CLINICAL PROGRESS

Respiratory Insufficiency and Chronic Cor Pulmonale

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This article attempts to apply the new knowledge of cardiopulmonary function to a clearer understanding of the pathophiology, diagnosis and therapy of respiratory insufficiency and chronic cor pulmonale. The reserves or margin of safety of pulmonary function are very large. Thus, the normal untrained individual can increase his oxygen uptake and ventilation to approximately 10 times the resting level before exhaustion supervenes. Even at this point the respiratory reserves are not exhausted, because the ventilation at exhaustion is usually not more than half of the maximum breathing capacity. The capacity for work in the healthy individual is limited by the cardiocirculatory system rather than by the respiratory system. The case with which pneumonectomy is tolerated, when the contralateral lung is normal, is a direct demonstration of this fact. It is not surprising, therefore, that severe degrees of respiratory dysfunction may be present without disability or respiratory insufficiency.

Chronic pulmonary disease and chronic cor pulmonale are more frequent in industrial urban centers, particularly in the north temperate regions, among laborers, and in mining regions. Fulton1 states that in Manchester, England, chronic pulmonary disease as a cause of death ranks in frequency with rheumatic, hypertensive and ischemic heart disease, not because of a specific industrial hazard, but because of a common factor, exposure to a humid, highly polluted atmosphere. Chronic cor pulmonale and chronic obstructive emphysema are much more common in men than in women.

Flint2 studied 300 patients admitted with congestive heart failure to Sheffield City Hospital in one year (1952–1953) and found that the cause of the heart failure in 40 per cent of the males and 8.5 per cent of the females was chronic cor pulmonale, usually due to chronic obstructive emphysema.

Improved treatment of pulmonary infections and increasing thoracic surgery indicate a future rise in the incidence of chronic pulmonary insufficiency and chronic cor pulmonale.

I. Respiratory Insufficiency

A. Physiology of Respiratory Insufficiency

The primary function of the lung is the addition of oxygen and the removal of carbon dioxide from blood. The chest wall, its musculature and the diaphragm function as bellows which communicates with the outside environment via an airway. Gaseous exchange occurs in the alveoli which fill the bellows. In order for this system to function properly: (1) the airway must remain patent, (2) the bellows must be able to function normally, (3) inspired air must mix with the air present in the alveoli, (4) blood must be evenly distributed to the various alveolar capillaries, (5) there must be an adequate amount of alveolar surface in contact with normally perfused capillaries and (6) there must be no impediment to diffusion of oxygen across the alveolar capillary membrane.

The major phases of lung function may be categorized as follows: (1) the ventilation function or the mass exchange of air between the lungs and the atmosphere, (2) the distribution function (intrapulmonary mixing) which deals with the distribution of inspired air to the alveoli, (3) the distribution of mixed venous blood to the alveolar capillaries or capillary per-
fusion and (4) the interface diffusion function which deals with the molecular exchange of gas across the semipermeable alveolar capillary membrane. The cleansing function of the lung which deals with the disposal of foreign material will be discussed separately from ventilation for purposes of emphasis. The circulation of the lung, exclusive of the distribution of venous blood to the capillaries, will be discussed in section II.

These phases of pulmonary function have been arbitrarily defined and represent only a small number of the known functions of the lungs. For example, the lung is richly supplied with sensory nerve endings which, in addition to their role in regulation of respiration, may be important in the control of the circulation. The greatly distensible vascular bed of the lung acts as a variable reservoir of blood which may, for example, temporarily protect against overload of the left ventricle. The respiratory bellows acts as a pump to aid venous return to the heart. The filtering function of the lungs is an important protective mechanism. By trapping white blood cells, the lungs may, under certain circumstances, help regulate the number of white cells in the peripheral blood.

1. Cleansing

Cleansing is effected by external and internal disposal of foreign material. Endogenous inflammatory exudate and inhaled foreign substances become mixed with the mucus, which coats the tracheobronchial mucosa, and are constantly wafted toward the pharynx by ciliary action. Peristaltic action in the smaller bronchi, especially during forced respiration, probably also assists in this oral motion. Ciliary function may break down when the secretion is voluminous, is excessively viscid, or contains noxious substances (such as bacterial toxins). Chronic bronchial inflammation may result in permanent destruction of the cilia, often associated with squamous metaplasia of the epithelium. Under these circumstances, cough becomes important in keeping the airways clear. Once the injurious substance has reached the alveoli, an additional method of cleansing occurs: phagocytosis by macrophages.

In order for cough to clear bronchial secre-
tion, the bronchus must not be continually oc-
cluded; air must be able to pass behind the secretion, at least, during the full inspiration which precedes cough. By using the intrinsic and accessory muscles of expiration against a closed glottis, the patient builds up a high intrabronchial pressure. The glottis is then opened suddenly, permitting a rapid flow of air to the outside. A pressure gradient is created which moves secretion toward the pharynx. The cough force will depend on the volume (mass) of air behind the obstruction and its acceleration produced by the sudden opening of the glottis.

Cough becomes ineffective with loss of expiratory force, such as occurs with asthenia or neuromuscular disorders. Cough effectiveness is reduced by a decreased vital capacity because the volume of air escaping after opening the glottis becomes too small to move secretion. Local restriction of pulmonary ventilation, due either to pleural or pulmonary fibrosis or to chest-wall deformity, results in regional impairment of the effectiveness of cough as a cleansing mechanism. Thus, such areas may be especially susceptible to secondary infection.

2. Ventilation

(A) Normal Ventilation. Normal ventilatory function requires maintenance of a patent airway, normal elasticity (compliance) of the lungs and an intact thoracic bellows. The latter includes the spine, rib cage and cartilages, the sternum, the intrinsic and extrinsic respiratory muscles, the pleura and the skin.

The actual ventilation for any given level of oxygen uptake depends on the stimulus to respiration, determined by an aggregate of many controlling factors. There are (1) chemical stimuli mediated directly through the respiratory center in the medulla or by way of the aortic and carotid bodies and possibly other chemoreceptors, (2) proprioceptive stimuli coming from the lungs themselves and from the musculoskeletal system and (3) controls from the higher centers of the brain as well as other nervous influences.

There are well-defined limits of normal ventilation for a given level of oxygen uptake. An excess of ventilation for a given oxygen uptake is referred to as hyperventilation, a de-
ficiency as *hypoventilation*. The best gage of maximum ventilatory capacity is the maximum breathing capacity test. This is the volume of air which can be breathed per unit of time (liters per minute) by means of maximum voluntary hyperventilation. The best measure of the reserve of ventilatory function present in any given metabolic state is the relation between the actual ventilation and the maximum breathing capacity.

The air present in the airways (mouth, nose, pharynx, larynx, trachea and bronchi down to the respiratory bronchiol) at the end of the inspiration does not take part in gaseous exchange. The volume of these passages is known as the *anatomic dead space*. Air enters the alveoli, partly by mass movement into alveoli which dilate during inspiration and partly by boundary diffusion between gas in the alveoli and the respiratory bronchiol. In the normal person at rest, all alveoli are not equally ventilated; some receive more and others less than their share of inspired air. As a result, the dead space measured by physiologic technics is larger than the anatomic dead space (see below). The total volume of the inspired air which does not take part in gaseous exchange is known as the *physiologic dead space*. Fowler has recently shown that the physiologic dead space is not constant. It averages about 150 ml for young men and about 100 ml for young women but varies with position, tidal volume, state of lung inflation, exercise and age; as a rule, it does not exceed 250 ml.

It is important to think in terms of *alveolar ventilation* rather than *total ventilation*, since with different breathing patterns the alveolar ventilation may vary considerably with the same total ventilation. A number of indirect technics have been used to measure the alveolar ventilation, but it can be quite adequately estimated for clinical purposes by assuming a dead space on the basis of the mean figures given above. For example, in a male with a total ventilation of 12 liters per minute at a rate of 20 respirations per minute, the tidal volume (T.V., fig. 1) will be 600 ml. Assuming the dead space to be 150 ml, the dead space ventilation will be 3 liters per minute and the effective alveolar ventilation will be 9 liters per minute.

If, in this patient, the rate is changed to 30 per minute, but the total ventilation remains unchanged, the tidal volume would become 400 ml. Since the dead space remains fairly constant, the effective alveolar ventilation will fall to 7.5 liters per minute. It has been demonstrated that some alveolar ventilation occurs even when the tidal volume is less than the dead space. This is so, partly because some centrally located alveoli have less dead space than peripheral ones and partly because inhaled gas moves as a spike with resultant diffusion between the gas in the alveoli and in the bronchiol.

The determination of lung volumes is often very helpful in assessing the functional effects of abnormalities of the lungs and the thoracic bellows. The various compartments of lung volume, as recently defined, can be related to the schema of the respiratory system (fig. 1). A stop has been placed in the bottom of the bellows so that it cannot be completely emptied. The air remaining in the bellows when it has been maximally compressed represents the *residual lung volume* (R. V.), or the amount of air remaining in the lungs at the end of a maximal expiration. When the bellows is fully extended, the air it contains represents the *total lung capacity* (T. L. C.). The *vital capacity* (V. C.) is the volume of air which can be exhaled after a full inspiration; this is total lung capacity minus the residual lung volume. When

![Fig. 1. The normal lung volumes and capacities.](http://circ.ahajournals.org/)

The *volumes* do not overlap and are primary. The *capacities* are made up of two or more volumes. I.R.V., inspiratory reserve volume; T.V., tidal volume; E.R.V., expiratory reserve volume; R.V., residual volume; T.L.C., total lung capacity; V.C., vital capacity; I.C., inspiratory capacity; F.R.C., functional residual capacity. Note, in the normal spiographic tracing, the vital capacity is an almost vertical straight line.
the force extending the bellows is removed and the bellows is allowed to find the point at which its retractile force is in balance with the factors tending to resist deformity, it will be at the resting expiratory position and the volume of air then in the lungs will represent the functional residual capacity (F. R. C.). The volume of air which can be exhaled starting at the expiratory end position is known as the expiratory reserve volume (E. R. V.). The functional residual capacity is the sum of the residual volume and expiratory reserve volume. The vital capacity minus the expiratory reserve volume is the inspiratory capacity (I. C.) or the volume of air which can be inhaled starting at the resting expiratory position. The residual volume and therefore the functional residual capacity and total lung capacity must be measured by indirect technics. All other compartments can be measured by simple spirometry. 7, 9a, 10, 11

(B) Abnormal Ventilation. Abnormalities of ventilation may be divided into obstructive and restrictive ventilatory dysfunction. Restrictive ventilatory dysfunction is caused by disordered action of the thoracic bellows or diminished pulmonary distensibility. Obstructive ventilatory dysfunction is caused by narrowing of the air passages. It is apparent that an obstruction of a given size will have a much greater effect on air movement in the smaller airways than in the larger.

