchitis and bronchiolitis in association with infection, smoking and air pollution appear as contributory causes. The so-called blue-bloater patient, with frequent and productive cough, cyanosis and other features to be discussed, often exhibits this form of emphysema.

Panlobular emphysema may exist without evidence of chronic bronchitis or bronchiolitis. However, a history of a nonproductive cough, later associated with sputum production, may be elicited. The "pink puffer," whose findings include a mild cough, significant dyspnea and absent or mild cyanosis, manifests this form of emphysema. In general, a grade III/IV anatomic severity must be present before there is general agreement of classic radiologic findings. As with centrilobular emphysema, the causes of these destructive lesions remain unknown.

While a clear separation between chronic bronchitis and centrilobular emphysema versus panlobular emphysema has been described anatomically, many patients suffer from degrees of both forms. The predominant *anatomic* pattern is established only at necropsy. Clinically, certain characteristics of one may predominate, i.e., a predominant chronic bronchitis pattern with a pulmonary emphysema component and vice versa, and one may be more specific in terminology than "chronic obstructive lung disease." By far, all are more common in male smokers over the age of 40, though, if females are affected, it is more likely to be panlobular emphysema. The role of asthma in the emphysema-bronchitis complex is controversial; an asthmatic component does exist in many of these patients, but classic episodic asthma alone rarely leads to pulmonary emphysema.

Since a recognition of these clinical forms aids in our understanding, it is of interest to clarify certain distinctive clinical and laboratory features. The pink puffer (PP type) or panlobular emphysema patient, whose *major disease* is diffuse alveolar destruction with a great loss in gas-exchange surface area, complains mostly of insidiously progressive *dyspnea*. The total lung capacity (particularly the residual volume) is increased, arterial blood remains relatively well saturated with oxygen, hypercapnia occurs late, increases in red blood cell mass are small, cor pulmonale is a late development and weight loss is an early feature. The chest x-ray reveals hyperlucent lungs with low, flat diaphragms, a paucity of normal peripheral vascular markings and a small, vertical heart. In contrast, the so-called blue bloater patient (BB or bronchitic type), often associated with centrilobular emphysema, exhibits a significant chronic *cough* with sputum production and dyspnea. Physiologically, the diffuse airway obstruction is responsible for a reduced alveolar ventilation relative to perfusion. These patients are cyanotic, with more severe hypoxemia, hypercapnia and respiratory acidosis, and manifest more marked pulmonary hypertension with the early development of cor pulmonale. The residual volume is very modestly increased. Weight gain with peripheral edema and secondary polycythemia are common. The radiologic features include increased bronchovascular markings, scattered fibrosis, prominent, but tapered, pulmonary arteries and right ventricular enlargement.

At postmortem, PP patients reveal more severe anatomic emphysema and less mucous gland hyperplasia. The impairment of simple ventilatory tests (FVC, $FEV_{1.0}\%$, MBC, MEFR, see Table 2) appears similar for both patient types (17). However, since the ventilatory equivalent for oxygen (the liter ventilation per liter of oxygen uptake) is greater in the PP individual at both rest and exercise, this may partially explain their more severe dyspnea relative to a greater oxygen cost of breathing. Filley has suggested that the reduced mean alveolar P_{AO_2} in BB patients cannot fully account for their arterial P_{aO_2}. The latter is due in part to associated ventilation/perfusion disturbances, and/or in part to a diffusion impairment resulting from reduced transit time of red blood cells in pulmonary capillaries through regionally hypoventilated alveoli (17).

The BB individual generally demonstrates a lower total ventilation, but has a greater cardiac index for a given O_2 uptake, and greater mean pulmonary vascular resistance due to hypoxemia, acidemia, hypervolemia and increased blood viscosity. Cardiac work is thereby greatly augmented in these patients, leading frequently to severe cor pulmonale with congestive heart failure. Up to a critical point of cardiac reserve and excessive pulmonary vascular resistance, the PP patient appears protected from congestive failure by a low or normal cardiac output.

In this context, the oxygen delivery of each type differs in that oxygen transport of the PP is less than the BB individual. With a low cardiac output and an unelevated red cell mass, the thin PP patient delivers relatively less oxygen to his tissues even though he maintains only mildly reduced arterial oxygen tensions. Such arterial O_2 tensions in the PP type are achieved by hyperventilation and/or exist because the disease does not favor wide variations in ventilation/perfusion relationships until superimposed processes or end-stage disease occur. The precise significance of these transport mechanisms on tissue oxygenation per se is presently unresolved.

Physiologic Considerations

Respiratory Mechanics

Respiratory work, operating a bellows-type system (lungs in the thoracic cage), is necessary for overcoming the elastic and frictional resistance properties of the lungs and thorax during inspiration in order to produce air flow and alveolar ventilation. Expiration occurs when inspiratory muscle activity terminates, allowing the elastic properties of the lung to passively return the system to its resting volume. The total applied work may be described in terms of pressure (P) forces:

$$P_{\text{total}} = P_{\text{elastic (compliance)}} + P_{\text{resistance}} + P_{\text{inertia}}$$

where

$$P_{\text{elastic}} = \text{Lung and chest wall compliance} + \text{surface tension forces} \tag{1}$$

$$P_{\text{resistance}} = \text{Air flow resistance} + \begin{array}{l}\text{frictional resistance of} \\ \text{lung tissue and} \\ \text{thoracic tissue}\end{array} \quad (2)$$

