Heart Failure and Lung Disease

By HANS H. HECHT, M.D.

THE multifaceted interplay of factors leading to the onset of heart failure secondary to lung disease (cor pulmonale) has made this type of heart disease of unusual interest. It is more common than previously realized. The relatively precise methods now available for assessment of both respiratory and circulatory functions permit a pathophysiologic analysis that goes beyond the purely clinical or pathologic descriptions of "cor pulmonale." It has become obvious that this term covers a number of unrelated conditions that have little in common beyond the fact that right ventricular failure occurs. It is, therefore, not surprising that a short definition of the term "cor pulmonale" meets with difficulties. In the following pages some of the concepts on the nature, diagnosis, and management of heart failure in various types of chronic pulmonary dysfunction have been summarized to provide a general orientation. For more complete information concerning the different phases of cardiorespiratory diseases, the reader is referred to several detailed reviews. The references cited are usually of recent origin and should be consulted for earlier observations.

PHYSIOLOGIC CONSIDERATIONS

Pulmonary Hypertensive Heart Disease

It seems clear that right ventricular failure may result from simple overtaxing of the right ventricular musculature similar to that which occurs in sudden or gradual obstruction of the pulmonary artery in animal experiments. In man, this type of right ventricular failure may properly be termed "pulmonary hypertensive heart disease." It is analogous to left ventricular failure of the heart in arterial hypertension or in aortic coarctation, with one significant difference: elevation of the mean systemic pressure to little more than twice the normal value may become critical for left ventricular function, whereas the right ventricle seems capable of tolerating well over 5 times the normal pulmonary artery or intraventricular pressures. In young individuals a rise in systolic right ventricular pressures alone from the normal of 20 mm. Hg rarely causes difficulties unless the pressure rises well above 100 mm. Hg.

The best example of pulmonary hypertensive heart disease is represented by the patient with diffuse proliferative arteritis of the lung, described earlier by Romberg and by Moenckeberg, a condition that deserves the term "essential pulmonary hypertension" ("pulmonary vascular obstruction syndrome," "primary pulmonary hypertension"). The term points to the analogy of this disease of the lesser circulation to essential arterial hypertension and replaces what has in the past usually been termed "idiopathic right ventricular hypertrophy." As in arterial hypertension, vasospasm has been assumed to be at least a concomitant feature, but its true etiology is unknown. If the medial layers of the pulmonary arterial tree are involved, a persistence of a fetal type of pulmonary vasculature may be conjectured; the disease may then be considered to result from an anomalous persistence of a feature which in the fetus or in examples of ventricular septal defects prevents excessive flooding of the lungs. On the other
hand, fibrous thickening of the intima and small thrombi may be considered secondary to pulmonary hypertension.

A functionally identical situation exists in pulmonary valvular stenosis where the obstruction, however, is moved from the lung periphery to the valves themselves. Failure occurs late, since the myocardium is usually intact, and appears only if the membranous obstruction is severe enough to raise systolic right ventricular pressures above 100 mm. Hg, a point of significance in the evaluation of such patients for corrective surgery.

Two additional obstructive vascular lesions result in relatively pure pulmonary hypertensive heart disease: (1) massive thrombosis of a major branch of a pulmonary artery,17 and (2) multiple, repeated emboli to the lung,18, 19 a pathologic condition that has been successfully reproduced in animals.20, 21 In either case, once an acute episode of embolization has been overcome, the clinical manifestations are primarily associated with right ventricular failure, and not with lung disease, though certain deficiencies in respiratory function may precede the onset of heart failure.19

A massive embolus may result in a sudden intolerable overload of an unprepared (non-hypertrophic) right ventricle; though physiologic data in man are not available, it may be suspected that “acute cor pulmonale” is simply the most dramatic form of pulmonary hypertensive heart disease.

In examples of pure mitral stenosis, a situation often arises that closely resembles this form of heart disease.22 Secondary vascular changes develop, apparently the result of longstanding pulmonary vascular congestion, high capillary and arteriolar pressure, and pericardial and interalveolar edema. Imperceptibly, the mechanical valvular obstacle is overshadowed by a secondary obstruction of the pulmonary vascular tree, the “pulmonary hypertension with malignant sclerosis” of Parker and Weiss.23 If this becomes excessive, the signs and symptoms then resemble those of “primary” pulmonary hypertension except for the additional presence of left atrial hypertrophy. This “secondary” pulmonary hypertension may rise to levels equal to those seen in the primary type, and cardiac work required in forcing blood through the pulmonary

### Table 1.—Type Cases of Heart Failure in Lung Disease, Hematologic Data and Blood Gas Analysis

<table>
<thead>
<tr>
<th></th>
<th>Ht %</th>
<th>Hb. Gm./100 ml.</th>
<th>Arterial Oxygen</th>
<th>Arterial CO₂ content/100</th>
<th>Blood pH units</th>
<th>Alveolar-arterial oxygen tension (Tension) mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>45-52</td>
<td>15.0</td>
<td>18.6</td>
<td>92-94*</td>
<td>47</td>
<td>7.43</td>
</tr>
<tr>
<td>Pulm. hypertensive ht. dis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential pulmonary hypertension. K.C., 22y,</td>
<td>46</td>
<td>13.5</td>
<td>17.0</td>
<td>92</td>
<td>42.0</td>
<td>7.43</td>
</tr>
<tr>
<td>F. U., 57y, α, (post)†</td>
<td>68</td>
<td>19.0</td>
<td>15.1</td>
<td>59</td>
<td>52.1</td>
<td>7.50</td>
</tr>
<tr>
<td>Emphysema heart (with erythrocytosis).</td>
<td>78</td>
<td>22.2</td>
<td>27.3</td>
<td>92</td>
<td>45.5</td>
<td>7.40</td>
</tr>
<tr>
<td>Mixed forms and allied conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cardio-myocardial syndrome (kypohesoceliosis).</td>
<td>60</td>
<td>16.8</td>
<td>14.8</td>
<td>66</td>
<td>55.0</td>
<td>7.39</td>
</tr>
<tr>
<td>Severe obesity (150 Kg.). E.B., 32y, α</td>
<td>56</td>
<td>16.6</td>
<td>18.2</td>
<td>82</td>
<td>44.5</td>
<td>7.38</td>
</tr>
<tr>
<td>Pulm. Silicofibrosis with erythema</td>
<td>73</td>
<td>18.4</td>
<td>22.4</td>
<td>91</td>
<td>42.0</td>
<td>7.40</td>
</tr>
</tbody>
</table>

Note: These are resting values and indicate a general trend. Examination on exercise will obviously alter blood gas data (see text).

* Value for altitude of 4800 feet above sea level (Salt Lake City).
† Post: Indicates that the diagnosis was confirmed by autopsy.
‡ Determination of alveolar-arterial oxygen tension gradient was determined at two levels of oxygenation by oxygen tension method of Riley. Most of these determinations were performed by Dr. I. Kurita and Dr. J. McClement.
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Table 2.—Type Cases of Heart Failure in Lung Disease, "Hemodynamic" Data

<table>
<thead>
<tr>
<th></th>
<th>Arterial-venous O₂ Diff. Vol. %</th>
<th>Cardiac output ml/min./M³</th>
<th>Pulm. art. pressure mm. Hg</th>
<th>Pulm. wedge pressure mm. Hg</th>
<th>Total pulm. resistance Units</th>
<th>Ratio© TSR TPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4.9</td>
<td>2.2-4.0</td>
<td>25/10</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Pulm. hypertensive ht. dis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential pulm. hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced mitral stenosis</td>
<td>10.8</td>
<td>1.1</td>
<td>110/85</td>
<td>36</td>
<td>40</td>
<td>0.9</td>
</tr>
<tr>
<td>Massive pulm. embolism</td>
<td>5.9</td>
<td>2.3</td>
<td>105/50</td>
<td>10</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Emphysema heart.</td>
<td>4.6</td>
<td>3.8</td>
<td>80/40</td>
<td>4</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>4.1</td>
<td>3.3</td>
<td>25/12</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Mixed forms, and allied conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cardioaortic syndrome (kypsoseilosis)</td>
<td>7.4</td>
<td>1.7</td>
<td>120/70</td>
<td>7</td>
<td>37</td>
<td>1.2</td>
</tr>
<tr>
<td>Severe obesity</td>
<td>5.1</td>
<td>3.0</td>
<td>60/22</td>
<td>5</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Silicofibrosis with erythremia</td>
<td>6.1</td>
<td>2.3</td>
<td>47/29</td>
<td>5</td>
<td>15</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Same cases as table 1.
* Figures corrected for body surface area.
† Pulmonary resistance given in units comparable to Ohm's Law: Resistance = potential gradient (pressure)/current flow (blood flow). To convert these units in dynes/cm.²/m², multiply by 80.
‡ Relative ratio of total systemic resistance to total pulmonary resistance. In normal resting subjects, left-sided resistance is usually five times the pulmonary resistance.
To obtain pulmonary arteriolar resistance, wedge pressure values have to be subtracted from pulmonary artery pressure values. Except in cases of mitral stenosis or severe left ventricular failure, this represents an almost negligible correction.