(1) Obstructive ventilatory dysfunction: The pathologic process resulting in airway obstruction may occur in the lumen of the bronchus, in the mucosa, in the wall of the bronchus or extramurally. The commonest pathologic process located in the lumen is tenacious secretion, the result usually of infection. Foreign bodies and neoplastic or inflammatory projections into the lumen are occasionally seen. The mucosa may be thickened and encroach on the lumen as a result of edema or congestion. Muscular spasm or inflammatory thickening of the bronchiolar wall narrows the lumen. The bronchus may be compressed extramurally by pathologic processes in the lymphatics such as lymphangitic carcinomatosis or by fibrosing processes in the pulmonary interstitium. Recent studies 12 have shown that loss of pulmonary elasticity, that is, loss of the power of the lung to retract after stretching, may also result in bronchial obstruction. The mechanism is that in order for air to leave the alveoli and enter the respiratory bronchiol during expiration, intra-alveolar pressure must become greater than intrabronchiolar pressure. Intra-alveolar pressure is exerted radially and tends to collapse the thin-walled respiratory bronchiol. This tendency toward collapse is normally resisted by the elastic retractile force of the lung. When the retractile force is decreased, bronchiolar collapse results. Since bronchiolar obstruction is associated with an increase in pressure gradient, bronchiolar collapse occurs much more readily in the presence of bronchiolar obstruction.

Airway obstruction results in an increased resistance to air flow which is manifested by a prolongation of the time necessary for expiration, as shown by the vital capacity breath in fig. 2. 12 The volume of the vital capacity may be normal or reduced, depending on the severity of airway obstruction, but the maximum breathing capacity is always reduced and is proportionally much smaller than the vital capacity. The work of breathing is increased. 12

Airway obstruction is always more marked during expiration than during inspiration because of the normal narrowing and shortening of the bronchi which occurs during expiration and because of the mechanism of bronchiolar collapse (described above). This results in the phenomenon of air trapping; since air can get

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**Fig. 2.** The lung volumes and capacities in obstructive ventilatory dysfunction. The residual volume (R.V.) and functional residual capacity (F.R.C.) are greatly increased, although the total lung capacity is normal. The vital capacity (V.C.) and expiratory reserve volume (E.R.V.) are decreased. Note the marked delay in the pressure-time curve of the vital capacity.
into the lungs more readily than it can get out, the lungs become hyperinflated or emphysematous. The airway obstruction and hyperinflation may occur acutely and be reversible as in asthma or may be chronic and irreversible as in chronic, diffuse obstructive emphysema. The hyperinflation is demonstrated by an increase in the residual volume and functional residual capacity and by reduction in the vital capacity in relation to the total lung capacity (fig. 2). Lung cysts or bullae which communicate poorly with the airways may not be included in the measured residual lung volume.

(2) Restrictive ventilatory dysfunction: This may be defined as impairment of the ability to move air into and out of the lungs as a result of a defect in the thoracic bellows or diminished pulmonary distensibility. The lung bellows is a very complex mechanism and a great many different pathologic conditions may affect its function. Bellows action is disturbed by impaired function of the respiratory muscles in poliomyelitis, myasthenia gravis or diaphragmatic paralysis. Less directly, it may be impaired by asthenia or by pain associated with pleurisy or with abdominal or thoracic surgery. The function of the bellows is impaired, if the mobility of its walls is impaired. This can result from loss of mobility of the bony framework, such as ankylosis of the costovertebral articulations in ankylosing spondylitis, or increased rigidity of the costal cartilages with advancing age. Loss of mobility and loss of volume of the bellows occur in kyphoscoliosis and after thoracoplasty. Thickening of the skin as in scleroderma or burn cicatrix and thickening of the pleura, as in pleural fibrosis, can decrease bellows mobility. Finally, all of the structures of the thoracic bellows may be intact but the distensibility of the lung may be reduced. This results from diffuse pulmonary fibrosis or congestion, or a process in the pleural space, such as pleural effusion or pneumothorax.

The position and mobility of the various structures of the thoracic bellows are the result of a balance of opposing forces so that loss of function of a portion of the bellows can often be partially compensated. When an artificial pneumothorax is induced, it can be shown that the volume of the lung decreases on the treated side, but the girth of that hemithorax increases. Similarly, an increase in excursion of the diaphragm follows restriction of the chest wall with a tight bandage.

Lung volume studies in restrictive ventilatory dysfunction show that the total lung capacity is reduced. The vital capacity is usually decreased proportionally to the reduction in total lung capacity, but the residual volume and functional residual capacity are either reduced or remain normal (fig. 3).

Restrictive ventilatory dysfunction often produces little pulmonary disability providing the airways remain patent. Although the stroke volume of the bellows or the vital capacity is reduced, in the absence of increased resistance to air flow, the patient can breathe with virtually all of the stroke volume at a more rapid respiratory rate. The maximum breathing capacity is thus proportionally much larger than the vital capacity.

(3) Combined ventilatory dysfunction: Restrictive ventilatory defects are often accompanied by an impairment of cleansing function; consequently, these patients show increased susceptibility to lower respiratory tract infection and, therefore, develop airway obstruction superimposed on the restrictive defect. This may be acute and transient, or may eventuate in the permanent structural changes of diffuse obstructive emphysema. Patients with combined restrictive and obstructive ventilatory dysfunction show a delay in emptying of the lungs during the vital capacity.
maneuver. Their total lung capacity is decreased and the residual volume and functional residual capacity are increased (fig. 4). Their maximum breathing capacity is proportional to the vital capacity or may even be proportionally smaller than the vital capacity.

3. Distribution

The normal occurrence of slight degrees of inequality of alveolar ventilation has already been noted above. However, uneven alveolar ventilation of more marked degree may lead to pulmonary insufficiency, even though the minute volume of breathing and the total alveolar ventilation are normal. Regional underventilation may be the result of bronchial obstruction or total loss of distensibility. Consider a situation where pulmonary capillary perfusion is uniform and alveolar ventilation is essentially even throughout the lung, except for one area where there is underventilation (fig. 5B). In the alveoli in this area, the partial pressure of carbon dioxide will be high and of oxygen, low. Consequently, the blood leaving this area will contain excess carbon dioxide and be undersaturated with oxygen. The excess carbon dioxide in the mixed arterial blood will stimulate the respiratory center resulting in an increase in total ventilation (fig. 5C). There will be a fall in carbon dioxide tension and a rise in oxygen tension in the normal alveoli which are being hyperventilated. The diffusibility of carbon dioxide is high and, therefore, the carbon dioxide tension will be low in the alveoli leaving these capillaries. Oxygen is much less diffusible than carbon dioxide and the shape of the dissociation curve of hemoglobin for oxygen is such that, in the range above 90 per cent, a considerable rise in partial pressure of oxygen results in only a very small rise in saturation of hemoglobin. Consequently, hyperventilation of normal alveoli cannot result in a marked increase in arterial oxygen saturation of the blood leaving their capillaries. The net effect of hyperventilation in this circumstance will be to correct the hypercapnia but not the hypoxemia. If the underventilation of alveoli is widespread, or if the impairment of ventilatory function is so great that the patient cannot hyperventilate adequately, hypoxemia will be associated with hypercapnia. This is the commonest mechanism of hypoxemia in pulmonary disease.

Figure 5F demonstrates a situation in which alveolar capillary perfusion and ventilation are uniform throughout except for a group of alveoli which are hyperventilated. The arterial blood leaving this latter area will have a slightly higher saturation with oxygen, and will contain less carbon dioxide than the blood from the rest of the lung. There will be little alteration of mixed arterial blood and the effect will be to increase the physiologic dead space.

4. Capillary Perfusion

Inequalities of perfusion also may have a profound effect on the results of uneven alveolar ventilation. Underperfusion of normally ventilated alveoli will have the same effect as hyperventilation of normally perfused alveoli, that is, the physiologic dead space will be decreased (fig. 5E). This occurs in areas of pulmonary embolization and in primary pulmonary hypertension. In the case of hypventilation of alveoli, if the alveolar capillaries are also underperfused (fig. 5D) the effect of underventilation on the arterial blood gases will tend to be nullified. Reduction of blood flow through underventilated portions of the lung occurs very frequently in extensive chronic pulmonary disease. The mechanism of local decrease in capillary blood flow in such instances is due to many factors which will be discussed in detail in section II. In some cases, there is an
FIG. 5. (Part 1) Schema of normal and abnormal states of alveoli. The following symbols are used: the stippled area in the bronchioles represents the respiratory dead space, the thickness of the vertical arrow in the bronchiole represents total ventilation; the thickness of the two smaller arrows represents alveolar ventilation; the solid black represents the alveolar capillary with mixed venous blood (v) entering at the top and mixed arterial blood (a) leaving at the bottom; the solid rectangle represents alveolar partial pressure of oxygen and the dotted rectangle alveolar partial pressure of carbon dioxide; SaO₂ represents saturation of arterial blood with oxygen; PaCO₂ partial pressure of carbon dioxide in arterial blood. N., normal; ↓, decreased; ↑, increased.

A. Schema of two normal alveoli with their bronchioles.

B. Regional hyperventilation due to airway obstruction. Regional bronchiolar obstruction is depicted by narrowing of the air passage to one alveolus. This results in reduced alveolar ventilation, with an increase in alveolar PCO₂ and decrease in alveolar PO₂. There is a consequent reduction in SaO₂ and increase in PaCO₂. The increased PaCO₂ may cause hyperventilation which is shown in C.

C. Regional bronchiolar obstruction with compensatory hyperventilation. The hyperventilation decreases PCO₂ and increases PO₂ in the normal alveoli with resultant elimination of excess CO₂ from arterial blood. Hyperventilation cannot compensate for the decreased SaO₂ of the blood coming from the hypoventilated alveoli and SaO₂ remains low.