$$P_{\text{inertia}} = \text{is small and ignored} \quad (3)$$

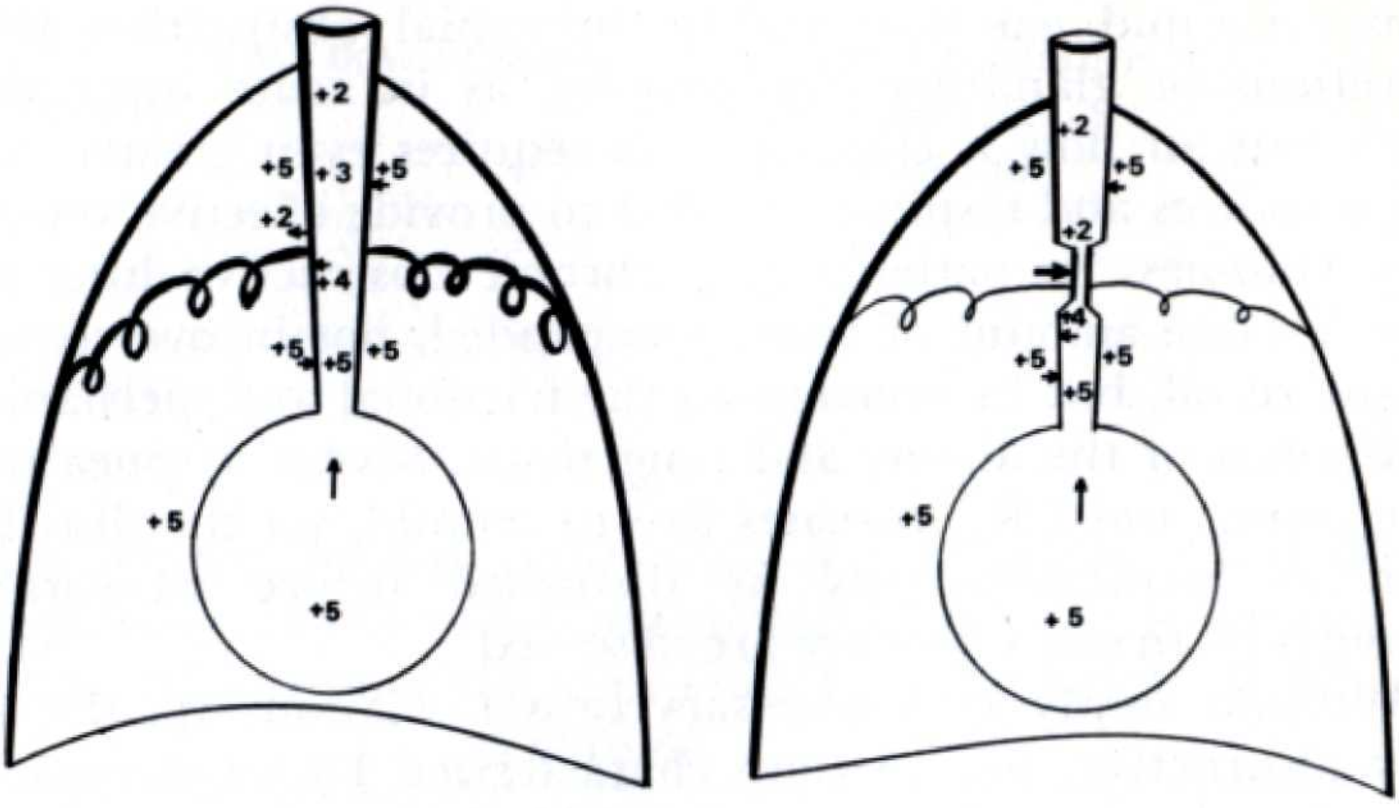
Compliance (elastic resistance) (C) describes the ease of distensibility of the lungs and/or chest wall and is defined as the gas volume increment produced as the result of a unit pressure change: $C = \frac{\Delta \text{ volume}}{\Delta \text{ pressure}}$, in $\frac{L}{\text{cm. } H_2O}$, specified at a given lung volume. Compliance measurements include the important contribution made by *surface tension forces.* In addition to pulmonary fibrosis, which may exist in chronic bronchitis, edema, infiltrations or atelectasis can reduce the lung compliance unevenly, and thereby may establish regional differences in alveolar ventilation ($\dot{V}_A$) by variable distensibility of alveolar groups. As a result, the respiratory work necessary to support an effective alveolar ventilation will increase, and this can eventually contribute to respiratory failure.

During inspiratory and expiratory gas displacement, thoracic forces must overcome the frictional resistance of tissues and of air moving through the tracheobronchial tree. Airway resistance (R_a) results from the friction of flowing gas molecules among themselves, and also between the gas molecules and the bronchial surfaces, and is expressed as the pressure gradient between alveoli and mouth per unit of volume flow change: $R_a = \frac{\Delta P}{\Delta \dot{V}}$ in cm. H_2O per liter per second (normal = 1.5–2.4). When flow is laminar, airway resistance (R_a) may be calculated:

$$R_a = K \times \frac{\text{gas viscosity} \times \text{tube length}}{\text{radius}^4}$$

Clearly, a small decrease in airway radius will lead to a significant increase in airway resistance. Additionally, under conditions of rapid gas flow and/or bronchial obstruction from secretions or glandular hypertrophy, as in acute bronchitis, turbulent air flow is created. This requires even greater driving pressures and respiratory effort to provide effective ventilatory volumes. In patients with chronic obstructive lung disease, a large amount of work is expended, not in overcoming elastic recoil, but in overcoming the frictional and mechanical resistances of the airway and lung tissue. Severe dyspnea may not appear until R_a increases five to tenfold, yet the distribution of ventilation may be disturbed before measurable changes in airway resistance are observed.