Table 3.—Type Cases of Heart Failure in Lung Disease, Respiratory data

<table>
<thead>
<tr>
<th></th>
<th>O₂ uptake* ml./min./M³</th>
<th>RQ</th>
<th>Ventilation l/min./M³</th>
<th>Vital cap.</th>
<th>% of norm.</th>
<th>Max. breath cap.</th>
<th>Total lung vol.</th>
<th>Resid. vol.</th>
<th>Ratio resid. vol./total cap. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulm. hypertensive ht. dis.</td>
<td>122</td>
<td>0.75</td>
<td>4.6</td>
<td>99</td>
<td>97</td>
<td>102</td>
<td>110</td>
<td>110</td>
<td>22</td>
</tr>
<tr>
<td>Essential pulm. hypertension</td>
<td>121</td>
<td>0.78</td>
<td>7.5†</td>
<td>80</td>
<td>90</td>
<td>77</td>
<td>72</td>
<td>72</td>
<td>29</td>
</tr>
<tr>
<td>Advanced mitral stenosis</td>
<td>136</td>
<td>0.76</td>
<td>5.4</td>
<td>90</td>
<td>50</td>
<td>120</td>
<td>130</td>
<td>130</td>
<td>34</td>
</tr>
<tr>
<td>Massive pulm. embolism</td>
<td>134</td>
<td>0.86</td>
<td>5.5</td>
<td>37</td>
<td>16</td>
<td>126</td>
<td>413</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Emphysema heart.</td>
<td>145</td>
<td>0.86</td>
<td>5.2</td>
<td>110</td>
<td>104</td>
<td>85[112]</td>
<td>28[112]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>136</td>
<td>0.80</td>
<td>4.1</td>
<td>62</td>
<td>92</td>
<td>74</td>
<td>108</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

Same cases as table 1.
* Corrected to STPD.
† Corrected to BTPS.
‡ Hyperventilation rest—see also O₂ data (table 1).
§ Normal values from Prediction Tables of Baldwin, Cournand, and Richardson.
|| These are average values for 5 cases reported by W. Newman et al.12

Circuit may be larger than that necessary to overcome the valvular obstruction. Under these conditions, even in the absence of frank failure, the diastolic murmur of mitral stenosis may become difficult to elicit, or may completely disappear, perhaps because the rate of flow may fall below the critical threshold required for the production of a murmur. In the absence of characteristic auscultatory signs and with a similar symptomatology, the distinction between advanced mitral stenosis and other types of pulmonary hypertensive heart disease may become very difficult at the bedside even on repeated examination (fig. 8). Indeed only a few specific findings such as left atrial hypertrophy seen by radiologic and electrocardiographic observations may eventually point in the right direction.
Fig. 1. This illustrates the relation of dyspnea to rate of ventilation \((V)\), and to maximum breathing capacity \((MBC)\). The first column represents the normal resting stage, the second illustrates an instance where dyspnea might occur with only a slight increase in ventilatory rate because of a sharp reduction in maximum breathing capacity, (example: poliomyelitis with paralysis of respiratory muscles). Dyspnea as the result of an increase in the ventilatory drive together with a decrease in the maximum breathing capacity is indicated in the last 2 columns. These depict the situation in lung disease (column 3) and in heart failure (column 4). The relationships may be expressed by what has been termed the "breathing reserve."'

Vital capacity has often been related to dyspnea. Since most conditions that demonstrate reduction in vital capacity also show reduced maximum breathing capacity and hyperventilation, the relation, though somewhat fortuitous, holds in most instances of heart and lung disease.

For the sake of completeness, elevation of right-sided pressures as the usual consequence of left ventricular failure should be mentioned. The presence of left ventricular disease as the primary cause can usually be surmised.

In pulmonary hypertension, the major pathology is found in the pulmonary vascular system at precapillary sites. It is, therefore, not surprising that, in general, no striking abnormalities in pulmonary gaseous exchange may be detected (tables 1-3). Gas exchange is not impaired though the capacity of the vascular bed to expand on exercise is diminished. The oxygen extraction, i.e., the amount of oxygen in milliliters consumed per liter of air ventilated, fails to rise on exercise and it is often lower than that expected at rest. This reduction results in part, if not entirely, from hyperventilation that may have been mediated by stimulation of pulmonary nerve endings. Overactivity of the Hering-Breuer reflex (regulation of the respiratory centers by the degree of pulmonary distension) seems related to impairment of pulmonary distensibility and loss of its elastic recoil. This ventilatory drive may become excessive, and will lead to the sensation of dyspnea if ventilation exceeds 30 per cent of the maximum possible breathing effort. If the maximum breathing capacity is also diminished because of the onset of heart failure and consequent muscular fatigue, the ratio of ventilation to maximum breathing capacity may be further altered and dyspnea becomes excessive and incapacitating (fig. 1). Because of the increased rigidity of the lungs, the muscular force necessary to raise ventilation is greatly increased in subjects with various types of cor pulmonale. This increased work may be related to the early onset of dyspnea during mild exercise in these patients.

Cardiac output is generally diminished and pulmonary artery pressures are excessively elevated. The wedge pressures (pulmonary end pressures) are normal (except in instances of mitral stenosis with excessive pulmonary hypertension). Consequently, the total pulmonary resistance, expressed as the mean pulmonary pressure divided by blood flow per second becomes excessively high (table 2). Because of the combination of generally reduced blood flow and increased pressure in the pulmonary circulation, conditions leading to pulmonary hypertensive heart disease show extreme values for pulmonary resistance, often exceeding those for the systemic circulation.

Arterial oxygen content and saturation are usually unimpaired or only slightly lowered, and CO\(_2\) content is normal unless it is lowered as the consequence of hyperventilation. This is to be expected, since alveolar-capillary gas exchange is generally intact (table 1), and any tendency to oxygen desaturation of the arterial blood is obviated by the hyperventilation. Therefore, cyanosis, when it occurs, is caused by the peripheral capillary stagnation of heart failure. Polycythemia is absent.

In summary, pulmonary hypertensive heart disease is the result of right ventricular overload and with the exception of the presence of hyperventilation, the signs and symptoms are
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those of heart failure. Pulmonary gaseous exchange is usually normal.

Emphysema Heart

Heart disease as the result of chronic obstructive emphysema with or without fibrosis has clinical features that are quite different from pulmonary hypertensive heart disease. It presents a complicated interplay of respiratory, hematologic, and circulatory adjustments, and shows the clinical triad of arterial desaturation, polycythemia, and evidence of pulmonary hypertension. This form of cor pulmonale in older subjects may be termed “pulmonary hypertensive heart disease with arterial oxygen desaturation and polycythemia.” It deserves the more convenient label of “emphysema heart.”

Arterial Oxygen Desaturation. Arterial oxygen desaturation is always present in the emphysema heart. It raises preexisting pulmonary hypertension by increasing blood flow through a restricted pulmonary vascular bed and perhaps by pulmonary arteriolar vasconstriction, in some way similar to the hypertension of the systemic circulation that generally results from anoxia. Whatever its cause, it has been clearly established that anoxemia raises the pulmonary artery pressure in human subjects as well as in the experimental animal.25, 31-36 In patients with emphysema a rise in mean pulmonary artery pressure also occurred when CO₂ tension of the inspired air was increased, a response that could not be elicited in normal subjects.37 Perivascular fibrosis may further contribute to pulmonary hypertension in this syndrome by limiting the distensibility of the pulmonary vascular bed. This by itself reduces the diffusion surface of the lung particularly on exercise.37 Pulmonary hypertension which may be present at rest, therefore, may rise sharply on exertion even without further arterial oxygen desaturation.