D. Reduced capillary perfusion with regional hypoventilation. There is a decrease in blood flow through the capillary of the hypoventilated alveolus and as a result the regional ventilation has no effect on mixed arterial blood.
**Fig. 5. (Continued)**

*E.* Reduced capillary perfusion with normal ventilation. Alveolar ventilation is normal, but there is a regional decrease in capillary blood flow. The effect is to increase the respiratory dead space without effect on arterial blood gases.

*F.* Regional hyperventilation with normal capillary perfusion. Capillary blood flow is normal but there is regional hyperventilation of alveoli which results in increased respiratory dead space.

*G.* Decreased maximum diffusing capacity for oxygen due to alveolar-capillary block. This results in a marked depression of $S\bar{a}_O_2$. There is also hyperventilation which causes a fall in alveolar and arterial $P_{CO_2}$. The latter is possible because the diffusibility of $CO_2$ is so much greater than that of oxygen.

*H.* Decreased maximum diffusing capacity of the lung is due to loss of area of functioning alveoli in contact with functioning capillary.
actual anatomic obliteration of the vascular bed, due to fibrosis or destruction of capillaries as in emphysema; in many cases, the localized increased resistance to blood flow may be a result of local hypoxia. Expansion of anastomotic channels between the bronchial and the pulmonary arteries in this area may result in a more “arterialized” mixture of blood passing through these hypoventilated areas with less contamination of systemic arterial blood. In still other disease states decreased distensibility of the vessels may result in locally increased resistance to flow as in fibrosis, pneumothorax or pneumonia.

5. Diffusion

To enter the blood, gases must penetrate the alveolar epithelium, the interstitial space of the alveolar septum and the capillary endothelium. This movement occurs mainly by a process of diffusion or the movement of molecules from a region of higher to one of lower partial pressure. The diffusing capacity of the lungs is defined as the quantity of a gas, usually oxygen, transferred each minute per millimeter of mercury difference in partial pressure of the gas across the alveolar capillary barrier.

The diffusing capacity of the lungs is determined by the surface area available for diffusion and the thickness and character of the tissues constituting the alveolar barrier. The total surface for gas exchange consists of the area of functioning alveoli in contact with functioning capillaries. In man, this area is estimated to be about 90 square meters at rest. It is enlarged during exercise, probably as a result of an increase in the number and size of patent capillaries and in the number of functioning alveoli. It is reduced following pulmonary resection, with destructive pulmonary disease and in pulmonary fibrosis (fig. 5H). A reduced oxygen diffusing capacity also may occur in pulmonary emphysema because many capillaries are in contact with poorly ventilated alveoli.

Thickening of the alveolar capillary barrier by disease will impede the passage of the oxygen molecules into the capillary blood and so will decrease the oxygen diffusion capacity of the lung19, 20, 22 (fig. 5G). Because of greater solubility, carbon dioxide is more than 20 times as diffusible as oxygen and is much less affected by thickening of the alveolar capillary membrane. Consequently, where the main abnormality is thickening of this membrane, severe degrees of hypoxemia may coexist with normal partial pressures of carbon dioxide in arterial blood. Indeed, the partial pressure of carbon dioxide in arterial blood may be low as a result of the associated marked hyperventilation usually seen in this condition.26

This thickening of the alveolar capillary membrane may occur as a result of intra-alveolar or interstitial pulmonary edema or it may be due to granulomatous or neoplastic infiltration. The term “alveolar capillary block” has been applied to conditions in which the chief disturbance in pulmonary function is a decrease in the diffusing capacity.22 In these cases there is usually restrictive ventilatory dysfunction, little or no reduction of maximum breathing capacity and no abnormality of distribution of inspired air. This has been found to occur at times in beryllium granulomatosis, certain types of diffuse pulmonary sarcoaidosis, pulmonary scleroderma, asbestosis and diffuse pulmonary endolymphatic carcinomatosis.

B. Relation of Function to Pathology

Many pathologic conditions affect the lung and produce functional disturbances. The same abnormal physiologic change may result from different pathologic conditions and a particular disease may give rise to many functional patterns. This discussion will, therefore, be confined to the relationships between the pathologic processes and derangement of function in interstitial pulmonary infiltration, or “pulmonary fibrosis,” and chronic diffuse obstructive emphysema.

The word “fibrosis” has been used in various ways by different observers. It has become a general term for a large number of conditions, in which the only common factor is the proliferation of connective tissue. For want of a better term, the word has persisted in the literature and in the day to day discussion of patients with pulmonary disease. However, the term is inaccurate, since the pathologic process in many conditions may be granulomatous or even neoplastic. Better perhaps would be “interstitial
pulmonary infiltration," which may then be qualified as to etiology, as to extent, and as to whether the process is predominantly fibrous or granulomatous. When the process is localized or focal, there are no demonstrable effects on cardiopulmonary function. The effect of diffuse disease depends to a large extent on the location of the disease with respect to the various functional elements of the lung. If the process is localized in the alveolar septa, it may result in alveolar capillary block with marked hypoxemia or may give rise to constriction of the vascular bed of the lung with resultant pulmonary hypertension. Chronic diffuse obstructive emphysema may result when there is loss of pulmonary elasticity and bronchiolar obstruction. When the process is located primarily in alveolar spaces and results in loss of both alveolar ventilation and capillary perfusion, little loss of function results unless the process is very extensive.

Chronic diffuse obstructive emphysema may be defined as a syndrome in which there is hyperinflation of the lungs associated with diffuse obstruction of the small airways and loss of pulmonary elasticity.

The process may be secondary to diffuse interstitial infiltration or may be of the type called idiopathic. While all agree that diffuse airway obstruction and loss of pulmonary elasticity are outstanding, there has been much controversy as to which of these processes is primary. The resolution of the problem is a difficult one since loss of pulmonary elasticity causes bronchiolar collapse during expiration. Certainly, in most cases it would appear that chronic bronchial infection with obstruction has been important in the genesis of the disease. However, there are occasional patients who are asymptomatic until an episode of lower respiratory tract infection makes evident the presence of diffuse obstructive emphysema. It is possible that in these patients a primary degenerative process has caused loss of pulmonary elasticity and bronchiolar obstruction. Some credence is lent to this theory by recent pathologic studies which have demonstrated almost complete obliteration of the intrapulmonary bronchial arteries.

Chronic diffuse obstructive emphysema is associated with an absolute increase in the residual volume and functional residual capacity and a decrease in the vital capacity and the maximum breathing capacity. There is a marked increase in the work of breathing. The increase in the functional residual capacity coupled with the widespread but irregular loss of pulmonary elasticity and bronchiolar obstruction results in a marked impairment of the distribution of inspired air. Under certain circumstances, obliteration of pulmonary capillaries is a feature and this, in association with a patchy increase in intra-alveolar pressure, results in inequality of capillary blood flow. In the earliest phases, impaired distribution is slight and the chief abnormality is the disturbed mechanics of ventilation. As the disease progresses, hyperventilation may result in a decrease of the partial pressure of carbon dioxide in arterial blood during exercise without significant hypoxemia. At a later stage, particularly when there is superimposed infection, hypoxemia occurs. Later, hyperventilation becomes inadequate and hypercapnia results. Finally, the respiratory center becomes relatively insensitive to carbon dioxide and hyperventilation results. Under these circumstances the chief stimulus to respiration is hypoxemia acting on the aortic and carotid chemoreceptors.

C. Diagnosis of Respiratory Insufficiency

1. Clinical Examination

The diagnosis of respiratory insufficiency generally requires an evaluation of dyspnea, since this is the commonest presenting symptom. Primary cardiac disease with secondary pulmonary congestion must be excluded. The history is of considerable help. Wheezing or a conscious difficulty in moving air indicates the presence of airway obstruction. Sighing respiration, hyperventilation at rest without associated effort dyspnea or gross inconstancy of the amount of effort causing dyspnea suggest a psychogenic origin of symptoms. The presence of chronic cough, often considered minor by the patient, and a history of recurrent lower respiratory tract infection point to respiratory insufficiency as a possible cause of dyspnea.
The physical examination is of value, chiefly in detecting the gross evidences of pulmonary disease. Inspection quickly discloses the presence of a thoracic deformity. The increase in anteroposterior diameter of the chest may be misleading. While it is often a prominent feature of chronic obstructive emphysema, it may also be present in simple overdistension of the lung as in senile emphysema, where there is very little functional impairment. An increased anteroposterior diameter may be absent in chronic diffuse obstructive emphysema associated with diffuse interstitial infiltration in which there has been a decrease of total lung capacity. Far more important is the frequent fixation of the chest near the position of inspiration with marked limitation of chest wall excursion. Diaphragmatic excursions as determined by percussion are decreased. Frequently one may see paradoxic outward bulging of the upper abdominal wall during expiration. Prolongation of the expiratory time, beyond the normal four seconds, during determination of vital capacity can be readily detected at the bedside. The intensity of the breath sounds on auscultation does not correlate well with the degree of ventilatory dysfunction. Rales serve only to indicate the presence of pulmonary disease without indicating functional significance. The importance of the elicitation of rhonchi or the localized wheeze cannot be overemphasized. These should be listened for during both quiet and forced expiration. Frequently, a wheeze can be detected only by listening to the dependent lung with the patient in the lateral recumbent position. Bronchiospirometric studies have shown that when the patient is in the lateral recumbent position the dependent lung carries out more of the total ventilation than when the patient is upright.  

2. Roentgenologic Examination

The single full inspiration chest roentgenogram may be misleading from the functional standpoint. Such a film serves to indicate the presence of pulmonary disease but gives no good indication as to the presence or extent of disturbed pulmonary function. Severe disturbances of pulmonary function may be present with little change in the roentgenogram. Extensive disease processes with much structural changes may heal without giving rise to any roentgenologic residual. Furthermore, abnormalities in bronchial function are not manifest in the roentgenogram.

Much more information is obtained by a careful fluoroscopy of the lungs oriented toward functional evaluation. The skilled observer can often make a remarkably accurate estimate of the type and degree of ventilatory dysfunction by this means. The degree of filling and emptying of the lungs can be estimated by changes in volume and density of the lungs. Airway patency can be judged from the rate of emptying. Localized inequalities of ventilation due to bronchial narrowing or loss of elasticity can be detected by trapping of air in these areas during forced expiration. Chest wall and especially diaphragmatic motion can be evaluated. Shift of the mediastinum from the midline during respiration indicates inequalities in emptying or filling of the two lungs. Chest roentgenograms taken in the frontal projection in both full inspiration and full expiration are better than the single inspiration roentgenogram but are no substitute for fluoroscopy.