Without implying a necessary causal relationship, the airway obstructive disorders are characterized by an increase in airway resistance (R_a), most marked during expiration. Expiratory air flow is dependent on the elastic behavior of the lungs and the resistance within the airways. Pure bronchitis is associated with increased airway resistance while pulmonary emphysema also manifests abnormal elastic properties. The mechanisms responsible for an increased airway resistance are due to the basic disease and/or superimposed acute precipitating factors: (1) loss of supporting elastic tissue elements resulting in a dynamic expiratory obstruction, (2) bronchial wall thickening from inflammation and glandular hypertrophy, (3) space-occupying luminal secretions (mucoid and/or purulent) with adverse adhesive and viscous properties, (4) bronchial (bronchiolar) fibrosis, (5) bronchospasm and (6) possible degenerative changes of cartilagenous supportive structures. Dayman suggests that loss of peribronchial supporting structures in emphysema subjects the bronchioles to direct alveolar pressure (18). This is particularly prominent with a forced expiration when the pressure drop within the bronchial tree becomes too large due to high flow rates, preventing the diminished elastic forces acting centrifugally from maintaining the patency of the airway and leading to airway collapse at a critical point during expiration when the peribronchial alveolar pressure exceeds the intraluminal pressure (Fig. 3). In the *normal* lung, within limits, there is a fairly good relationship between the degree of applied pressure and the rate of air flow generated; maximum flow rates occur at maximal lung inflation since airway resistance is least in this state. Additionally, strenuous expiratory



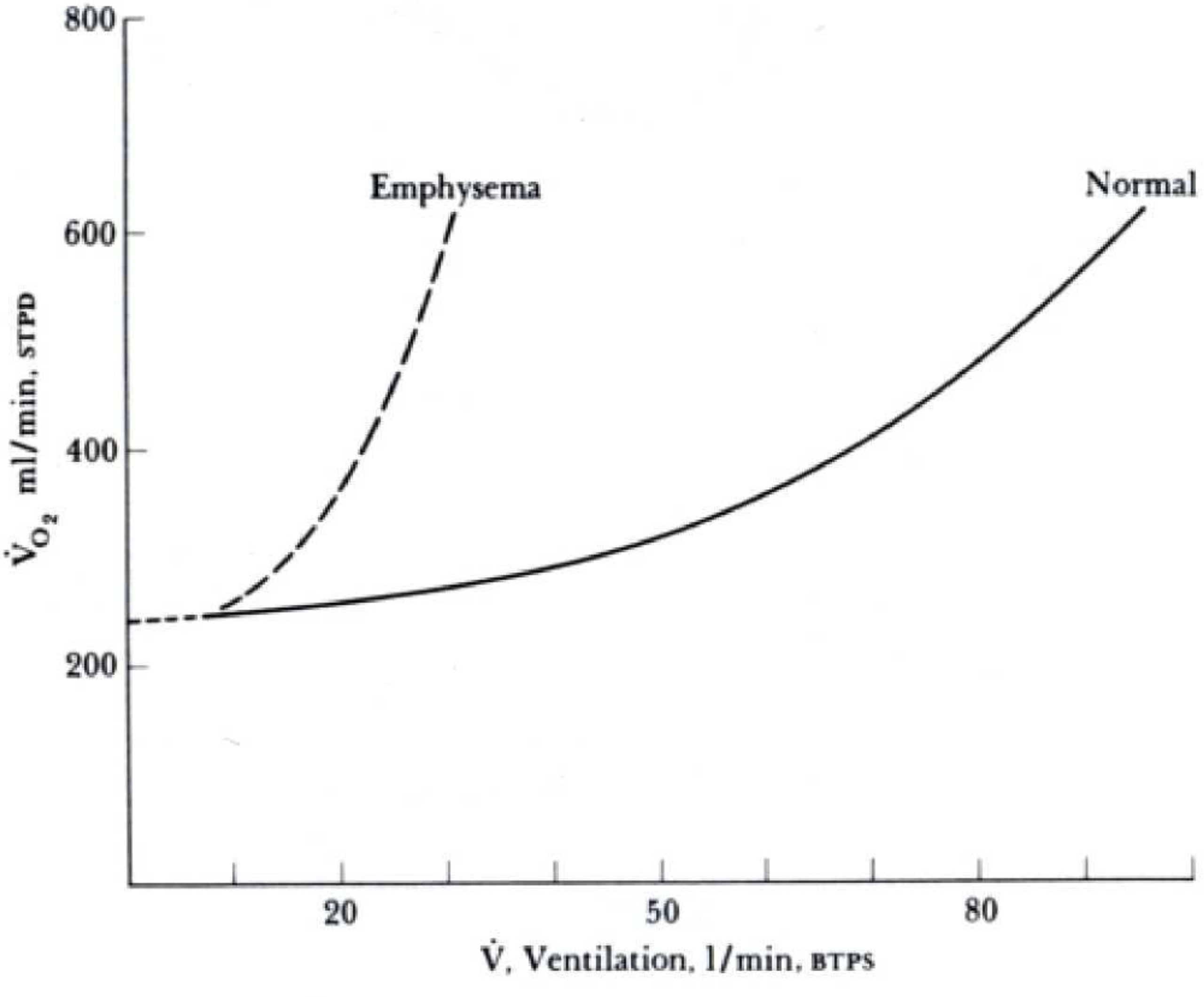
NORMAL EMPHYSEMA

FIG. 3.—A simplified diagram of the transmural bronchial forces during a forced expiration. Normal is depicted on the left, and emphysema with destruction of elastic supporting architecture and peripheral airway wall disease on the right. As a result of loss in airway tractional support, a premature, dynamic constriction develops at a critical point *(arrow)* where extraluminal exceed intraluminal forces. The resulting collapse will cause greater resistance to expiratory air flow. Numbers refer to intrathoracic, recoil and airway pressures. (See text.)