In contrast to pulmonary hypertensive heart disease, the emphysema heart is associated with striking changes in respiratory function. Vital capacity and maximum breathing effort are sharply diminished, ventilation is increased, a certain amount of air is trapped following deep inspiration, the total lung volume is usually augmented, and characteristically the residual lung volume, the amount of air remaining in the lungs after a maximal expiration, is strikingly increased (table 3). One may say that emphysema is present when the residual air exceeds 30 per cent of the total lung capacity.1 The unequal ventilation of the hyperinflated lung results in lowering of alveolar oxygen tension and, in the later stages, in retention of carbon dioxide. The changes in alveolar gas concentration are reflected in the blood because the normal alveolar capillary membrane permits free gaseous interchange. The gas-blood interface, the exchange of gases from alveolar space to the arterial capillary system is not impaired until very late, and in most instances the alveolar-arterial gas gradient is only moderately increased. In the emphysema heart, elevation of arterial CO₂ content and arterial oxygen desaturation are, therefore, primarily the consequences of imperfect ventilation, which in turn is the result of deficiency in the bellows function of the chest, usually also associated with loss of pulmonary resilience. The degree of oxygen desaturation varies with the degree of impairment of chest motion and with the partial pressure of oxygen of the environment. In contrast to arterial oxygen desaturation on the basis of venous admixture (congenital heart disease, pulmonary arteriovenous aneurysms), which is independent of alveolar oxygen tension, the anoxia of the emphysema heart becomes a function of the altitude (see below). Arterial anoxia is also dependent on how much blood perfuses localized diseased areas in the lung. Ample evidence has been presented which demonstrates that blood may be shunted away from lobes made hypoxic.38-41 This mechanism may operate in examples of extensive pulmonary fibrosis often associated with emphysema. It may represent a self correcting mechanism, the basis of which is not clear. Another factor that may counteract arterial desaturation is the presence of collateral channels between bronchial and pulmonary arteries. This may be beneficial as long as desaturated arterial blood is recirculated through ventilated areas; it is
FIG. 2. Arterial oxygen content and cardiac output ("internal oxygen transport"). Internal oxygen transport, a hypothesis relating arterial oxygen content to total blood flow delivered at the tissue site. $O_2$ = Oxygen content in arterial blood. CO = Cardiac output. The onset of heart failure is arbitrarily indicated by the wavy line. It should occur when cardiac output is diminished and arterial oxygen saturation is normal (Decreased A), or when arterial oxygenation is sharply reduced without a corresponding compensatory increase in blood flow (Decreased B). In normal subjects arterial desaturation causes a compensatory rise in flow (Compensated A) which does not occur or occurs only insufficiently in the emphysema heart (Decreased B). By increasing the amount of available oxygen carriers—erythrocytosis—transport can be increased (Compensated B). Polycythemia may be considered to represent a compensatory mechanism.

The hemodynamics of the emphysema heart are likewise different from pulmonary hypertensive heart disease. Cardiac output, which was low in the latter group, is usually normal or higher than normal in spite of the fact that heart failure is present.\textsuperscript{32, 33, 42-46} Its relation to arterial desaturation has been mentioned.\textsuperscript{46, 47} The elevation of the pulmonary artery pressure is generally of moderate degree in the resting subject and, therefore, the quotient of pressure/flow, the pulmonary resistance, is only moderately elevated or may be normal (table 2). It seems clear that the alterations in vascular pressures are usually not of sufficient magnitude to cause overtaxing of an otherwise normally functioning myocardium: they can be tolerated for decades, particularly in younger subjects, before the findings of an emphysema heart become evident.

It is quite apparent that arterial oxygen desaturation assumes a pivotal role in emphysema heart. However, arterial desaturation of a degree encountered in human subjects does not by itself cause heart failure. The supply of desaturated blood to the coronary arteries\textsuperscript{47} will have an adverse influence in older subjects who may already have a poorly functioning myocardium, particularly if cardiac work is increased by even a moderate pulmonary obstruction, and by the hypoxia itself. It seems necessary to assume the presence of a "myocardial factor" in the emphysema heart. Except to state that degenerative heart disease of the arteriosclerotic type is likely to be present in these older subjects, no information is available that would allow a more precise definition. The myocardial component as a contributory source of heart failure in emphysema may be demonstrated if one considers that the supply of oxygen to the tissues is not only dependent on the tension of oxygen and carbon dioxide at the delivery site, but also on the total amount of oxygen delivered per unit time. This "internal oxygen transport"\textsuperscript{79} is the product of blood flow and arterial oxygen content (fig. 2). It will be diminished if blood flow is reduced and arterial oxygen content remains normal (low output failure), or if blood flow and cardiac output remain normal but arterial oxygen content is decreased (emphysema heart). As stated, in normal subjects arterial oxygen desaturation raises cardiac output, so that the transport mechanism remains effective in the face of a low arterial oxygen content. If a "myocardial factor" such as arteriosclerotic heart disease impairs the capacity to increase cardiac output sufficiently, internal oxygen transport will become deficient and the signs of forward failure may become evident. This type of heart disease then would be another type of a low output failure. Though cardiac output is "normal" by comparison to a subject with normal arterial oxygen saturation, it is too low for a subject with arterial oxygen desaturation. This concept of emphysema heart fits several observed facts, as for example the sharp decline in renal blood flow in the face of a normal output.\textsuperscript{35, 48}

Cyanosis. These unfortunate subjects often show intense cyanosis, and the term "black cardinals" has been reserved for them.
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Cyanosis is primarily dependent on the amount of reduced hemoglobin circulating through the capillary bed. In normal subjects approximately 3–4 vol. per cent of reduced hemoglobin is present in capillary blood, equivalent to about 3 Gm. reduced Hb./100 ml. (1 Gm. Hb. = 1.34 vol. per cent oxygen). It takes 5 Gm. of reduced Hb. in the capillary bed to cause a cyanotic appearance irrespective of the total circulating hemoglobin. In a normal subject with 15 Gm.Hb., cyanosis will not be noted unless ½ of the total hemoglobin is in the reduced form. In abnormal subjects cyanosis depends on the arteriovenous difference in oxygen concentration and the degree of arterial desaturation. In a polycythemic subject with a Hb. of 20 Gm./100 (middle bar), only ⅔ of the circulating hemoglobin must be in reduced form before cyanosis appears (5 Gm. of 20 Gm.), while an anemic subject with 10 Gm. Hb./100 ml. would not become cyanotic unless ⅔ of his circulating hemoglobin were in the reduced form (5 Gm. of 10 Gm.). A subject with only 5 Gm. Hb./100 ml. should never be cyanotic. The chart illustrates that the level of hemoglobin is an important determinant for the appearance of cyanosis. Other factors are listed in the text.

![Graph showing the effect of reduced hemoglobin on cyanosis](image)

**Fig. 3. Visible cyanosis: mean capillary oxygen unsaturation of 6–7 vol. per cent or 5 Gm. reduced Hb./100 ml.** Cyanosis is primarily dependent on the amount of reduced hemoglobin circulating through the capillary bed. In normal subjects approximately 3–4 vol. per cent of reduced hemoglobin is present in capillary blood, equivalent to about 3 Gm. reduced Hb./100 ml. (1 Gm. Hb. = 1.34 vol. per cent oxygen). It takes 5 Gm. of reduced Hb. in the capillary bed to cause a cyanotic appearance irrespective of the total circulating hemoglobin. In a normal subject with 15 Gm.Hb., cyanosis will not be noted unless ½ of the total hemoglobin is in the reduced form. In abnormal subjects cyanosis depends on the arteriovenous difference in oxygen concentration and the degree of arterial desaturation. In a polycythemic subject with a Hb. of 20 Gm./100 (middle bar), only ⅔ of the circulating hemoglobin must be in reduced form before cyanosis appears (5 Gm. of 20 Gm.), while an anemic subject with 10 Gm. Hb./100 ml. would not become cyanotic unless ⅔ of his circulating hemoglobin were in the reduced form (5 Gm. of 10 Gm.). A subject with only 5 Gm. Hb./100 ml. should never be cyanotic. The chart illustrates that the level of hemoglobin is an important determinant for the appearance of cyanosis. Other factors are listed in the text.

is dependent on an absolute amount of reduced hemoglobin present in the capillary bed, (fig. 3). In heart failure, cyanosis appears, because sluggish capillary flow results in excessive unloading of oxyhemoglobin in the periphery. In the emphysema heart, in addition, as the result of arterial desaturation an abnormal amount of unoxygenated hemoglobin is present at the capillary level before utilization and unloading occurs. The two factors, one central, one peripheral, combine to make cyanosis intense. Furthermore, in a polycythemic subject, the absolute amount of reduced hemoglobin in the capillary bed (5 Gm./100) related to visible cyanosis, is exceeded at levels of arterial desaturation which in a normal subject will not cause cyanosis. The intense cyanosis of these “black cardiaques” has, therefore, a sound physiologic basis. Cyanosis, be it central or peripheral, is greatly modified by the thickness and pigmentation of the skin: it is more apparent in Mediterranean races and American Indians than in races of northern European extraction. The cyanotic appearance is, therefore, the resultant of many factors, and it cannot be used to assess degrees of arterial oxygen desaturation at the bedside. It is of interest that Ayerza, who described the “black cardiaques,” must have referred to the emphysema heart, but his students attributed the clinical picture to (syphilitic) pulmonary endarteritis (essential pulmonary hypertension). “Ayerza’s disease” (cyanosis with pulmonary endarteritis) may really only be seen in examples of excessive pulmonary hypertension with venaarterial shunts (pulmonary hypertension associated with a patent ductus arteriosus or a septal defect).