3. Pulmonary Function Studies

A complete physiologic evaluation is impossible without pulmonary function studies. The technics of pulmonary function testing have been amply reviewed recently and will be dealt with only briefly here. Ventilatory function can be evaluated by means of determination of lung volumes, tidal volume and minute ventilation during rest and exercise, and maximum breathing capacity. Alveolar ventilation can be calculated on the basis of an assumed physiologic dead space. Reversible airway obstruction can be studied by determining the effect of a bronchodilator drug on the maximum breathing capacity, or on one of the tests which relate the vital capacity to time. The distribution of inspired gas can be evaluated during measurement of the functional residual capacity or by one of the single breath tests using rapid electronic analyzers. The maximum diffusing capacity of the lung requires more elaborate analytic technics, but its impairment can often be inferred if there is
arterial hypoxia without significant dysfunc-
tion of ventilation or distribution. Much
information can be obtained by study of arterial
oxxygen saturation while the patient is breathing
room air and while breathing oxygen. The
determination of partial pressure of carbon
dioxide, by calculation from the determined
carbon dioxide content and pH of the blood, is
of great value for diagnosis and for following
the course of patients.

Pulmonary function tests attain their great-
est usefulness when carefully evaluated in
conjunction with clinical and roentgenologic
studies. Pathologic processes may be quite ex-
tensive and yet be accompanied by little or no
abnormality of pulmonary function tests. Loss
of function following disease must be quite
large for the test to be outside the wide range
of normal. Function tests, furthermore, do not
make a pathologic or etiologic diagnosis. Accord-
ingly, we have found it helpful in planning
and evaluating therapy to record a physiologic
as well as a pathologic and etiologic diagnosis.
This is similar to the practice introduced some
years ago for heart disease by the New York
Heart Association and adopted by the Ameri-
can Heart Association.

II. Chronic Cor Pulmonale

A. General Considerations

Chronic cor pulmonale may be defined as
right ventricular hypertrophy resulting from
disease involving the lung and the pulmonary
circulation. Right ventricular failure need not
be present. Excluded from this category are
other causes of right ventricular hypertrophy
such as mitral stenosis, congenital heart disease
and left ventricular failure.

Only in recent years is the true incidence of
chronic cor pulmonale being recognized. In
the past, cases were overlooked not only in
clinical studies but also at necropsy. The
cachexia of chronic pulmonary disease is often
associated with some degree of atrophy of the
entire heart, so that relative hypertrophy of
the right ventricle may be overlooked. With
the employment of technics, in which a ratio of
left to right ventricular weight or left ventricu-
lar and septum to right ventricular weight is
obtained, a higher necropsy incidence of chronic
cor pulmonale is already being reported.

B. Causes of Chronic Cor Pulmonale

From the definition given of chronic cor pul-
monale it is obvious that the primary cause is
usually some form of pulmonary disease. How-
ever, the involvement of the lungs must be
bilateral and diffuse, and not unilateral or focal.
In the past, chronic cor pulmonale has
usually been classified on the basis of the
anatomic location of the pulmonary disease
which causes it. A more useful classification
relates anatomic and functional abnormalities
and, in addition, has important therapeutic
implications. It divides the causes of chronic
cor pulmonale into two main categories: Type
I, pulmonary diseases associated with chronic
diffuse obstructive emphysema and type II,
pulmonary diseases in which the pathologic
process is localized in or about the pulmonary
vessels. These two types are not rigidly ex-
clusive.

1. Type I: Pulmonary Disease with Predomi-
nant Chronic Diffuse Obstructive Emphysema

Chronic diffuse obstructive emphysema is
the commonest cause of chronic cor pulmonale
in the United States. Therapy tends to be
much more satisfactory in this group than in
chronic cor pulmonale, due to disease mainly
localized in or about the pulmonary vessels. In
the former condition intensive treatment of
infection produces an adequate airway, im-
proves alveolar ventilation, enlarges the pul-
monary vascular bed and abolishes hypoxia,
thus reversing the very changes which caused
the chronic cor pulmonale.

The commonest cause of chronic diffuse ob-
structive emphysema is chronic bronchitis,
often, but not necessarily, associated with
bronchiectasis. Chronic bronchitis is, there-
fore, the commonest cause of chronic cor pul-
monale in this country.

Bronchial asthma produces chronic cor pul-
monale only if it is severe, of long standing and
associated with a secondary infectious bron-
chitis. Excluded from this discussion is the
acute transitory elevation of pulmonary artery
pressure observed during an acute prolonged episode of bronchial asthma (status asthmaticus).

Kyphoscoliosis, when of more than moderate severity, frequently leads to chronic cor pulmonale. In kyphoscoliosis, respiratory embarrassment and eventually cardiac dysfunction are usually not present early in life but develop only after the passage of time. This time interval is an important clue to the pathogenesis of the pulmonary and circulatory changes. During this interval, these patients suffer from acute recurrent and chronic bronchopulmonary infections because of interference with bronchial cleansing, impairment of the bellows action of the chest wall and diaphragm and because of a poor tussive mechanism. These eventuate in the development of chronic obstructive emphysema. We have not seen chronic cor pulmonale in such patients in the absence of these changes. There is no evidence that kinking of the main pulmonary artery is important in this regard.

Tuberculosis is not an infrequent cause of chronic cor pulmonale. In most instances, the tuberculosis has been of long standing and has resulted in severe chronic obstructive emphysema. Again, it is the bronchial factor which is important. Associated extensive loss of pulmonary parenchyma by necrosis with scarring, marked pleural reaction, extirpative surgery and collapse measures often play a secondary role.

Sarcoidosis causes chronic cor pulmonale only when the pulmonary involvement is diffuse. The roentgenographic appearance may be deceptive; usually the pulmonary involvement is more marked than is evident. Pulmonary sarcoidosis severe enough to cause chronic cor pulmonale may be of two types. In the first type, the granulomata are predominantly peribronchial and endobronchial in location, causing diffuse bronchial obstruction and severe obstructive emphysema. In the second type, the granulomata are located predominantly interstitially and in the interalveolar septa, compressing arterioles and capillaries. If the changes of this latter type predominate, this group will fall into the type II category of causes of chronic cor pulmonale. A patient however may have varying combinations of both types.

2. Type II: Pulmonary Disease with Predominant Involvement of Vessels

This category of pulmonary disease leading to chronic cor pulmonale includes diseases with involvement predominantly of the pulmonary vessels (intraluminal or extraluminal). Among the intraluminal processes are multiple repeated small pulmonary emboli, the importance of which has only recently been fully recognized. The embolizations may take place over protracted periods of time, frequently without the usual clinical manifestations, and eventually lead to a marked reduction in the pulmonary vascular bed. The emboli are recognized only when lung sections are examined pathologically. With organization and recanalization, many of the vessels show changes that resemble arteriosclerosis, especially fibrous intimal thickening. Such cases in the past have not infrequently been considered as examples of primary pulmonary hypertension. However, it seems quite certain now that primary pulmonary hypertension as an entity does exist. In this condition, there are progressive right heart enlargement and right heart failure, no signs of pulmonary disease at autopsy, but the advanced cases show extensive changes in the pulmonary arterioles and arteries. There is suggestive evidence that these sclerotic changes are secondary to some unknown factor causing an increase in pulmonary arterial pressure.

Sickle cell anemia with multiple small pulmonary capillary thromboses has also been described as causing chronic cor pulmonale. Schistosomiasis, due to Schistosoma mansoni or hematobium, may cause an extensiveobliterating endarteritis due to massive and repeated infections of the lung with the ova of the parasites. It is a rather common cause of chronic cor pulmonale in Egypt. The obliterating endarteritis is often followed by canalization of the occluding tissue by newly formed capillaries that sometimes dilate to form angiomatoid structures. These have been considered as typical of pulmonary schistosomiasis, and in some way an adaptation to the obstruction to the pulmonary circulation.
Extraluminal processes include granulomatous or fibrous proliferation in the interstitial tissue of the lung, particularly in the interalveolar septa. These conditions, in addition to producing alveolar capillary block, also cause a marked reduction in the caliber of the pulmonary vascular bed, thus increasing greatly the resistance to blood flow. In this group may be placed beryllium granulomatosis, scleroderma, acute interstitial fibrosis of the lung (Hamman-Rich syndrome), silicosis, sarcoidosis, of the second type discussed above, and other diffuse pulmonary granulomatoses of undetermined etiology. Metastatic carcinomatosis of the lung, with perivascular lymphatic spread, may produce a carcinomatous endarteritis as well as mechanical compression of the arteries and arterioles by the desmoplastic character of the cords of carcinoma cells. Extension of such endolymphatic carcinomatosis into the interalveolar septa may also produce alveolar capillary block to a varying degree. Further reduction of the pulmonary vascular bed may sometimes result from multiple emboli, composed of either tumor tissue or blood clot from deep vein thromboses in the lower extremities. The progression of events leading to right heart hypertrophy, dilatation and failure is often so rapid that this type has been called subacute cor pulmonale. Marked compression of the main pulmonary artery or both of its major branches, while strictly speaking not pulmonary disease, has been reported to cause chronic cor pulmonale. This has been described with an aneurysm of the concave portion of the ascending aorta or due to carcinomatous lymph nodes. Massive thromboses in the main pulmonary arteries, usually secondary to emboli, but sometimes autochthonous, are also on record as a rare cause of chronic cor pulmonale.

3. **Combinations of Types I and II**

Combinations of conditions in the above two categories may occur. The commonest combination arises from the complicating presence of chronic obstructive emphysema in conditions in which the pathology tends to be localized primarily about the pulmonary vessels, as in sarcoidosis (see above). In some cases of silicosis the predominantly perivascular location of the nodules was the main cause of the pulmonary hypertension and chronic cor pulmonale. However, in most cases of silicosis when severe respiratory insufficiency and chronic cor pulmonale occur, there is complicating severe diffuse obstructive emphysema. The latter is chiefly responsible for the development of chronic cor pulmonale. In some silicotic patients, thrombosis of a major branch of the pulmonary artery occurs and contributes to the reduction in the pulmonary vascular bed.

C. **Pathogenesis of Type I Chronic Cor Pulmonale**

The development of hypertrophy of the right ventricle in chronic diffuse obstructive emphysema is a result of right heart strain. The increased work of this chamber results from increased resistance to pulmonary blood flow and sometimes from augmented cardiac output. In considering particular pathologic processes in detail, it is important to note whether or not they are reversible, since it is this very element of reversibility which offers hope when therapy is attempted.