effort induces expiratory airway collapse primarily at small lung volumes and with high alveolar pressures. In patients with reduced bronchial tissue support, however, such collapse will occur at progressively larger lung volumes and with much less expiratory effort. Furthermore, greater effort will not necessarily increase, and may further reduce, air flow by the above-cited compression effect. Thus, a slow expiratory effort, being associated with slower airflow rates and lower pressure gradients, has a less adverse effect on the geometry of the airways and may allow for larger expiratory volumes. Studies with normal lungs indicate that 75% of the total airway resistance resides in the central or larger bronchi ($>$ 2 mm. diameter) (19). Recent work suggests that there are two zones of airway obstruction in emphysema; of lesser magnitude are the zones in the larger bronchi due to dynamic compression (loss of elastic support and intrinsic fibrosis) and present only in expiration. Of greater significance is the resistance in the smaller peripheral airways due to obliterating organic disease and secretions, and which is present during both inspiration and expiration (19). During acute airway insult, the latter sites are particularly responsible for increases in airway resistance (estimated to be four to fortyfold), and are especially important since these processes are potentially reversible.

With progressive airway obstruction, expiratory resistances hinder the elastic recoil forces developed in inspiration from passively returning the lung to the resting expiratory level. These elastic forces may already be reduced by pathological destruction or the normal aging process. Active work is then necessary during expiration, enhancing the mechanical work of breathing. As the result of destructive disease with dilated and confluent lung units, and with a less-than-optimal expiratory time, air trapping ensues and the functional residual capacity (FRC), in particular the residual volume, rises, i.e., a hyperinflated chest. The adverse effects of this state include some limitation in mechanical thoracic efficiency, a reduced inspira-

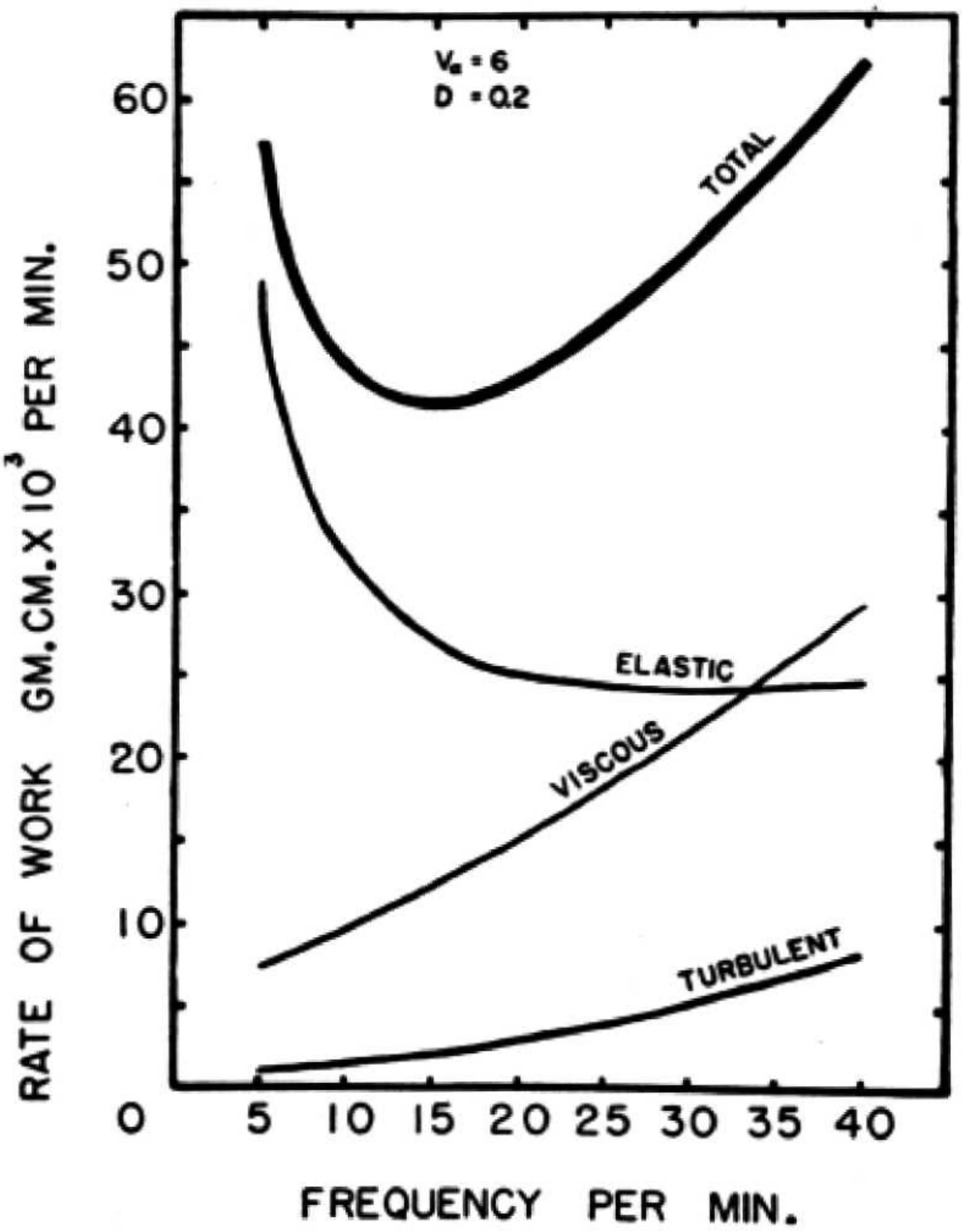
FIG. 4.—The oxygen consumption associated with an increased ventilation in a normal person versus a patient with bronchial obstruction (emphysema). The rate of an increasing cost of breathing becomes more disproportionate as the ventilation is increased. (See text.)



tory volume (since the movements of a caudally displaced diaphragm are less efficient), and an increase in anatomic dead space. On the other hand, since elastic recoil varies directly with lung volumes, this rise in FRC may augment expiratory flow rates by tending to increase airway diameter. Flow eventually becomes independent of heightened driving pressures, and further effort will not increase expiratory flow rates.