**Erythrocytosis.** Arterial oxygen desaturation causes a relative and absolute increase in red cell mass: erythrocytosis (“secondary” polycythemia). This is the third of the triad that is present in heart disease associated with emphysema. This particular type of erythrocytosis usually does not appear until arterial oxygen saturation falls to 70–75 per cent of normal. This polycythemia disappears when arterial saturation rises above this value as it might after surgical correction for congenital heart disease. It should be made clear that the threshold of “trigger value” which initiates erythropoiesis must be maintained over long time periods; an occasional higher resting value obtained in a polycythemic and emphysematous subject under treatment does not negate this relationship, since subjects who are mildly anoxic may become much further desaturated during periods of muscular work or during sedation and sleep.

The exact mechanism by which this type of polycythemia is produced has not been elucidated. The concepts that arterial anoxia stimulates the bone marrow directly and that bone marrow anoxia represents the primary stimulus for erythropoiesis have been entirely conjectural. Measurements of “bone marrow
oxygen tension” from blood samples obtained by sternal or iliac crest puncture may by themselves leave room for argument. Such measurements, reported in cases of polycythemia vera, or in anemia with evidence of erythropoietic activity, have not differed from normal. In polycythemic subjects with cor pulmonale or congenital heart disease, values did not differ from those of other subjects in congestive heart failure, and were usually slightly above those for mixed venous blood. On the other hand, anoxia has been shown to be related to erythropoietic substances in the circulating blood (“hemo-poietines”). Recent observations on erythropoiesis in parabiotic rats with one member made anoxic, the appearance of polycythemia in litters of mice and rats whose mothers were kept in low pressure chambers, and reticulocyte stimulation by plasma of anemic rabbits lend support to the concept that this type of polycythemia occurs as an indirect effect of lowered arterial oxygen tension on bone marrow activity.

Erythrocytosis and heart failure occur in close association with each other, but one is apparently not the cause of the other. Heart failure obviously does not cause a relative erythrocytosis though it may, of course, result in an increase in total circulating blood volume. It is not clear whether a marked increase in red cell mass with an increase in blood viscosity may raise intravascular pressures and may constitute an additional cardiac load. Though we have seen an instance in which cardiac changes seemed related to the level of red cell mass, the infrequent occurrence of heart failure in polycythemia vera and in arteriovenous aneurysms of the lung makes it likely that such a relationship is not the usual one. On the other hand, as figure 2 shows, the increased capacity to carry oxygen in erythrocytosis, the consequence of an increased red cell mass, may be considered beneficial from a hemodynamic standpoint. However, it is rarely an effective compensatory mechanism.

In emphysema heart disease, the anoxic stimulus for erythrocytosis is opposed by a mechanism that prevents an effective rise in red cell mass, so that the polycythemia is considerably less than expected when compared to the response of normal subjects to decreased oxygen tension by altitude. (fig. 4). It has been claimed that this blocking effect may be the result of an iron deficiency (“anemic polycythemia”) or that it may be on the basis of frequent and recurrent pulmonary infections. The polycythemia of chronic lung disease, however, need not necessarily be considered the equivalent to the erythrocytosis of high altitudes. Even superficially, there are important differences. The changes occurring in response to altitude are invariably accompanied by hyperventilation and are associated with low CO₂ tension and alkalosis, while high CO₂ tension and low pH are the rule in emphysema. The polycythemic response to altitude appears gradual and linear, while in congenital venoarterial shunts as well as in chronic lung disease polycythemia, as stated, seems to require a threshold level of sustained desaturation. At any rate, the defect in emphysema involves cellular hemoglobin production since, as table 4 demonstrates, the mean corpuscular hemoglobin concentration is

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**FIG. 4. Arterial oxygen saturation and erythrocytosis.** In chronic pulmonary disease, production of hemoglobin in response to arterial desaturation is impeded when compared with the response seen in residents at high altitude reported by Hurtado. A more normal response is seen in patients whose arterial desaturation is on the basis of a congenital venoarterial shunt. X represents a subject with "Monge's" disease. The boxes represent the normal values for hemoglobin and arterial oxygen saturation at 3 different altitudes.
significantly lower than normal and the polycythemic cells are often hypochromic.

In summary, the emphysema heart is associated with the triad of pulmonary hypertension, arterial desaturation, and polycythemia. None of these alone is severe enough to result in right ventricular failure, but they act in unison on a poorly functioning myocardium. Since pulmonary function is also grossly impaired, the disease involves the entire cardio-respiratory mechanism. It is possible that the "myocardial factor" is senile heart disease and that the pulmonary dysfunction merely changes the clinical manifestations of arteriosclerotic heart disease to those of the emphysema heart. The possible pathways leading to this type of heart disease are indicated in Table 5.

**Mixed Forms**

The two types of heart failure in chronic lung disease are not always sharply separated and features of one may overlap that of the other. Severe emphysema in young individuals may show many of the features common to the simple hypertensive type, and the former may begin to resemble emphysema heart if arterial desaturation becomes evident. Recently, heart failure secondary to ineffective pumping action of the chest cage, resulting in imperfect ventilation but not associated with emphysema, has been reported in an example of amyotrophic lateral sclerosis, and in a case of extensive calcification of the pleura. Similar changes may occur in extremely obese individuals, who may show arterial desaturation and pulmonary hypertension (see tables 1–3). Under these circumstances, changes in cardio-respiratory function occur that are similar to those seen in the emphysema heart.

In certain types of congenital heart disease, venoarterial shunts with severe arterial desaturation on the basis of venous admixture may be found where the right ventricle has to work against the peripheral arterial system. Again, the triad of arterial desaturation, polycythemia, and increased right ventricular pressures ("systemic right ventricle") appear. The situation is entirely analogous to the steps leading to emphysema heart. Heart failure is not frequent, however, once survival beyond

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**Table 4.** Table showing mean corpuscular hemoglobin concentrations (MCC) in emphysema heart. The table includes columns for No. of Cases, MCC (%), S.D., and p-values.

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
<th>MCC (%)</th>
<th>S.D.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Present series</td>
<td>19</td>
<td>32.3</td>
<td>1.8</td>
<td>—</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>12</td>
<td>31.5</td>
<td>1.5</td>
<td>—</td>
</tr>
<tr>
<td>Erythremia</td>
<td>5</td>
<td>31.1</td>
<td>1.4</td>
<td>Not sign.</td>
</tr>
<tr>
<td>Emphysema heart Present series</td>
<td>23</td>
<td>29.5</td>
<td>2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>14</td>
<td>29.6</td>
<td>1.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Similar data have been reported by Hurtado and associates. Altitude polycythemia shows normal values for MCC.

S.D. — Standard deviation.

p: Probability. Values smaller than 0.05 are considered statistically significant.

**Table 5.** Table showing factors of importance in the development of heart failure in chronic lung disease. The table includes columns for various factors and their corresponding significance.

The complex interrelationship of multiple factors leading to heart failure is indicated. The thickness of the arrows is somewhat proportional to the importance of the factor from which the arrow originates.

the first few months of life has occurred, and very excessive degrees of desaturation and of polycythemia are tolerated for many years. This again suggests that an essential "myocardial factor" is present in the older subjects with emphysema and fibrosis.