1. **Increased Resistance to Pulmonary Blood Flow**

Increased resistance to blood flow through the lungs in chronic obstructive emphysema results from: (A) a reduction in the cross-sectional diameter and distensibility of the pulmonary vascular bed, (B) increased viscosity of the blood if polycythemia has developed and (C) possibly certain dynamic consequences of an expansion of intrapulmonary vascular shunts.

(A) **Reduction in Cross-Sectional Diameter and Distensibility of the Pulmonary Vascular Bed.** Normally, the pulmonary circulation operates under low pressure with a low resistance to blood flow. This low resistance is a result of the large capacity and caliber of the vascular bed, and the marked distensibility of the pulmonary vessels. In normal man in the upright position, pressure in the pulmonary artery remains unchanged even when the cardiac output is doubled. Brofman was able to show in a patient with hyperthyroidism, that even with the right pulmonary artery occluded...
by means of an inflatable balloon-tipped cardiac catheter and with a left lung flow of approximately eight times normal, only a moderate increase in pulmonary artery pressure resulted. He concluded that in the presence of a competent left ventricle, the left lung in man accommodates 8 to 10 times normal flow without increments in pressure or evidence of right ventricular failure. Thus, a marked increase in pulmonary blood flow may occur, with only an increase in velocity of flow and in the caliber of the vascular bed, but with little or no increase in pulmonary artery pressure. Contributing to the increase in size of the vascular bed is not only the distensibility of the individual vessels, but also the opening up of vessels formerly not functioning for flow. The distensibility of the pulmonary vascular bed may be lowered by a reduction in the total number of vessels in the lung (since each vessel contributes its increment of distension), by a reduction in caliber of the vessels, and by conditions making the individual vessel walls more rigid.

The following pathologic changes contribute to the reduction in cross-sectional diameter and distensibility of the pulmonary vascular bed:

1. Rupture of interalveolar septa, with the conversion of many small air spaces into fewer larger air spaces and bullae, results in a true loss of capillary bed. In addition, many of these bullae actually compress surrounding parenchyma and so collapse some of the remaining capillary bed. Treatment may reduce the size of bullae.

2. Further reduction in the vascular bed in the lung results from loss of pulmonary parenchyma in areas of necrosis with replacement by scar which is relatively avascular, and which frequently is supplied with blood from the bronchial rather than the pulmonary arteries.

3. Vascular narrowing and diminished distensibility may result from a number of changes. Actual compression of vessels occurs in the scattered areas of alveolar exudate, atelectasis and entrapment of air; this is reversible. Cuffing of arterioles by inflammatory exudate and fibrosis will also produce narrowing. In many of the arterioles, capillaries, and sometimes small pulmonary arteries, actual thrombosis occurs. These changes may be partially reversible, the perivascular inflammation resolving without the development of scar tissue and the thrombotic vessels becoming recanalized. Vessel changes secondary to the development of increased intravascular pressure also contribute to vascular narrowing. These include endarteritis obliterans, medial hypertrophy, occasionally actual necrotizing arteriolitis, and not infrequently pulmonary atherosclerosis. These changes increase resistance to blood flow and hence pulmonary vascular pressure; the latter furthers the secondary hypertensive vascular morphologic changes. A vicious cycle thus may become established. It is obvious that the changes in the small vessels are more important than atheromatous changes in the pulmonary arteries unless the latter lead to actual thrombosis. It is known from studies of the lungs in other conditions where secondary vascular changes occur, such as mitral stenosis and some types of congenital heart disease associated with pulmonary hypertension, that many of the secondary vessel changes are reversible, particularly the endarteritis obliterans and the medial hypertrophy.

4. Hypoxia is an important cause of vascular narrowing and increased pulmonary artery pressure. Hypoxia produces an increase in pulmonary vascular resistance by an actual reduction in the caliber of the lung vessels, apparently by a direct action; the exact site of this vascular constriction is as yet unknown—various investigators have placed it in the pulmonary arterioles, capillaries or venules. Hypoxia may cause an increase in the residual blood in the lungs by a redistribution from the systemic circulation; this would limit further increase in pulmonary vascular capacity. Hypoxia produces an increase in cardiac output; in the face of an already restricted pulmonary vascular bed, this contributes to the pulmonary hypertension. Hypoxia and its effects are reversible.

(B) Polycythemia. Secondary polycythemia when present is the result of direct hypoxic stimulation of the bone marrow. However, in spite of the presence of marked arterial oxygen
desaturation, many patients with chronic obstructive emphysema are not polycythemic. It has been suggested that chronic infection (bronchopulmonary) may be one of the factors causing failure of the hematopoietic response.

Secondary polycythemia is associated with an increased blood viscosity and an increased blood volume. The increased viscosity increases the resistance to blood flow in the lungs, but to what extent is unknown.

The increased blood volume in secondary polycythemia is due almost entirely to an increase in red cell mass; the plasma volume is usually normal except in the presence of congestive failure, or immediately after recovery from failure. This hypervolemia is usually associated with an increased venous return, an increased cardiac output and probably an increased residual volume of blood in the lungs. An increase in the residual blood in the lungs in the face of an already limited pulmonary vascular capacity may result in a further encroachment on the ability of the pulmonary vascular bed to accommodate an increased blood flow without an increase in pressure. Since satisfactory methods are not available for determining pulmonary residual blood volume, the importance of this factor cannot be evaluated.

Lewis and associates\(^\text{53}\) have stressed that oxygen transport (product of cardiac output and arterial oxygen content) is frequently more important than cardiac output alone. Thus, secondary polycythemia in patients with chronic obstructive emphysema is an attempt at compensation, not only because the polycythemia may lead to an increased oxygen content of the arterial blood, but because the hypervolemia by increasing venous return to the heart helps to increase cardiac output and maintain a high pulmonary blood flow. Such indeed occurs in normal people exposed to high altitudes, where the adjustment to hypoxemia includes polycythemia, and often also increased cardiac output. However, in a patient with chronic obstructive emphysema, the deleterious effects of the polycythemia probably outweigh at some point the possible compensatory advantages, because the lungs have a vascular bed which is reduced in size and distensibility. It is possible that in the future the exact extent to which phlebotomy should be employed in therapy will be determined from correlative studies of viscosity, pulmonary vascular resistance, pulmonary residual blood, total blood volume and cardiac output. At present, we feel that phlebotomy should be utilized moderately in therapy, always in conjunction with all the other therapeutic procedures available to treat the pulmonary disease.

(C) Intrapulmonary Vascular Shunts. While there is not complete agreement about the extent or even the existence of precapillary anastomoses between the bronchial arteries and the pulmonary arteries in the normal human lung,\(^\text{54} \text{55}\) their presence and considerable size has been clearly demonstrated in diseased lungs.\(^\text{55}\) In dogs, following ligation of one pulmonary artery, collateral circulation from the bronchial arteries will expand to such an extent that one third of the cardiac output can be carried by the bronchial arteries on that side.

Large and numerous precapillary shunts between the bronchial and pulmonary arteries have been demonstrated in lungs with chronic bronchial infection, tuberculosis and chronic fibrosing disease. The expansion of these anastomoses in chronic obstructive emphysema has been related to their development or enlargement in granulation tissue, in areas of organizing pneumonitis, in the walls of bronchiectatic sacs and in areas of lymphoid hyperplasia and hypertrophied bronchial smooth muscle.

What could be the consequences of these functioning anastomoses between a high and low pressure system? (1) They might act to shunt desaturated pulmonary artery blood away from poorly ventilated areas of the lung in which they occur to the greatest extent; thus, whatever blood does pass through these poorly ventilated areas would have a higher oxygen content and less pollution of the systemic blood would occur. (2) They increase the blood flow through the lungs and, in the presence of a restricted vascular bed, serve to elevate further pulmonary artery pressure (3) They tend to increase the work of the left ventricle, since in effect they are a shunt between the left ventricle and the left atrium. (4) They may produce an actual local reversal
of blood flow in the pulmonary artery towards the hilum in some areas; catheterization of patients with extensive bronchiectasis limited to one lung has been shown to yield blood from the pulmonary artery on the affected side that was almost arterial in character.

The existence of anastomoses between the bronchopulmonary veins and the pulmonary veins was first described in normal lungs by Zuckermandl in 1882. The bronchopulmonary veins are usually called bronchial veins, but the former term is preferable because they drain not only the bronchi but also interstitial pulmonary tissue. The smaller bronchi are drained by the pulmonary veins, while the bronchopulmonary veins drain the proximal two to three orders of branches of the trachea and surrounding interstitial tissue. The bronchopulmonary veins drain into the azygos and hemiazygos system, the pulmonary veins into the left atrium. Normally, blood flow across these anastomotic channels is from the pulmonary veins to the bronchopulmonary veins thence to the azygos or hemiazygos veins. The pressure in the left atrium then in the right atrium and valves at the site of entrance of the bronchopulmonary veins into the azygos and hemiazygos veins insures this unidirectional flow. The value of these anastomoses is seen where suppuration exists in the lungs, causing thrombosis of pulmonary veins. Then blood is drained away from the area by the bronchopulmonary veins.

In chronic obstructive emphysema great expansion in the extent and size of these anastomotic venous channels has been demonstrated. The causes of this expansion are not completely understood. Liebow has suggested that changes in the respiratory pumping action in chronic obstructive emphysema which affect the truly pulmonary venules to a greater extent than the more protected bronchopulmonary venules might favor this expansion. Bullae have been shown to represent expanded parts of the respiratory tract more proximal than alveoli, and the venous drainage of these structures is by way of the bronchopulmonary veins rather than the pulmonary veins, just as their arterial supply comes from the bronchial arteries. Also, it has been shown that the walls of bullae contain granulation tissue and much smooth muscle. During the formation of granulation tissue these anastomotic channels form and persist even after resolution of cicatization.

In chronic obstructive emphysema an actual reversal of flow in these expanded channels may occur, so that blood would flow from the bronchopulmonary veins into the pulmonary veins. This might occur particularly in chronic cor pulmonale with right heart failure where the pressure in the azygos-hemiazygos system will exceed that in the pulmonary veins. In addition, dilatation of the bronchopulmonary veins will cause stretching of the valve rings at their connections with the azygos or hemiazygos veins, producing incompetency of these valves. Such reversal of blood flow would tend to cause pollution of systemic arterial blood by desaturated hypercapnic venous blood, and could thus furnish an important proportion of the venous admixture in the arterial blood.