Normally, at rest, the respiratory muscles consume less than 2% of the total O_2 uptake (normal = 250 ml. minute) in performing work. With advancing airway obstruction, the thoracic mechanical work responses necessary to maintain or to restore any blood gas change toward normal become ineffi-

FIG. 5.—The relationship between respiratory frequency and the mechanical work of breathing when alveolar ventilation is 6.0 liters/minute, and the physiologic dead space is 200 ml. Note that for nonelastic properties, which include tissue viscous and airway resistances (labeled viscous and turbulent in the illustration), respiratory work is least at lower respiratory rates.



cient. Eventually, a point occurs, in advanced lung disease, when the excessive oxygen cost of breathing results in a carbon dioxide production greater than the gas exchange gained by the augmented ventilation (Fig. 4). Thus, in acute respiratory failure due to airway obstruction, oxygen requirements are increased and exaggerated respiratory work may become a limiting factor. These may become, therefore, indications for oxygen therapy and mechanical ventilator support (20). Figure 5 illustrates the relationship between total respiratory work per minute and respiratory frequency. Of clinical interest, with obstruction of the airways, less work is expended at low respiratory frequencies and greater tidal volumes in contrast to the disorders of reduced compliance, where high breathing rates and small tidal volumes diminish the work necessary to overcome lung stiffness (21).

INSPIRED AIR

The distribution of inspired air through the bronchial tree to the alveoli is influenced by the factors of regional compliance and airway resistance (time constant of Otis *et al.*) (22). Depending on the relative amount and regional distribution of destroyed or diseased lung tissue and compromised airways, changes in *temporal* (air flow or terminal gaseous diffusion) or *spatial* (compliance) relationships will create uneven alveolar ventilation ($\dot{V}_A$). This is compounded by high respiratory frequencies, often associated with respiratory failure, which preferentially direct gases toward the paths of lowest resistance, perpetuating regional inequalities of $\dot{V}_A$ and contributing to ventilatory failure.

Briscoe and Nash have observed that the lungs of *some* patients with predominantly chronic bronchitis manifest a slow nitrogen washout during oxygen breathing and a significant "slow space" ventilation (23). This slow space occupies two-thirds of the FRC, but is ventilated by only one-tenth of the alveolar ventilation and is perfused by about one-half of the cardiac output. The degree of slow space ventilation and perfusion, rather than total lung ventilation, determines the arterial oxygen saturation. Patients who depend physiologically on this slow space for survival are subject to critical changes in ventilation or perfusion and to tissue O_2 requirements. A flare-up of bronchitis with the obstruction distributed in the slow space bronchi can result in respiratory failure.

GAS EXCHANGE

Two processes are distinguished: (1) *generalized* or *global* alveolar hypoventilation and (2) *regional* alveolar hypoventilation or *ventilation-perfusion imbalance.* In pulmonary emphysema or chronic bronchitis, hypoxemia alone is caused by uneven ventilation-perfusion relationships, while hypoxemia with hypercapnia is created by an extension of these abnormalities or generalized alveolar hypoventilation (Table 6).

GENERALIZED ALVEOLAR HYPOVENTILATION.—This mechanism reduces the total volume of fresh air washing in and out of the alveoli and results in hypoxemia *and* hypercapnia simultaneously. Changes in respiratory control or limited thoracic expansion due to toxic or drug-induced central nervous system depression, neuromuscular disease, extrapulmonary or idiopathic factors with *normal* airway and parenchymal structures are causative (see Table 3). In obstructive lung disease, these same factors may also contribute to alveolar hypoventilation. Since effective alveolar ventilation

$$\frac{\dot{V}_A = CO_2 \text{ production} \quad (\text{ml./minute}),}{Paco_2 \qquad\qquad (\text{mm. Hg})}$$

it should be clear that changes in $Paco_2$ *reflect* the adequacy of alveolar ventilation. If $\dot{V}_A$ is decreased by 50% (assuming $\dot{V}co_2$ is a steady state), then $Paco_2$ will rise from a normal of 40 mm. Hg to about 80 mm. Hg. Additionally, during generalized hy-

TABLE 6.—ETIOLOGY OF HYPOXEMIA AND HYPERCAPNIA

HYPOXEMIA
Decreased inspired oxygen concentration
Generalized or global alveolar hypoventilation*
Ventilation/perfusion imbalance (regional alveolar hypoventilation)*
Diffusion defect
Right-to-left anatomic shunt, intrapulmonary or intracardiac

*Also produces hypercapnia.

poventilation in normal lungs, the rise in alveolar P_{ACO_2} approximates the fall in alveolar P_{AO_2} (if RQ = 0.8 and barometric pressure 760, then $P_{AO_2} = 149 - \frac{P_{ACO_2}}{0.8}$). In patients with chronic obstructive lung disease, however, the gas tension findings in arterial blood may be *disproportionate* because of *associated regional* ventilation-perfusion inequalities. Nevertheless, it is important to recognize that the clinical use of narcotics, sedatives, tranquilizers, or poorly controlled therapeutic oxygen may initiate generalized alveolar hypoventilation or contribute further to acute respiratory failure from other causes.