In normal subjects, transfer of oxygen from the gaseous to the liquid phase across the alveolar capillary membrane occurs with only a slight loss of oxygen tension from the alveoli to that end of the pulmonary capillary which drains into the pulmonary venous system. This "diffusion capacity" may be impaired in various granulomatous diseases of the lung or in diffuse interstitial fibrosis producing the syndrome of "alveolar capillary block." The impedance of gas transfer is rarely severe
enough to cause arterial desaturation at rest, largely because of a compensatory increase in ventilation. The syndrome is characteristically associated with arterial oxygen desaturation appearing on exercise, because the increase in ventilation is now insufficient to provide the needed compensation.

Such low diffusion capacities with or without emphysema have been observed in various granulomatous lesions of the lung such as sarcoidosis, acute hematogenous ("miliary") tuberculosis, chronic consolidation, scleroderma, beryllium fibrosis. None of these conditions is likely to result in heart failure unless fibrosis and emphysema are also present. The increase in the alveolar-arterial gradient, therefore, should not be a significant factor in the development of cor pulmonale, and heart failure in this group is usually the consequence of associated pulmonary hypertension (pulmonary hypertensive heart disease).

**Kyphoscoliotic Heart Disease.** Pulmonary cardiac failure or kyphoscoliotic heart disease is one type of cardiorespiratory involvement that represents a clear combination of the two types of involvement. Obviously, the respiratory functions are grossly impaired because of the severe chest deformities, and ventilation is inadequate. As a consequence, arterial desaturation and polycythemia are frequently present. Somewhat surprisingly, extremely high pulmonary artery pressures, in the range of those seen in essential pulmonary hypertension, have been recorded. The combination of these factors leads to early heart failure, even in young subjects, and in the face of a normally functioning myocardium. The reason for the excessive elevation of pulmonary artery pressure that we have observed in all cases of this type remains unexplained. It is quantitatively not reasonable that purely mechanical factors, which have been implicated, account for the elevation of pressures.

The relatively rare instances of heart failure following thoracoplasty seem to belong to this group.

**Diagnosis**

Precise measurements of hemodynamic and respiratory function have served to clarify the significance of several physical findings and have helped to quantitate some of the radiologic and electrocardiographic observations encountered in various cardiorespiratory disorders. No attempt is made in this section to give a complete discussion of the symptoms and signs of cor pulmonale in its various forms. A few observations, however, have been particularly helpful in clarifying certain interrelationships commonly encountered in heart failure and lung disease.

**Clinical Diagnosis**

This history of pulmonary hypertensive heart disease, particularly that due to essential pulmonary hypertension, is remarkably short. Dyspnea and fatigue are rapid in onset as one might expect if these are to a large extent the signs of an acutely failing heart. One of our patients worked full time as an operating room nurse until 3 months before death; another subject was an amateur long-distance runner until 1 month before his first hospitalization. In contrast, in emphysematous subjects, dyspnea usually precedes heart failure for years. The symptom here is linked to the pulmonary disease and the abnormality of the chest cage rather than to myocardial failure. In a polycythemic subject, the presence of dyspnea, in contrast to fatigue and lassitude, favors the diagnosis of erythrocytosis ("secondary" polycythemia). Dyspnea is not a feature of polycythemia vera (erythremia). On the other hand, patients with erythrocytosis have a distinct set of symptoms that apparently are related to the plethora, the overfilling of the vascular bed. These subjects usually complain of headache, dizziness, roaring, a "tight" sensation, tingling and itching when vasodilation is produced, as in a warm bath. These symptoms are relieved by bleeding. If these signs are present in erythrocytosis ("secondary polycythemia"), they are superimposed on dyspnea and on the other symptoms of pulmonary and cardiac disease. Bleeding in these patients may alleviate this portion of their complaints though it may not improve the cardiorespiratory symptomatology.

Chest pain as a manifestation of pulmonary hypertension is another symptom often elicited.
It has the characteristics of angina pectoris and may be relieved by nitroglycerin. It has been claimed that the pain is caused by overdistention of the pulmonary artery, but there is little objective information that could not apply equally to the concept of coronary insufficiency on the basis of excessive right ventricular hypertrophy with the muscle mass outgrowing its own blood supply. That the pain occurs on exercise is not surprising, since, under these conditions, a sharp increase in total pulmonary resistance associated with increased work performance occurs frequently.

The demonstration at the bedside of right ventricular hypertrophy by palpation of the precordium is usually possible, even in adults; but the expanded fixed “inspiratory” position of the chest cage in ventilatory defects commonly makes it difficult to demonstrate this component directly in the emphysema heart. Therefore, the accentuation of the second pulmonary sound assumes added significance. An accentuated, snapping second sound can be considered definite evidence of pulmonary hypertension unless right ventricular failure is present (fig. 5). By “accentuation” is implied that the second pulmonary sound (1) is much louder than the first, (2) is louder than the second sound in the aortic area, and (3) that first aortic and pulmonary sound are of about equal intensity. The sign is of value only if one can be assured that aortic and pulmonary sounds are being transmitted to the precordial areas with equal loudness. Since observations correlating this sound with intraventricular or pulmonary artery pressures are generally not based on simultaneous recordings, only a rough quantitation is possible.

Increased pulmonary artery flow into a relatively normal pulmonary vascular bed also causes accentuation of the second pulmonary sound, a characteristic finding in interatrial septal defects. Without additional laboratory information the separation of moderately increased flow from increased pressure with normal or reduced flow on the basis of clinical findings is difficult, if at all possible. Interatrial septal defects occasionally show splitting of the pulmonary second sound as well. Evidence of an increased blood flow, rather than increase in pressure but with reduced flow, may also be surmised from the fluoroscopic picture of dense lung fields with expansible pulsation of major branches of the pulmonary artery ("hilar dance").

In pulmonary hypertension, whatever the cause, loud systolic murmurs may appear
Along the left sternal border which may be transmitted to the apex and into the back. These may be loud enough to simulate congenital heart disease or mitral insufficiency.\textsuperscript{12, 17} An almost unbelievable example in a patient with essential pulmonary hypertension is illustrated in figure 6. Since the findings of an incompetent tricuspid valve are absent, the significance of these murmurs has remained obscure. In addition, a dilated pulmonary valve ring may cause the high-pressure diastolic blow of pulmonary regurgitation (Graham Steell), and in some instances a semilunar opening click\textsuperscript{74, 75} may appear as an extra sound over the pulmonary artery in early systole. It is of interest that cardiac irregularities—particularly atrial fibrillation—are quite infrequent in any type of cor pulmonale.

One feature characteristic of marked restriction of the pulmonary vascular bed and, therefore, common in various states of heart failure associated with lung disease is the occurrence of paradoxical pulsations or rather the accentuation of the normal inspiratory decrease in pulse amplitude. This may be so marked that constrictive pericarditis may be suspected.

\textbf{Radiologic and Electrocardiographic Diagnosis}

\textit{X-ray Diagnosis.} The radiologic picture of emphysema need not be discussed. It should be remembered that in addition to the characteristic chest cage and pulmonary findings, the heart shadow in the anteroposterior view often demonstrates a lifted apex, due to right ventricular hypertrophy, and a bulging pulmonary artery, but that a completely normal cardiac shadow may be observed in the face of arterial desaturation, pulmonary hypertension, and erythrocytosis (fig. 7).\textsuperscript{76-78} The radiologic findings of pulmonary hypertensive heart disease and particularly of essential pulmonary hypertension have emerged as helpful and almost pathognomonic findings.
As figures 7 and 8 demonstrate, the films are characterized by (1) a normal chest cage, (2) cardiac enlargement, often of an unusual degree, (3) heavy central hilar vascular shadows with an accentuated pulmonary conus, (4) a striking decrease in vascularity of the distal pulmonary fields, and (5) absence of left atrial distention. Essential pulmonary hypertension can be differentiated radiologically from the pulmonary hypertensive heart disease secondary to massive unilateral emboli or thrombosis in situ because, in the latter, decrease of vascularity and accentuation of the central vessels are confined to one lobe or one lung in posteroanterior films or during angiocardiography. Massively unilateral embolism often demonstrates distention and pulsation of the vessels leading to the involved lobe, occasionally resulting in a localized or unilateral “hilar dance.”