This expansion of the bronchial arterial and bronchopulmonary venous systems in chronic obstructive emphysema has not been quantitatively evaluated in any given case. Nor has it been possible to estimate its relative importance during exercise and at rest. Yet, evidence for its existence should stimulate the development of methods for this type of assessment.

Precapillary anastomoses between pulmonary arteries and the pulmonary veins have been demonstrated in normal man, but they are apparently not extensive enough to be significant. The perfusion of poorly ventilated parts of the lung is equivalent in effect to shunting blood from the pulmonary arterial to the pulmonary venous system. However, this phenomenon is minimized, since blood flow through these areas usually is reduced markedly by all the mechanisms described as causing an increased resistance to blood flow.

2. Cardiac Output

The cardiac output in chronic cor pulmonale due to chronic obstructive emphysema has been the subject of some controversy. Some observers have been impressed by the frequency of high cardiac output and others have emphasized the presence of low cardiac output. The cardiac output at any particular
time will depend on the complex interplay of the many variables. It will depend not only on the type and extent of pulmonary disease present but also on the stage in which the patient is being studied, and will thus be affected by the presence of intercurrent acute bronchitis or pneumonitis, the degree of hypoxia, the presence and severity of polycythemia, the blood volume and the presence and degree of heart failure.

The following mechanisms act to increase cardiac output in chronic cor pulmonale. Hypoxia acts directly to increase cardiac output. If polycythemia is present, the associated hypervolemia will also contribute to increased cardiac output. The activity of the inflammatory process in the lung, since bronchopulmonary infection is always present, tends to increase oxygen consumption and, thereby, leads to an increase in cardiac output, even in the absence of fever. The increased muscular work of breathing in chronic obstructive emphysema also disposes to an increased cardiac output. If cardiac failure occurs at a stage during which cardiac output is increased, some fall in cardiac output will occur, but the output may still be higher than normal. The paradox of high output failure may thus be explained by the state of the circulation just preceding failure of the right ventricle. When congestive heart failure is present, an increase in plasma volume also often helps maintain the cardiac output, but later by contributing to the overdistension of the right ventricle may help to lower it. All the factors which tend to increase cardiac output are potentially reversible by intense treatment; a patient in whom cardiac output is high during a desperate stage in his illness may have a normal output after a successful course of treatment.

If the factors described above which tend to increase cardiac output are less marked in extent or of shorter duration, a normal cardiac output may be observed. Cardiac output which was not markedly elevated may be lowered to what is determined as normal cardiac output during a period of moderate right ventricular failure.

A low cardiac output may be observed in chronic cor pulmonale due to chronic obstructive emphysema under various circumstances. Cardiac output may be lowered by severe cardiac failure. If all the factors tending to produce high cardiac output are present, but pulmonary vascular resistance is high (over four times normal), cardiac output will be low. In such cases the vascular bed of the lung has become reduced to such an extent that it acts much like a “tight mitral stenosis” in limiting cardiac output. This marked increase in pulmonary vascular resistance may be due to severe anatomic changes in the lungs associated with chronic obstructive emphysema as described above, or may be due to a complicating disease such as multiple pulmonary emboli.

Since adequate treatment of the bronchopulmonary disease increases the size of the pulmonary vascular bed, as well as reduces hypoxia with its attendant changes, it is difficult to know which abnormality is most responsible for the precipitation of right heart failure. It is quite likely that the relative importance of each factor varies from case to case, and that in some cases therapy is effective mainly because it actually reduces the extent of anatomic restriction of the pulmonary vascular bed.

D. Pathogenesis of Type II Chronic Cor Pulmonale

Where chronic cor pulmonale is due to pulmonary disease with the pathology localized mainly in or about the pulmonary vessels the most important factor in pathogenesis is the reduction in caliber of the pulmonary vascular elements. In most of these cases, in the earlier stages, hypoxemia is not present at rest but appears only with exercise, and then mainly because of the factor of alveolar-capillary block. If the patient does not die of pulmonary insufficiency, he may later develop resting hypoxia and sometimes even polycythemia, so that the additional abnormalities will also act to increase the load on the right ventricle as they do in chronic obstructive emphysema.

Chronic cor pulmonale has been recorded in silicosis without significant chronic obstructive emphysema where the silicotic nodules appeared to be located mainly about vascular channels. Here, arterial oxygen desaturation was frequently not present at rest, but appeared only on exercise, and cardiac output tended
to be normal or low. However, chronic cor pulmonale develops much more frequently in silicosis complicated by emphysema and here the changes are like those in chronic cor pulmonale due to chronic obstructive emphysema alone, except that cardiac output tends to be normal or low. In chronic cor pulmonale occurring in diffuse granulomatosis of the lungs as in sarcoidosis or berylliosis, and in scleroderma, arterial oxygen saturation is found to be normal or only slightly reduced at rest, but falls markedly on exercise. Polycythemia is not common in the early stages perhaps because of the absence of prolonged hypoxia at rest. Yet, in the absence of cardiac failure, cardiac output in these patients is frequently found to be elevated. It has been postulated that this high output in the absence of continual hypoxia is due to the increased metabolism resulting from the active inflammatory granulomata in the lungs, and increased work of breathing. While most of these patients die of pulmonary insufficiency some eventually develop marked arterial oxygen desaturation and right heart failure, at which time cardiac output is found to be low. The pulmonary hypertension in these conditions usually cannot be reversed.

In chronic cor pulmonale due to repeated pulmonary embolization and in that due to primary pulmonary hypertension, the cardiac output tends to be low. This is a result of the very marked increase in pulmonary vascular resistance. In primary pulmonary hypertension, cyanosis and polycythemia usually occur only late in the disease, unless a patent foramen ovale is present, when a right to left shunt through the foramen may occur.

The term “Ayerza’s Disease” has been used in many ways in the medical literature. Originally, it was a term used by Arrillago, a pupil of Ayerza, to signify a condition of right heart failure with severe cyanosis and polycythemia (“black cardiac”) associated with pulmonary disease presumed to be syphilitic in origin. However, the term has been used to describe everything from chronic cor pulmonale due to chronic obstructive emphysema with secondary pulmonary arteriosclerosis to primary pulmonary hypertension. It would be best dropped from usage.

In patients with chronic pulmonary disease with markedly restricted pulmonary vascular bed, the abrupt development of some pulmonary catastrophe, such as lobar pneumonitis, or massive collapse of a lung, which produces a critical increase in pulmonary vascular resistance, may cause a rapid dilatation of the right ventricle associated with myocardial ischemia and death. The clinical picture, the electrocardiographic changes and the pathologic findings will be those of acute cor pulmonale, although no pulmonary embolization has occurred.

E. Diagnosis of Chronic Cor Pulmonale

1. General Considerations

The diagnosis of chronic cor pulmonale would be made only in far advanced cases if it were to depend on the detection of right ventricular hypertrophy, since early right ventricular enlargement is almost impossible to recognize. It is only when the examiner has a high index of suspicion and correlates many suggestive findings that the presumptive diagnosis can be made before the disease is far advanced. While the presence of pulmonary hypertension does not necessarily mean that right ventricular hypertrophy has already developed, when it is demonstrable clinically in a patient with chronic obstructive emphysema, right ventricular hypertrophy is usually present.

2. Clinical Examination

The existence of chronic cor pulmonale should be suspected in patients with chronic obstructive emphysema of more than minimal degree. By the time arterial blood gas abnormalities become demonstrable, chronic cor pulmonale may be assumed to be present. The presence of secondary polycythemia is thus usually good evidence that right ventricular hypertrophy has already developed. Clubbing of the digits and pulmonary hypertrophic osteoarthropathy do not necessarily indicate the presence of chronic cor pulmonale, since they may occur with very small focal lesions in the lung, such as bronchogenic carcinoma or fibrous mesothelioma.

The presence of overdistended lungs with the accompanying changes in the contour of
the chest make the detection of the usual signs of pulmonary hypertension and right heart enlargement difficult. Thus, the fact that the heart tones are frequently very faint interferes with auscultation of the heart. Changes in the position of the heart as in thoracic deformity and after resectional pulmonary surgery may affect not only the physical findings but also the electrocardiogram and x-ray appearance.64 One of the earliest direct signs of pulmonary arterial hypertension is accentuation of the second pulmonic sound, often to the extent that it becomes louder than the second aortic sound. Lower sternal dullness, a useful sign of right ventricular enlargement in other types of heart disease, is often absent because of the hyper-resonance of the entire chest. A systolic murmur at the pulmonic area is frequently audible, due apparently to dilatation of the main pulmonary artery just distal to the pulmonic valve ring. However, a systolic murmur at the base of the heart is not an infrequent finding in senescence, so that this may be a suggestive sign only in younger patients. In more advanced cases a high pitched, blowing, early diastolic murmur at the pulmonic area may occasionally be heard, presumably due to dilatation of the pulmonic valve ring. Arrhythmias are quite unusual. By the time the usual peripheral signs of right ventricular failure appear, the recognition of right heart involvement becomes easy. Pleural effusions due to congestive failure are rare; if they occur a postpneumonic empyema or pulmonary infarction should be suspected. Moderate elevation of peripheral venous pressure in the absence of congestive heart failure may occur because of the increased intrapleural pressure present in many patients with chronic obstructive emphysema; however, marked elevation of venous pressure is usually a sign of right heart failure.

3. Roentgenologic Examination

In general, careful fluoroscopic examination of the cardiac silhouette in the posterior-anterior, in both obliques and in the lateral projection is superior to roentgenograms, although the latter may be valuable for serial studies. Fluoroscopy also offers valuable information regarding pulmonary function at the same time. While roentgenologic signs of chronic cor pulmonale also occur rather late in the course of the disease, they appear earlier than the physical signs.