VENTILATION-PERFUSION DISTURBANCES ($\dot{V}_A/\dot{Q}_C$).—In the normal lung, gas exchange depends on (1) appropriate pulmonary capillary blood volume, distribution and flow, (2) adequate volume, distribution and flow of air in and out of the alveoli and (3) the proper matching of this alveolar capillary blood to these ventilated alveoli. The ideal relationship between alveolar ventilation ($\dot{V}_A$) and alveolar capillary perfusion ($\dot{Q}_C$) is described by the $\dot{V}_A/\dot{Q}_C$ ratio (normal =4 liters/minute/5 liters/minute = 0.8). This ratio is not uniform, even in a normal individual, because of regional pressures and mechanical and gravitational forces. Yet the regional distribution of blood is generally matched by a preferential distribution of ventilation to these same areas; this process contributes to the remarkable efficiency of the lung as a gas exchange organ. Disease frequently magnifies and distorts the inequalities; and in the chronic obstructive airway disorders, established $\dot{V}_A/\dot{Q}_C$ abnormalities initially create hypoxemia, with carbon dioxide retention developing as these regional inequalities become more widespread. Any acute *superimposed* bronchial, parenchymal or vascular pathologic process will intensify the existing $\dot{V}_A/\dot{Q}_C$ imbalance and will cause further deterioration of the arterial blood gas (and pH) parameters. This is due, in part, to inadequate regional compensation of ventilation and/or perfusion, allowing ventilation and perfusion to *remain* distributed unevenly in relation to each other (24). Compensatory hyperventilation to hypoxemia is relatively minor until the arterial oxygen tension falls to levels of 60 mm. Hg.

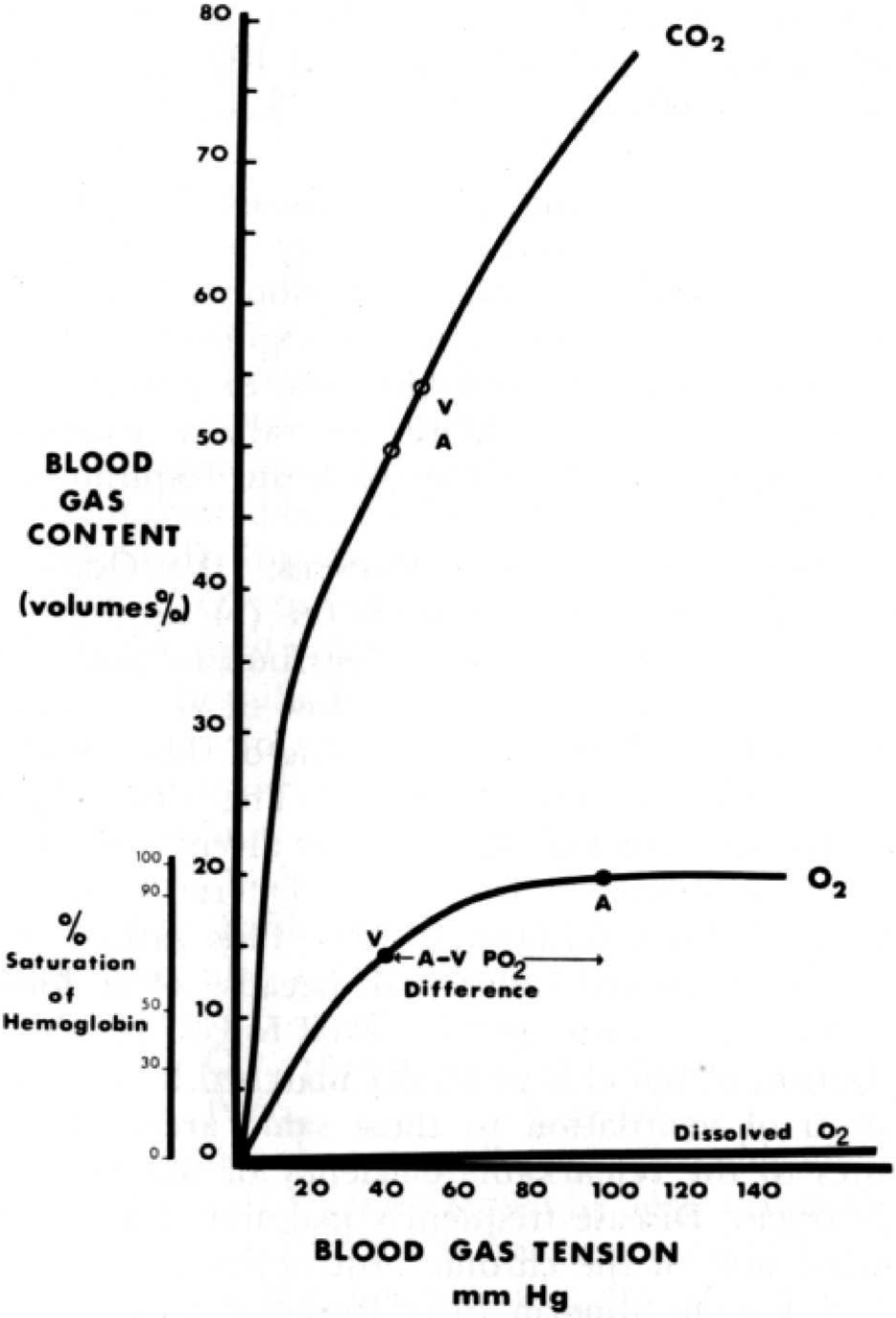


FIG. 6.—The carbon dioxide and oxyhemoglobin dissociation curves. The normal values for arterial and mixed venous blood are indicated at points A and V respectively, as well as approximate normal A-V O_2 and A-V CO_2 differences. Acidemia and increased temperature shift the oxyhemoglobin dissociation curve to the right. Note the essential linearity of the carbon dioxide relationships within the usual physiologic range. Dissolved oxygen in physical solution (volumes %) contributes a relatively small amount of oxygen carried in the blood within the physiologic ranges of O_2 tensions. Adapted from Senior and Fishman (25).