Electrocardiographic Diagnosis. In pulmonary hypertensive heart disease the electrocardiogram usually shows the classical evidence of right ventricular hypertrophy. In the emphysema heart, more commonly right bundle-branch block, complete or incomplete, or less well defined stages of conduction disturbances of the right ventricle may be present. The relation between predominant right ventricular hypertrophy, with the characteristic tall R waves over the right ventricle, to that of complete right bundle-branch block has been described as one of concentric hypertrophy versus dilatation. This applied to instances of sudden overloading, as in acute pulmonary embolism where disturbances in right ventricular conduction are frequent, as well as to those in whom chronic right ventricular dilatation is present to an excessive degree. In pulmonary hypertensive heart disease with a firm hypertrophic myocardium the tall R wave pattern characteristic of an anterior rotation of the QRS loop in the horizontal plane is more common. Rotation occurring only in the frontal plane (right axis deviation without changes in precordial leads), often simply the result of cardiac rotation around the longitudinal axis.
may still be a sign of right ventricular enlargement, but with a lesser degree of involvement of the right ventricular outflow tract. It is more likely encountered in mitral valve disease or in the emphysema heart than in pure pulmonary hypertension because in these conditions a certain degree of left ventricular hypertrophy often coexists. “Incomplete right bundle-branch block,” on the other hand, seems to occur in instances of delayed activation caused by hypertrophy of the right ventricular conus region and the upper portion of the ventricular septum, which is even normally the latest portion of ventricular musculature to undergo excitation.

In the emphysema heart in particular, righthsided precordial leads often show a qR pattern, a Q wave followed by a late R. It has been pointed out that these changes might be caused by an unusual position of the heart allowing the effects of the upper portion of the septum, including what has been termed the “crista supraventricularis” to be recorded from the precordium. In changes of this type, the right atrium was usually dilated and the right ventricle assumed a more diaphragmatic position. In many instances of cor pulmonale, leads from the ensiform process (V₆) are often helpful in proving the presence of right ventricular hypertrophy.

The electrocardiographic evidence of predominant right ventricular hypertrophy is complex but a reasonably clear correlation exists between electrocardiograms of normal QRS configuration, “right axis deviation” only, “incomplete right bundle-branch block,” and classical right ventricular hypertrophy, on the one hand, and progressive increase in pulmonary arteriolar resistance and increase in the external work performed by the right ventricle, on the other. In man, this correlation between evidence of right ventricular hypertrophy by electrocardiography and pulmonary artery pressures was first established in Courand’s laboratory, has since been confirmed, and may be seen in figure 9.

In the emphysema heart, other combinations of electrocardiographic findings often occur that are almost pathognomonic for this condition. In addition to the signs of right ventricular hypertrophy and its variants described above, positional changes of the heart,
secondary to the chest deformity, result in the appearance of deep S waves in all standard limb leads. This is a sign of an altered chest-heart relationship due to emphysema and is not indicative of cor pulmonale by itself. This applies also to the appearance of unusually large but not widened P waves in V_{1} and in leads II and III ("P pulmonale"). Though their significance is not quite evident, they are not a sign of right atrial hypertrophy, since they may regress to normal on digitalis therapy.

The spatial angle of the mean axis of QRS and of T, a fairly fixed value of the normal electrocardiogram, is not altered in many instances of predominant right ventricular hypertrophy. When the angle increases, an abnormal ventricular gradient results and inverted T waves appear in the precordial electrocardiogram in those leads that demonstrate largely upright QRS complexes. These changes are evidence of an abnormal ventricular recovery process and imply that the musculature has outgrown its own blood supply ("ventricular strain").

**Differential Diagnosis of "Polycythemia"**

When heart failure is present, dyspnea striking, and pulmonary disease evident, the diagnosis of "secondary" polycythemia (erythrocytosis) is not difficult. This may not always be obvious; the expiratory chest position and the use of auxiliary muscles of respiration may have escaped attention or one may find excessive polycythemia in a patient considered an indication of right ventricular enlargement of moderate degree, or right ventricular hypertrophy complicated by associated left ventricular enlargement. In many instances, this may be caused simply by rotation of the heart on its longitudinal axis ("vertical" position).

The "balanced" pattern may of course be a normal electrocardiogram. When associated with high pulmonary artery pressures it indicates associated left ventricular enlargement.

The wavy line arbitrarily divides considerable and marked elevation of PA pressures from normal or slightly elevated pressures. It is thought that slight elevation of pressures might not be associated with electrocardiographic changes.

**MS**—mitral stenosis, **MI**—mitral insufficiency, **IASD**—intra-atrial septal defects, **IVSD**—intraventricular septal defects, **EPH**—essential pulmonary hypertension.
that obviously has only mild pulmonary fibrosis or emphysema. As was stated before, the diagnosis of erythrocytosis as the consequence of lung disease requires, above all, arterial oxygen desaturation of an advanced degree generally associated with cyanosis. Lung disease and pulmonary hypertension are invariably present unless one deals with obvious venous admixture caused by venoarterial shunts. Because the level of desaturation of arterial blood is approximately the same for the stimulus of erythropoiesis as it is for the onset of heart failure, these two frequently occur together and one can safely assume that "cor pulmonale" is present when erythrocytosis is found in a patient with chronic lung disease. Examination of the bone marrow may show relative hyperplasia only of the nucleated red cell series in contrast to the hyperplasia of all cell elements found in true erythremia.87

In "secondary" erythrocytosis, then, the diagnostic findings mentioned above are present, and, in particular, one or the other or all of the characteristic electrocardiographic abnormalities are found. In contrast, erythremia (polycythemia vera, Osler-Vaquez) represents a primary blood dyscrasia with an increase in all cellular elements ("panmyelopothy" of Dameshek88). Arterial oxygen saturation is normal in most instances.89-91 The increase in red cell mass lends these patients a characteristic reddish plethoric complexion quite different from the distressed, purplish appearance of the erythrocytotic subject. Radiologic and electrocardiographic observations are normal and hemodynamic as well as respiratory functions are usually unimpaired.92, 93 Difficulties arise because mild emphysema or pulmonary or coronary thrombosis may complicate erythremia, and leukocytosis or a palpable spleen may be seen in erythrocytotic subjects as the consequence of unrelated diseases. The presence of systemic hypertension is much more frequently associated with erythremia, and is uncommon in cor pulmonale. By the use of these various parameters it is usually, but not always, possible to arrive at the correct diagnosis. Typical examples of erythrocytosis and of erythremia and an example of erythremia with pulmonary fibrosis are given in tables 1-3. Clubbing of the fingers—a form of "pulmonary osteoarthropathy"—is not of great help, since it has been observed in erythremia and may occur as a familial disorder in the absence of lung disease or polycythemia.

Erythrocytosis with arterial desaturation, but without demonstrable pulmonary disease, of course points to a venous admixture syndrome, either on the basis of congenital defects of the heart, including reversal of flow through a patent ductus arteriosus or a septal defect, or as the result of a pulmonary arteriovenous aneurysm. In the former, the shunt is usually demonstrable by cardiac catheterization or by dye injections; in the latter, characteristic pulsatile shadows may be seen in the lung fields radiologically in the absence of cardiac hypertrophy, electrocardiographic anomalies, elevated pulmonary vascular pressures, or abnormal catheterization data. Dye curves may also be normal. Occasionally the tell-tale x-ray findings may be absent, and under these circumstances the diagnosis has to be made by exclusion.

Monge's disease (chronic mountain sickness) has to be considered in the differential diagnosis of arterial desaturation in certain areas.94 It has not been described in the United States, but one patient from Climax, Colorado has been examined by us and demonstrated evidence of chronic nonemphysematous pulmonary disease, apparently too mild to be of consequence at sea level. The "emphysematous types" of chronic mountain sickness described by Monge appear to be simply instances of the emphysema heart.95

MANAGEMENT

The logical management of cor pulmonale must be concerned with the many interrelated pathophysiologic factors that have been discussed in an attempt to break a chain of events such as has been outlined in table 5. The management is essentially palliative, since the ultimate causes for emphysema and for pulmonary hypertension are unknown, and the treatment of such factors as heart failure, arterial oxygen desaturation, and polycythemia are supportive and temporary. Nevertheless,
certain polypragmatism is indicated and appears to be effective generally.

Heart Failure in Cor Pulmonale

The treatment of heart failure in cor pulmonale and its subgroups differs in no way from other types of heart disease. The statement that digitalis is less effective than in other types of low-output syndrome may have been based on the misinterpretation of dyspnea. Many patients receive digitalis for decades because of this symptom of pulmonary disease and obviously are not relieved by it. Digitalis, diuresis, and low-sodium intake are effective in failure of cor pulmonale, though larger doses than usual are occasionally needed. The immediate effect of digitalization in these subjects may be a further rise in pulmonary artery pressure as the result of increased myocardial function. Eventually, pulmonary artery pressures and cardiac output decrease as full compensation is restored and arterial oxygenation improves. The choice of the digitalis preparation seems immaterial, and the claim that strophanthus glycosides are superior in any type of cor pulmonale has not been substantiated.