The earliest abnormality to become apparent is enlargement of the pulmonary artery trunk and its main branches. This abnormal dilatation is due to the pulmonary arterial hypertension, and must be differentiated from the normal prominence of the pulmonary artery trunk in a vertically placed heart which is rotated clockwise about its longitudinal axis. This positional change of the heart is the usual one occurring in chronic obstructive emphysema where the diaphragm is depressed and the lungs are overdistended. In borderline cases, therefore, it is sometimes difficult to know at what point the main pulmonary artery is enlarged, and when its prominence is due merely to rotation of the heart. This enlargement of the pulmonary artery trunk is best seen with the patient in the right anterior oblique position. As the dilatation becomes more marked, it becomes visible as a convexity of the left middle salient in the posteroanterior projection. If the diameter of the right inferior pulmonary artery at its widest point is over fifteen millimeters in the posteroanterior teleroentgenogram, the presence of pulmonary arterial hypertension is strongly suggested, since Schwedel found this relationship to hold in mitral stenosis.67 Hilar dance is usually not present, since the degree of augmentation of pulmonary blood flow necessary to produce this phenomenon is usually not found in chronic cor pulmonale. Calcification in pulmonary arterial atheromata may rarely be seen.

Hypertrophy alone of the free wall of the right ventricle in chronic cor pulmonale is undetectable roentgenologically; enlargement of the right ventricle becomes visible only when considerable dilatation occurs. As right ventricular dilatation increases it eventually becomes visible as an anterior bulging in the region of the outflow tract of the right ventricle, best seen encroaching on the retrosternal space in the lateral and right anterior oblique views. In the presence of marked left ventricular enlargement, anterior bulging in the right an-
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terior oblique view cannot be considered as evidence for right ventricular enlargement, since under these circumstances the left ventricle may encroach on the retrosternal space. In chronic cor pulmonale, an enlarged right ventricle never forms part of the left border of the cardiac silhouette in the poster-anterior projection. However, when enlargement of the right ventricle is marked an increase in the transverse diameter of the heart in the posterior-anterior projection may appear; this is due to displacement of the left ventricle, the right ventricle still being anteriorly placed. This is a late development; in most cases of chronic cor pulmonale an increase in the transverse diameter of the heart in the posterior-anterior projection does not appear. Displacement of the left ventricle by a markedly enlarged right ventricle so that clearing of the spine does not occur with rotation up to 65 degrees in the left anterior oblique view may also be seen. When congestive failure develops, enlargement of the right atrium and dilatation of the superior vena cava may be observed.

Angiocardiography is not particularly useful for the diagnosis of chronic cor pulmonale but sometimes may be of value in the differential diagnosis if it helps exclude congenital heart disease, or if it discloses an arteriovenous fistula in the lung.

4. Electrocardiography

Like all other diagnostic criteria, electrocardiographic abnormalities also occur late. However, they frequently demonstrate alterations as early as the roentgenologic examination. In addition to the usual leads, special precordial leads over the right chest (V_{4R}, V_{5R}) may give valuable additional information.

The changes which are most frequently seen in chronic cor pulmonale due to chronic obstructive emphysema are those which are not themselves pathognomonic of right ventricular hypertrophy. As a result of the over-distended lung and the depressed diaphragm in chronic obstructive emphysema, the heart assumes a more vertical position, and is rotated clockwise about its longitudinal axis, sometimes with backward displacement of its apex. This is usually manifested in a mainly inverted QRS in aV_{L} and an upright QRS in aV_{P}, and a shift of the transitional zone over the pre-cordium to the left, with the presence of S waves in all the limb leads and the persistence of S waves in V_{1} and V_{6}. The QRS complexes may sometimes be of low voltage, especially in the precordial leads. This may be due to the increased volume of air-containing lung between the heart and chest wall, or due to a positional change in the heart so that the direction of the QRS vector becomes perpendicular to the frontal plane. All of these changes will often simulate or be exaggerated by the presence of right ventricular hypertrophy or dilatation, since right ventricular enlargement will produce the same kind of rotation of the heart as the pulmonary changes associated with chronic emphysema. When in a patient with chronic obstructive emphysema, P pulmonale is present with these changes, the diagnosis of chronic cor pulmonale becomes extremely likely even though these changes per se are not the result of hypertrophy of the right ventricle.

P pulmonale is a tall peaked P wave in leads II, III and aV_{P}. Usually it is also seen to be small in lead I, inverted in aV_{L}, and often diphasic (plus minus) in V_{1} and V_{2}. It is often associated with a depression of the P-Q segment, due to the prominent negative Tp waves. This is apparently a secondary T-wave change, since it is associated with high voltage upright P waves. In some patients it may revert to normal on treatment. The exact mechanism for its production is unknown. While in some cases it may be associated with hypertrophy or dilatation of the right atrium, it frequently is present when these are absent. In most cases it is probably due to positional change; in a markedly vertical heart with a low diaphragm the apex is displaced in such a way that higher upright P-wave potentials, ordinarily facing towards the back or other parts, are now directed to the feet.

The appearance of an M shaped QRS complex (rsR'), with R' taller than r, in leads over the right precordium (V_{4R}, V_{1} and V_{2}), which has been called incomplete right bundle branch system block by some, is usually good evidence of right ventricular strain and hence chronic
cor pulmonale. However, it is sometimes difficult to know whether a small R' in V1 or V2 is due to this incomplete right bundle branch system block, or whether it is merely a manifestation of the normal late activation of the pulmonary conus. Indeed, in some cases it is possible that this R' becomes apparent mainly because of the downward displacement of a vertical heart associated with the low diaphragm which causes V1 and V2 to assume a higher position than usual relative to the heart. The normally delayed activation of the pulmonary conus (which may or may not be dilated) now becomes more readily evident. This may explain the observation by Thomas that leads taken in the third left intercostal space (V2 3ics) may be helpful in indicating the presence of right ventricular strain if they show an R' taller than 4 mm. This would also explain the occasional transient appearance of rsR' complexes over the right precordium in acute cor pulmonale where right ventricular hypertrophy cannot have had time to develop. In some cases, complete right bundle branch system block with QRS duration longer than 0.12 second may also result from right ventricular involvement in chronic cor pulmonale.

The presence of a typical right ventricular hypertrophy pattern (a relatively tall late R in aVR, V4R or V1) is usually definite evidence of chronic cor pulmonale. The tall R may sometimes be preceded by a tiny Q wave; in such a case, care must be taken that an initial tiny R wave is not being overlooked, since then the complex would be of the rsR' type.

Our experience suggests that the first type of right ventricular enlargement pattern (rsR' over the right precordium) occurs somewhat more frequently in chronic cor pulmonale due to chronic obstructive emphysema, and that the second type (tall late R over the right precordium) occurs more often in chronic cor pulmonale due to pulmonary disease with predominant vascular involvement. This may be a manifestation of the greater frequency of augmented input loading of the right ventricle in the first type of chronic cor pulmonale where hypervolemia and increased cardiac output are more common. The relationship between the type of overload on the right ventricle and type of electrocardiographic evidence of heart strain has been described by Donzelot and Cabrera C. For example, in interatrial septal defect an input overload pattern (surcharge) is usually seen (rsR') while in congenital pulmonic stenosis a resistance overload pattern (barrage) is usually found (tall R over right and much of left precordium with depressed ST and inverted T). However, this simple relationship is complicated by the fact that in chronic cor pulmonale due to chronic obstructive emphysema, resistance overloading also occurs because of the increase in pulmonary vascular resistance and pressure. Moreover, with the development of right ventricular failure and dilatation of the right ventricle, input overloading occurs even in chronic cor pulmonale of the second type due to pulmonary disease where the pathology is largely localized in or about the pulmonary vessels. Complete evaluation of this difference in incidence of right heart strain pattern await correlative studies of the type of pulmonary disease, the pulmonary vascular resistance and pressure, the blood volume, the degree of hypertrophy and the degree of dilatation of the right ventricle.

Frequently, the presence of a right ventricular strain pattern is associated with the presence of inverted T waves in V2 through V6. These often become upright after treatment. The reason for the inversion of these T waves is not fully understood as yet. They may be caused by right ventricular dilatation, reflecting merely an increased clockwise rotation of the heart about its longitudinal axis, acute right heart strain or ischemia of the anterior wall of the heart. That the first mechanism is probably operating most often is borne out by the observation that after successful treatment, some cases demonstrate a shift in the transition zone over the precordium to the right, and a reduction in size of the S waves in the limb leads and in V5 and V6. This is not associated with demonstrable change in position of the diaphragm, but there has been abolition of congestive failure and hence presumably a re-
duction in right ventricular dilatation. Absence of a prolonged Q-T interval may help rule out anteroseptal infarction when the T waves are inverted over the right precordium, since it has been reported that the Q-T interval is normal in patients with chronic cor pulmonale in the absence of other types of heart disease.74

5. Cardiac Catheterization

Right heart catheterization offers the best method for the early detection of pulmonary hypertension and also may give much additional information about the disturbed hemodynamics in a given case. As yet it cannot be justified as a routine procedure but in some cases, in combination with blood gas studies and pulmonary function tests, it helps greatly in management. Cardiac catheterization on occasion may also be very useful to rule out the presence of a congenital cardiac defect.

There must be a stage in the development of chronic obstructive emphysema when pulmonary hypertension is present before right ventricular hypertrophy has yet occurred. If the clinical picture of chronic obstructive emphysema is typical with regard to the appearance of the lung and by function testing, the presence of pulmonary arterial hypertension at rest is good evidence that hypertrophy of the right ventricle is already present, even though there may be no evidence of this hypertrophy in the electrocardiogram or on fluoroscopy. Early, pulmonary artery pressures may be normal at rest and become elevated only with exercise; later, pulmonary hypertension is present at rest. Often, in a patient with chronic cor pulmonale in congestive failure with marked pulmonary hypertension and increased cardiac output, repeat catheterization after intense pulmonary and cardiac therapy will show the cardiac output to be normal, and the pulmonary artery pressures normal or nearly normal at rest, becoming elevated only with exercise.53

In these patients with pulmonary arterial hypertension, Dexter52 has demonstrated a normal pulmonary arterial wedge pressure. This differentiates the pulmonary hypertension present in chronic obstructive emphysema from that which may be present in patients with mitral stenosis or left ventricular failure where both the pulmonary arterial wedge and the pulmonary arterial pressures are elevated.