The two major types of $\dot{V}_A/\dot{Q}_C$ disturbances will be described. In the presence of complete or incomplete airway obstruction by bronchial secretions or with pneumonia, atelectasis or pulmonary edema, for example, local alveolar ventilation is reduced relative to continuing regional perfusion (low $\dot{V}_A/\dot{Q}_C$, < 0.8). This important process is termed increased *physiologic shunting* (venous admixture or shunt-like effect), and is a common cause of hypoxemia. Compensatory hyperventilation of any "normal" $\dot{V}_A/\dot{Q}_C$ ratio units *will not* significantly raise the O_2 content of the arterial blood, since the hemoglobin leaving these areas is already essentially fully saturated. Increases in their O_2 tension by overventilation can lead only to a small rise in plasma O_2 tension or hemoglobin saturation, i.e., the plateau of oxygen association-dissociation curve (Fig. 6). Thus, mixed venous blood perfusing any hypoventilated alveolar units will admix with blood from relatively well-ventilated areas, causing net hypoxemia. Carbon dioxide transfer, however, is less affected, because its dissociation curve is basically linear (Fig. 6), and provided other regional alveolar-capillary units are functioning, hyperventilation (within limits) will lower carbon dioxide tensions. Thus, depending on the magnitude of involvement, the final pulmonary venous blood may reveal hypoxemia, and hypocapnia, normocapnia or hypercapnia. With incomplete airway obstruction, if oxygen enrichment is provided in the inspired air, arterial oxygen tensions are increased, but where complete airway obstruction isolates the alveoli from the inspired oxygen, a right-to-left shunt exists.

The second abnormality arises under conditions of limited perfusion as with pulmonary emboli, reduced cardiac output, vascular obliteration associated with emphysema, hypotension or when large bullae are present. Here a significant portion of the minute ventilation is "wasted" on alveoli that are not perfused, or are poorly perfused; this is termed *increased physiologic dead* space ventilation $\dot{V}_A/\dot{Q}_C$, > 0.8). Normally, 25–30% of the minute ventilation is distributed to the physiologic dead space; the remainder contributes to alveolar ventilation and thereby gas exchange. Since $\dot{V}_A$ (alveolar ventilation) $= \dot{V}_E$ (minute ventilation) $-\dot{V}_D$ (dead space ventilation), it is clear that $\dot{V}_A$ depends on both $\dot{V}_E$ and $\dot{V}_D$ and that even where a known minute ventilation at the mouth is constant or increased, $\dot{V}_A$ is not defined unless $\dot{V}_D$ is known, and the latter may be extremely variable in disease. This latter point

TABLE 7.—EFFECT OF DEAD SPACE VENTILATION ON ALVEOLAR VENTILATION AT A CONSTANT MINUTE VOLUME: RELATIONSHIP OF RESPIRATORY FREQUENCY AND TIDAL VOLUME ON DEAD SPACE VENTILATION

RESPIRATORY RATE/MIN.	TIDAL VOLUME (ML.)	DEAD SPACE VOLUME (ML.)	$\dot{V}_E$ L./MIN.	$\dot{V}_D$ L./MIN.	$\dot{V}_A$ L./MIN.
40	187	150	7.5	6.0	1.5
30	250	150	7.5	4.5	3.0
10	750	150	7.5	1.5	6.0

and the adverse result of rapid, shallow breathing on $\dot{V}_D$ are clinically significant in management (Table 7). This dead space mechanism thereby reduces the total number of *effectively* ventilating alveoli. As a result, total ventilatory requirements must be proportionally increased to maintain an adequate alveolar ventilation. When over-all ventilation cannot be further increased and/or sustained to compensate for the dead space effect, progressive respiratory failure may ensue.

The distribution of $\dot{V}_A/\dot{Q}_C$ ratios at any given time will vary with local pathologic conditions, regional alveolar ventilation, perfusion and generalized ventilatory function. Since a documentation of both ventilation and perfusion is necessary for interpretation of $\dot{V}_A/\dot{Q}_C$ disturbances, and since $\dot{V}_A/\dot{Q}_C$ ratios vary widely in a given lung, a practical clinical approach presently employed for detecting such inhomogeneity is to measure arterial Pao_2, $Paco_2$ and pH when the patient in respiratory failure is breathing room air. Where hypoxemia *alone* exists, ventilation-perfusion inhomogeneity is the mechanism, provided anatomic shunting, reduced inspired O_2 concentration and diffusion barriers are absent. When both hypoxemia and hypercapnia are present, advanced inhomogeneity of ventilation-perfusion relationships prevails from extensive pulmonary disease, and/or generalized alveolar hypoventilation factors are operative, e.g., drug depression.

The distribution and volume of pulmonary capillary blood in bronchitis or emphysema may be altered by (1) hypoxic or acidotic vasoconstrictive influences and (2) actual vascular destruction. These factors increase vascular resistance, necessitating greater pressures in the pulmonary artery to maintain a given blood flow, and cor pulmonale may develop as a result of pulmonary hypertension. In addition, any reduction in *effective* blood volume (shock, anemia) will impair the diffusion of gases, since the latter is dependent on an adequate red cell mass transported with an appropriate contact time in the pulmonary capillary bed.