Pulmonary Disease

The treatment of "chronic lung disease" and the correction of the abnormal mechanics of respiration is approached in two ways. First, pulmonary and bronchial infection and bronchospasm are frequent and often sustained either as the result of or, at least in part, as an etiologic factor in the ventilatory defect. The infection should be treated with vigor, since thereby one of the frequent precipitating causes of heart failure may be removed. By opening narrowed and inspissated airways, alveolar ventilation is improved, and, in consequence, arterial oxygen saturation rises, pulmonary artery pressure falls, and CO2 retention decreases. This may be so effective that the stimulus for erythropoiesis is withdrawn and the erythrocytosis of anoxia may disappear. Thus it is possible by the judicious use of antibiotics, parenteral or rectal theophylline, by oral administration of expectorants and bronchodilators, and particularly by aerosol inhalation of various epinephrine congeners, detergents, or trypsin to reverse the course of the syndrome. The use of adrenal steroids or adrenocorticotrophin has been suggested, and may be based on a reduction of certain phases of the inflammatory response. The need for such therapy seems less well established, and the possibility of accelerating preexisting fibrosis by cortisone must be kept in mind. Postural drainage, advocated in young subjects with bronchiectasis and emphysema, is rarely feasible in patients with emphysema heart, but intermittent periods of positive-pressure breathing with air, oxygen, or oxygen-helium mixtures (80 per cent helium, 20 per cent oxygen) may be effective in improving alveolar ventilation. Respiratory irritants, such as house dust, smoke, odors, and rapid temperature changes, should be avoided. Various types of city "smogs" are poorly tolerated.

A second approach in the management of some forms of pulmonary disease leading to heart failure consists in an attempt to influence directly the abnormal mechanics of breathing. This may be accomplished by regular breathing exercises or, at least, by elevation of the foot of the bed. The benefits claimed for various abdominal belts, or for pneumoperitoneum, designed to place the diaphragm in a more advantageous position for ventilatory work, have remained of questionable value. As a desperate measure, mechanical tank respirators have been used in an effort to ventilate the lungs. This is obviously impractical except as an emergency procedure.

Oxygen, Carbon Dioxide, and Respiratory Acidosis

Anoxia may be so severe that there may not be time to wait for the gradual improvement in alveolar ventilation, or the mechanical difficulties are so pronounced that the measures outlined may not be fully effective. It is then necessary to improve oxygenation by more direct means. Administration of oxygen at tensions above those of the environment usually corrects arterial desaturation, even in the face of a moderate diffusion defect or of some
CLINICAL PROGRESS

Table 6.—Carbon Dioxide Narcosis, L.A., Male, Emphysema Heart, Age 61

<table>
<thead>
<tr>
<th>Date</th>
<th>Arterial Oxygen</th>
<th>Arterial CO₂</th>
<th>Clinical status and therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Content vol.%</td>
<td>Tension mm.</td>
<td>pH at 37°</td>
</tr>
<tr>
<td>Normal</td>
<td>19.5</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>5-10-55</td>
<td>9.1</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>5-11-55</td>
<td>11.3</td>
<td>65</td>
<td>42</td>
</tr>
<tr>
<td>5-16-55</td>
<td>10.8</td>
<td>59</td>
<td>35</td>
</tr>
<tr>
<td>5-23-55</td>
<td>15.4</td>
<td>84</td>
<td>55</td>
</tr>
</tbody>
</table>

This patient was admitted after having been treated with repeated venae sections and oxygen. He received continuous oxygen by mask during 100-mile trip by ambulance and arrived hyperventilating and responsive. As the excitement of the transport abated, he became delirious and appeared moribund (5-10-55). Note that as acidosis increased, CO₂ tension rose, though CO₂ content fell slightly (5-11). Improvement occurred gradually, presumably as the result of intensive therapy with digitalis, antibiotics, and bronchodilators. Neither Diamox nor positive pressure breathing seemed to be particularly effective. On 6-1-55, pulmonary function studies revealed a ratio of residual volume to total capacity of 64 per cent, a large physiologic dead space, alveolar-arterial gradient of 17 mm.

venous admixture through capillary bypasses. Oxygen administration is effective in several ways: in addition to the rise in oxyhemoglobin, the oxygen content of the plasma may be raised and pulmonary artery pressure may decline, often appreciably, and without a significant concomitant fall in cardiac output. This improvement may occur even in apparently “fixed” pulmonary hypertension of long standing.3, 117

Carbon dioxide elimination is not aided by oxygen administration. In fact, it has been pointed out that many subjects with arterial oxygen desaturation and elevated blood carbon dioxide levels are dependent for their respiratory drive on the anoxic stimulus of the chemoreceptors in the aortic and carotid bodies rather than on the blood CO₂ level. If anoxemia is even partially corrected by oxygen therapy, respirations might decrease for lack of a stimulatory drive, and, in consequence, CO₂ content may rise further to levels that induce excitement, drowsiness, or loss of consciousness.3, 61, 118-120

Hypoventilation and CO₂ narcosis leading to uncompensated respiratory acidosis can also be induced by oversedation, and opiates should, therefore, be used with great reservations. The resulting respiratory acidosis raises CO₂ tension for a given content, so that a high CO₂ content is of even greater significance when pH is low. If respiration is artificially stimulated in the face of very high CO₂ content, the pH of the blood may rise, tension may be lowered, and coma and delirium may at least temporarily be held in abeyance.120 The interplay between some of these factors is illustrated in table 6. Carbon dioxide narcosis may be prevented by the intermittent use of lower concentration of oxygen and by low flow rates. Fear of this syndrome should not preclude the use of needed oxygen in the acutely distressed subjects.

The problem of respiratory acidosis with CO₂ retention is one that represents an additional complication in cor pulmonale and cannot be fully discussed here in all its ramifications. Recently, attempts have been made to influence plasma bicarbonate levels and CO₂ narcosis by the use of carbon anhydrase inhibitors, imposing a moderate metabolic acidosis on a preexisting respiratory acidosis121-124 It is not clear whether carbon anhydrase inhibitors exert their effect by influencing blood gas concentration, or by a reflex stimulation of the respiratory center causing hyperventilation. The decreased responsiveness of the center to CO₂, typical of chronic lung disease, is not altered by prolonged administra-
tion of a carbon anhydrase inhibitor. The usefulness of carbon anhydrase inhibitors is still not definitely established, since in most instances heart failure coexisted and the improvement seemed to occur concomitant with diuresis.

Since blood and alveolar gas tensions maintain an equilibrium, changes in altitude—by causing a change in partial pressures for oxygen in the atmosphere—will influence arterial oxygen saturation, as the example of altitude anoxia demonstrates. The peculiar S-shaped form of the oxygen dissociation curve of the blood, however, insures a normal subject a stable oxygen saturation in the face of large variations in alveolar and arterial oxygen tension. If alveolar oxygen content is lowered by imperfect ventilation, or by an increase in dead space or both, the subject may become highly sensitive to a further decrease in atmospheric oxygen tension (fig. 10). Patients with moderate arterial desaturation at sea level may do very poorly on moving to even moderate altitudes such as may prevail in the intermountain region, providing the oxygen desaturation is primarily on the basis of altered alveolar ventilation and is not the result of venous admixture. For the same reason subjects with emphysema heart residing in these areas may show a remarkable improvement in their symptoms, a rise in arterial oxygen saturation, and a disappearance of their erythrocytosis upon a sojourn to sea level. It is tempting to assume that a similar mechanism—the combination of moderate pulmonary disease not readily detectable and asymptomatic at sea level, plus altitude—may be involved in chronic mountain sickness (Monge’s disease).

Recent suggestions that massive doses of salicylates might restore the reduced sensitivity of respiratory center to CO₂ and may thereby be used therapeutically to reduce the hypercapnia of emphysema, are viewed with some concern. The effects of salicylism are produced only at high plasma salicylate levels. In addition to the toxic metabolic effects and psychoses, may have a direct myocardial stimulating effect and, furthermore, may cause a sharp increase in circulating plasma volume: total circulating CO₂ transport is therefore not necessarily lowered and congestive heart failure may be precipitated.