In chronic cor pulmonale in congestive failure the administration of digoxin intravenously may cause a paradoxic rise in pulmonary artery pressure. This can be explained by the fact that digoxin causes an increase in cardiac output and probably a better emptying of the failing right ventricle. The resultant increased blood flow through a pulmonary vascular bed which is reduced in size and in distensibility causes a rise in pulmonary artery pressure. Acute digitalization in patients with cardiac failure with chronic pulmonary disease and pulmonary hypertension, but with arteriosclerotic or hypertensive heart disease, causes a fall in pulmonary artery pressure. This thus differentiates pulmonary hypertension due to a reduction in the pulmonary vascular bed and that due to left ventricular failure.84

III. Treatment

A. General Considerations

Until recently, most reports have emphasized the futile aspects of the treatment of chronic cor pulmonale. This attitude arose mainly because of inadequate treatment of the pulmonary disease. No attempts were made to correlate the variations in response to therapy with the type of pulmonary disease which caused the chronic cor pulmonale; the pathologic physiology of chronic cor pulmonale was incompletely understood, symptoms due to pulmonary disease were not adequately separated from those due to cardiac failure and some of the more helpful technics of therapy of chronic bronchopulmonary disease were not available. Where the chronic cor pulmonale is due to chronic obstructive emphysema and many of the pathologic changes are partially reversible, there is good reason to expect that real improvement will result from treatment. If the chronic cor pulmonale is due to pulmonary disease where the changes localized mainly in or about the pulmonary vessels are mostly irreversible, the outlook for treatment is more dismal.
B. Treatment of Type I Chronic Cor Pulmonale

1. Prophylaxis

If the specter of chronic cor pulmonale is kept before us, we can realize the need for more intense and careful management of patients with chronic bronchopulmonary disease, especially chronic bronchitis. Recurrent and lingering episodes of bronchitis in patients should be treated vigorously. Their effect may be cumulative and lasting. Climate, poverty and air pollution are undoubtedly of great importance; every attempt should be made to remedy the latter by industrial and social safeguards. When chronic obstructive emphysema is already present, acute respiratory infections should be treated as major illnesses, since the first episode of congestive failure in chronic cor pulmonale usually follows an acute respiratory infection with its invidious sequence of events. Impeding circulatory and pulmonary breakdown frequently may be predicted by watching for signs of increasing pulmonary insufficiency, polycythemia and abnormalities in the blood gases.

2. Active Treatment

Intensive treatment of the bronchopulmonary disease is as important, and usually more important, than specific cardiac measures. Congestive heart failure can be alleviated only by at least partially reversing many of the pathologic changes in the lung which are responsible for the anatomic reduction in the pulmonary vascular bed and the hypoxia.

The objectives of therapy are to combat infection, produce an adequate airway and improve effective alveolar ventilation. The use of antibiotics orally, by injection, and especially by inhalation are of paramount importance. Bronchodilator drugs are invaluable for aiding in bronchial drainage and improving ventilation. They also help in the control of infection. Patency of airways and resolution of infection are promoted also by the use of sputum liquefiers, correction of dehydration and facilitation of cough and expectoration. Occasionally, bronchial aspiration by catheter or bronchoscope is lifesaving. Pulmonary ventilation can often be markedly improved by breathing exercises; pneumoperitoneum and abdominal belts have been disappointing. In desperate cases and where airway obstruction is very severe, the use of adrenal corticosteroids or corticotropin may be necessary to reduce secretions and bronchial edema; however, their use is fraught with danger because of their effect on the body defenses against infection and because of their tendency to cause salt and water retention.

Treatment of the hypoxia is essential. Although direct treatment with oxygen is hazardous, it is often necessary. Such treatment must be controlled by careful observation of the patient. The respiratory system in these patients is usually nonresponsive to carbon dioxide; the tachypnea may be maintained mainly because of the presence of hypoxemia. Correction of the hypoxemia may lead to hypoventilation with carbon dioxide retention, acidosis and death. If oxygen is administered, it should be given well humidified, in low concentrations, intermittently and only if the patient is under constant observation by a physician, not a nurse; control of the oxygen therapy will depend on its effect on the frequency and depth of respiration, the clinical appearance of the patient and, finally, wherever possible, by serial determinations of the arterial blood gases. The latter techniques, while not always available, are nonetheless extremely important, since the clinical appearance of the patient may be deceptive. It is often preferable to use oxygen with some type of mechanical respiratory aid such as a tank-type body respirator to hyperventilate the patient in an attempt to "wash out" retained carbon dioxide at the same time that oxygen is being administered; this may have to be continued over a period of several weeks. It is not sufficiently appreciated that the carbon dioxide stores in the body are not confined to the blood alone, but include those present in all of the body fluids as well. Acetazolamide (Diamox), a carbonic anhydrase inhibitor, has proved useful in the treatment of respiratory acidosis.

Its diuretic action is also valuable. Respiratory depressant drugs, such as morphine, are strongly contraindicated. The usefulness of
intermittent positive pressure breathing apparatus has not been completely evaluated.78-80

These patients are critically ill, and their treatment requires meticulous attention to detail. They are frequently somnolent, confused and uncooperative, a result of hypoxia and hypercapnia. Cerebrospinal fluid pressure is often increased,81 and even papilledema has been observed in many of these patients with hypercapnia.9 Restoration of alertness is of prime importance, since it will permit more effective coughing and expectoration of sputum and greater cooperation with therapeutic procedures.

Specific cardiac therapy may be effective, if combined with the pulmonary measures just described. Digitalis, contrary to some earlier reports, has been shown definitely to improve cardiac performance in patients with chronic cor pulmonale in congestive failure. It is therefore indicated in the presence of cardiac failure and should be continued indefinitely after the failure has disappeared. Mercurial diuretics and salt restriction are also useful, but electrolyte imbalance should be carefully watched for in these patients. Rest is extremely important to minimize the body’s metabolic requirements in the face of pulmonary and circulatory insufficiency. Phlebotomy is an important adjunct to therapy when polycythemia and hypervolemia is present. Both the adaptive significance and the disadvantages of the polycythemia and the hypervolemia have been discussed above. The red blood cells in secondary polycythemia are often hypochronic, so that attention should be paid to the hematocrit as well as the red blood cell count and the hemoglobin.90 Bleeding is advisable when the hematocrit is above 55; 300 to 500 ml. of blood may be removed every 3 to 5 days to bring the hematocrit down to 50, and the hemoglobin to about 14 Gm. The usefulness of ganglionic blocking agents, such as tetraethylammonium and Priscoline, in lowering pulmonary arterial pressure in chronic cor pulmonale in chronic obstructive emphysema has not been demonstrated.

Many of these patients with chronic cor pulmonale have associated arteriosclerotic or hypertensive heart disease, and while the presence of some degree of left ventricular failure may be difficult to prove, their response to specific cardiac therapy may be especially gratifying.

In our own experience, as well as in that of others,1 peptic ulcer has been noted to occur with increased frequency in patients with chronic obstructive emphysema with or without polycythemia. Routine examination of the stomach and duodenum is, therefore, indicated. We have also noted an increased frequency of cholelithiasis in those patients who have secondary polycythemia. The development of pain in the right upper quadrant of the abdomen may thus result from acute cholecystitis as well as hepatic congestion associated with right heart failure.

C. Treatment of Type II Chronic Cor Pulmonale

Therapy of chronic cor pulmonale in patients with pulmonary disease where the pathology tends to be localized in or about the pulmonary vessels is unsatisfactory. Where broncho-pulmonary infection or chronic obstructive emphysema is present as a complication it should be treated intensively. The latter especially may complicate such conditions as silicosis and diffuse pulmonary sarcoidosis. Diffuse pulmonary granulomatosis may be treated with cortisone or corticotropin, but whether resolution or fibrosis of the granulomata will occur in a particular patient cannot be predicted. Cournand has advised marked restriction of physical activity to reduce cardiac work as one of the few helpful procedures available, since the restriction of the pulmonary vascular bed in these patients is largely irreversible. When congestive failure develops, they usually die in a matter of weeks.92

SUMMARY

Because of newer technics of treatment, a small but ever increasing number of patients with chronic pulmonary disease are surviving long enough to develop chronic cor pulmonale. An attempt has been made to correlate the newer knowledge of aberrations of cardiovascular and respiratory physiology in chronic pulmonary disease.

Respiratory insufficiency may be due to
varying proportions to the following: (1) ventilatory dysfunction or impairment of the ability to move air into or out of the lungs; this may be of two types: (a) obstructive, due primarily to airway narrowing and (b) restrictive, due to disordered function of the thoracic bellows or diminished pulmonary distensibility; (2) unequal distribution of inspired air to the alveoli (intrapulmonary mixing); (3) uneven perfusion or distribution of capillary blood flow; (4) impaired diffusion or transfer of oxygen across the alveolar capillary barrier and (5) impaired cleansing of the lung.

The same abnormal physiologic change may result from pathologic conditions which differ widely in etiology; furthermore, a particular disease may give rise to widely differing functional patterns.

The types of pulmonary disease causing chronic cor pulmonale may be divided into two main categories: (1) Type I, pulmonary diseases associated with chronic diffuse obstructive emphysema. (2) Type II, pulmonary diseases in which the pathologic process tends to be localized in or about the pulmonary vessels. In some instances, a case belongs mainly in one category but may demonstrate some features of the other.

The strain on the right ventricle is a result of: (1) increased resistance to pulmonary blood flow and (2) increased cardiac output (when present). Increased resistance to pulmonary flow may be due to: (a) reduction in caliber and distensibility of the pulmonary vascular bed which may be structural or related to hypoxia, (b) polycythemia and (c) intrapulmonary vascular shunts.

Respiratory insufficiency may be suspected from the history. Physical and roentgenologic examinations may be confirmatory, but pulmonary function tests are necessary for a precise evaluation of the functional abnormalities. The recording of a physiologic, as well as a pathologic diagnosis, is a useful practice in the individual case.

The presence of right ventricular enlargement can only be detected clinically when the chronic cor pulmonale is moderately advanced. However, clinical and roentgenologic evidence of pulmonary hypertension in chronic pulmonary disease indicates that right ventricular hypertrophy is probably present. The electrocardiogram may be helpful even in the absence of a definite right heart strain pattern since the electric position of the heart is often suggestive. Cardiac catheterization provides the best method for the early detection of pulmonary hypertension.

The treatment of chronic cor pulmonale is much more hopeful today than in the past. It is most satisfactory when cor pulmonale is due to pulmonary disease of type I. Intensive therapy of the bronchopulmonary disease is as important as specific cardiac measures. The objectives of therapy are to combat infection, produce an adequate airway and improve effective alveolar ventilation. This may partially reverse many of the pathologic changes in the lung which are responsible for hypoxia and the anatomic reduction in the pulmonary vascular bed.

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Respiratory Insufficiency and Chronic Cor Pulmonale
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