The treatment of hypoxemia and hypercapnia resulting from the above-described mechanisms is clarified by a consideration of the precipitating events; while hypoxemia alone is treated with oxygen, hypercapnia may require artificial ventilator support and elimination of respiratory depressant factors. We cannot emphasize too strongly that, as a practical clinical guide, precipitating causes of regional and/or generalized hypoventilation creating unfavorable changes in ventilation, perfusion and diffusion must be recognized.

Based on such pathophysiologic data, it should be apparent that the sequelae of the acute insult may be profound respiratory *and* cardiac failure, over and above that caused simply by irreversible destruction of gas exchange units in pulmonary emphysema. The key features in any patient are the *extent of parenchymal destruction* and the degree of *reversible* disease (e.g., infection, bronchospasm, secretions, heart failure). The role of the latter is critical, since these events compromise the significant cellular, immunologic and physiologic functional reserve. The practical clinical consequences of this concept are obvious: namely, the identification and treatment of reversible airway and parenchymal factors leading to acute respiratory and cardiac failure.

PRACTICAL DIAGNOSTIC GUIDELINES

The onset of acute respiratory failure may be insidious, and its effects difficult to recognize clinically. The usual evaluation (history, examination, x-ray, EKG, sputum characteristics) is useful in assessing the *nature* and *impact* of the disorder. The *diagnosis* of respiratory failure must be made by measurement of arterial $\mathrm{Pa_{O_2}}$, $\mathrm{Pa_{CO_2}}$ and pH. The arterial puncture is a safe, direct method for rapidly documenting this state. We have found the indwelling plastic arterial cannula valuable for the serial measurements necessary in proper care. The diagnostic feature of an arterial puncture is the intermittent spurt; color criteria are of little value, due to oxygen deficiency. Presently available pH meters are rapid, accurate and capable of handling small samples (1 ml.). Similarly, direct measurements of P_{O_2}, polarographically, by the Clark electrode, and P_{CO_2} by the Severinghaus electrode have facilitated the intelligent management of these disorders. All samples should be drawn anaerobically, limiting the volume of added heparin, since this may lower the pH. Assays should be performed quickly, but where delay is unavoidable, the sample should be on ice to retard deterioration.

HYPOXEMIA.—Any Pa_{O_2} must be interpreted in the context of adequate tissue delivery, i.e., cardiac output, hemoglobin levels, blood flow. A Pa_{O_2} of 100 mm. Hg in a patient whose hemoglobin is only 3 Gm. per 100 ml. reflects normal lung gas transfer of O_2 but will result in tissue hypoxia.

1. Clinical setting: Suggestive only.
2. Cyanosis: Unreliable index until saturation $< 70–75\%$ ($Pa_{O_2} = 40$ mm. Hg at pH 7.40).
3. Pa_{O_2} (arterial O_2 tension): Key measurement.
4. Blood hemoglobin O_2 saturation = arterial blood O_2 content per 100 ml./arterial O_2 capacity per 100 ml.: Important consideration.
5. Cardiac output: Important consideration.
6. Mechanical ventilatory tests (forced expired volume, MBC): indicate obstructive ventilatory defect but no necessary correlation with Pa_{O_2}.
7. For clinical purposes arterialized capillary blood may be analyzed for P_{O_2}, P_{CO_2} and pH.

HYPERCAPNIA AND EFFECTIVE VENTILATION

1. Clinical setting: Suggestive only.
2. Adequate ventilation.
    a. Minute volume, respiratory rate: Usually not valid.

  - *b.* CO_2 content, combining power: Not adequate.
  - *c.* End tidal CO_2: Limited value.
  - *d.* Rebreathing or arterialized venous P_{CO_2}: Reasonable; rebreathing method does not provide PO_2 or pH.
  - *e.* Arterial P_{CO_2} tension: Best.
  - *f.* "Effective" alveolar ventilation: Use Pa_{CO_2} as index; or measure $\dot{V}_{CO_2}$ and calculate

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{Pa_{CO_2}} \times .863 \ \frac{(CO_2 \text{ production in milliliters/minute})}{\text{arterial } CO_2 \text{ tension}},$$

in milliliters.

3. Acid-base status; pH_a.
  - *a.* Direct electrode: Best.
  - *b.* HCO_3 from nomogram by:

$$pH_a = 6.1 + \log \frac{(HCO_3)\ \text{mEq./liter}}{0.03\ Pa_{CO_2}\ \text{mm Hg}}.$$

OF INTEREST, NOT MANDATORY

1. Physiologic dead space/tidal volume ratio (normal = 0.33):

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2}},$$ or dead space estimated by

$$\dot{V}_D = \dot{V}_E - \dot{V}_A \text{ (minute-alveolar ventilation)}$$

2. Forced expiratory volume (FEV), maximum expiratory flow rate (MEFR), $FEV_{1.0}$, MBC: As tests of (a) obstructive ventilatory impairment and airway resistance and (b) deteriorating or improving ventilatory capacity.
3. Metabolic demands: $RQ = \frac{\dot{V}_{CO_2}}{\dot{V}O_2}$, normal 0.8.
4. Alveolar-arterial PO_2 gradient: (normal = 10–15 mm. Hg), increased with $\dot{V}_A/\dot{Q}_C$ imbalance, right-to-left shunting, or diffusion defect.
5. Shunt mechanisms: Pa_{O_2} following 100% O_2 for 30 minutes. Normal $\geqq$ 560–600 mm. Hg.

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