Improving arterial oxygen content by whatever means may cause disappearance of erythrocytosis. It was pointed out that polycythemia may be looked upon as a compensatory event and its removal (by bleeding or otherwise) in the face of unchanged arterial oxygen content may precipitate heart failure because of a further reduction in oxygen supply (fig. 2). Usually bleeding does not by itself improve oxygenation, does not alter carbon dioxide retention, nor does it lower pulmonary artery pressures. Therefore, from the standpoint of cardiorespiratory function, bleeding an erythrocytotic subject has little to recommend (fig. 11). Temporary subjective improvement, however, is occasionally
COR PULMONALE: HEMODYNAMICS BEFORE AND AFTER PHLEBOTOMY. (10 SUBJECTS)

Fig. 11. Cor pulmonale, hemodynamic response to repeated bleeding. In spite of a sharp reduction in the volume of packed red cells and in oxygen content in this series, there were no striking changes in pulmonary artery pressure or in oxygen saturation following several phlebotomies. Internal oxygen transport decreased. In a patient who has received maximum benefit from other therapeutic measures, phlebotomies seem to be of little additional benefit.

noted because the symptoms of plethora mentioned above may be relieved. Furthermore, the fluidity of the blood decreases in a nonlinear fashion as the volume of packed red cells/100 ml. increases. Its reciprocal, viscosity, the force required to produce a unit rate of shear, is a function of the physical properties of the fluid, and in a non-Newtonian fluid, such as blood, varies with flow rates (level of cardiac output) and with the size of the vessels. Measurements of viscosity are usually based on artificial systems comparing steady flow of the test fluid through rigid tubes of constant diameter with the flow of water. Few measurements were made in living systems and in consequence there is little information on “viscosity” of blood in the intact organism at rest, on exercise, and in various parts of the vascular system. All one can say is that it seems reasonable to assume that viscosity in larger vessels rises with an increase in the volume of packed red cells, and that its effects should be greater in patients with congestive heart failure than in normal subjects. At hematocrit levels above 60–65 per cent in patients with decompensated cor pulmonale, blood stagnation with thrombus formation may, therefore, occur, and for this reason only correction of an excessive erythrocytosis seems reasonable. A complete correction to normal levels of packed red cells, however, is neither necessary nor desirable.

Treatment of Pulmonary Hypertension

The procedures outlined in the preceding section may lower pulmonary artery pressure if this was related to arterial desaturation and to carbon dioxide retention. In pulmonary hypertensive heart disease, no obvious impairment in respiratory function is present, arterial oxygenation is not severely impaired, and none of the measures outlined are effective. It is obvious that little can be accomplished if organic luminal obstruction is advanced; treatment of this phase of cor pulmonale has been least effective. In consequence, in pulmonary hypertensive heart disease the treatment of heart failure has been almost the only
form of management available with the exception of mitral valve surgery in the “secondary” type. A recent report has pointed to the efficacy of Priscoline in reducing pressure in the pulmonary vascular obstruction syndrome.12 A few observations on the use of ganglionic-blocking agents in lowering elevated pulmonary arterial pressures have appeared,12–14 though these seem ineffective in changing normal or slightly elevated pressures. Preliminary observations in our laboratory have tended to confirm these pressure-lowering effects of Priscoline in almost any type of hypertension of the lesser circulation in the face of a regularly increased cardiac output. There is, as yet, no information whether these pharmacologic responses can be translated into lasting therapeutic effects, but it is of note that the changes were associated with considerable subjective improvement which could be sustained by prolonged oral administration of Priscoline (50 mg. 4 or 5 times daily). Still, the outlook, particularly in essential pulmonary hypertension, is grave: perhaps because patients with these disorders do not seek medical attention until they have entered the final episode of their disease.

SUMMARY

The confusing and complex interplay of factors leading to “cor pulmonale” may be somewhat clarified if the effects of excessive pulmonary hypertension causing right heart overloading (“pulmonary hypertensive heart disease”) are separated from the ventilatory defects that result in arterial desaturation, erythrocytosis, and moderate pulmonary hypertension (“emphysema heart”). In the former group, heart failure dominates the clinical picture; in the latter, it is assumed that heart failure occurs on the basis of a “myocardial factor”—presumably arteriosclerotic heart disease—whose manifestations are colored and modified by the coexisting and contributing respiratory dysfunction. Overlapping of these two distinct forms occurs frequently, and pulmonary hypertension may be severe enough to be the chief precipitating cause of failure in emphysema, particularly in young subjects and in patients with kyphoscoliosis. Respiratory disturbances, fibrosis, and loss of pulmonary elasticity may accompany heart failure secondary to right ventricular overloading which may ultimately lead to significant arterial desaturation at rest and the development of polycythemia, even in this group. It is typical, however, that the disturbances leading to cor pulmonale rarely, if ever, involve the actual pulmonary function of alveolar-capillary gas exchange; they are confined to the abnormalities of the precapillary pulmonary vasculature and to the mechanical apparatus of the chest cage and of the pulmonary parenchyma concerned with breathing mechanisms.

Pulmonary hypertensive heart disease, whatever its cause, has a monotonous symptomatology that is dominated by the signs of heart failure. In cor pulmonale due to emphysema and its allied types, the clinical picture is varied, and oxygen deficiency with arterial desaturation is of central significance. It raises pulmonary artery pressure by a mechanism not fully understood, and it stimulates erythropoiesis. When erythrocytosis has occurred, heart failure from cor pulmonale will soon make its appearance. Unless the arterial oxygen content falls sharply on exercise, resting oxygen saturation values in excess of 80 per cent do not cause this type of polycythemia; nor does polycythemia as such, as in erythremia (“vera”), result in significant arterial desaturation, pulmonary hypertension, or heart failure. However, little is known concerning the hemodynamic load imposed by an increase in blood viscosity.

The management of cor pulmonale must recognize the multiplicity of factors that are concerned and should weigh their relative significance in any given subject. The kaleidoscopic appearance of cor pulmonale requires flexibility of therapy based on a grasp of the individual pathophysiologic interrelations, which may differ from patient to patient.

SUMMARIO IN INTERLINGUA

Le confuse e complexe interaction de factora que resulta in le eventuation de “corde pulmonal” deveni un pauco plus clar si on separa (1) le effectos del excessive hypertension pul-
monar que causa un supercarga del corde dextere ("morbo cardial pulmono-hypertensive") ab (2) le defectos ventilatori que resulta in dissaturation arterial, erethryctosis, e moder-ate hypertension pulmonar ("corde a emphy- syma"). In le prime de iste situations, disfallimento cardiac es le dominante aspecto clinic; in le secunde le disfallimento cardiac pare occurrer super le base de un factor myo-cardial (probablemente morbo cardial arterio-sclerotic) con manifestaciones que es colorate e modificate per le coexistencia contribuente de dysfunctionamento respiratori. Le delimitation mutual de iste duo distincte formas es fre-quentemente pauc definit, e hypertension pulmonar pote esser satis sever pro ager como le principal causa precipitante de disfallimento in emphysea, specialmente in juvene individuos e in patientes con cyphoscoliosis. Dis- turbaciones respiratori, fibrosis, e perdita de elasticita pulmonar pote accompaniar le disfallimento cardiac como phenomenos secundari a supercargas dextero-ventricular que resulta a vices in le curso del tempore in significative dissaturation arterial in stato de reposo e in le disveloppamento de polycythemia. Nonobstante, il es caracteristic que le disturbations responsable pro le disveloppamento de corde pulmonal involve marmente (si unquam) le function pulmonar mesme del excambio al-veolo-capillar de gas. Illos es restringite a anormalitates del precapillar vasculatura pulmonar e al apparato mechanic del thorace e del parenchyma pulmonar concernente con le mechanismo respiratori.

Morbo cardial pulmono-hypertensive (de qualcunque causa) ha un symptomatologia monotone que es dominante per le signos de disfallimento cardiac. In casos de corde pulmonal debite a emphysea (e in le typos affin), le aspecto clinic es de character variabile, e deficientia de oxygeno con dissaturation arterial ha un signification central. Illo augmenta le pression pulmono-arterial per un mechanismo que es non ancora completely clar, e in plus illo stimula le activitate erythropoietic. Si erethryctosis ha occurrirre, disfallimento cardiac ab corde pulmonal va evenir sin grande retardamento. Exepte in casos in que le contento arterial de oxygeno es marca-mente reducite per exercitios, nivellos de satura-


