Cause of low arterial oxygen saturation in pulmonary fibrosis

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Since the description of 'alveolar-capillary block' by Austrian, McClement, Renzetti, Donald, Riley, and Cournand (1951), impairment of diffusion across the alveolar-capillary membrane has been regarded as an important factor in the production of low arterial oxygen saturations in patients with diffuse pulmonary disease. However, Luchsinger, Moser, Bühllmann, and Rossier (1957) suggested that restriction of the capillary bed might be responsible, and the demonstration by Roughton and Forster (1957) that the relatively slow chemical reaction with haemoglobin was a major resistance to the absorption of respiratory gases lent support to this view. More recently, Motley (1958) and Finley, Swenson, and Comroe (1962) have shown the importance of uneven distribution of ventilation and perfusion in producing hypoxaemia.

In view of the doubt as to the importance of diffusion in gas absorption, Cotes (1963) has suggested the non-committal term 'transfer factor' instead of 'diffusing capacity' (DL) to describe the process. Roughton and Forster (1957) showed that it was possible to separate the red cell and the membrane components of gas transfer by making use of the competition between carbon monoxide and oxygen for the available haemoglobin (Fig. 1). This technique gives an estimate of the volume of the pulmonary capillaries (Vc) if the rate of combination of the gas with blood (θ) is known. However, both the capillary volume (Vc) and the membrane component (DM) estimated in this way are probably influenced by uneven distribution effects (Hamer, 1963b) which limit the contact between alveolar gas and capillary blood. The relation between the factors is given by the formula

\[ \frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{θVc} \]

In the present study, the technique of Roughton and Forster (1957) was used to analyse the process of gas transfer in seven patients with diffuse interstitial pulmonary fibrosis and two with diffuse metastatic carcinoma of the lung. The findings are compared with the changes reported in 30 patients with pulmonary sarcoidosis (Hamer, 1963a). Cardiac catheterization was performed in four of the patients with interstitial pulmonary fibrosis and four of the sarcoidosis group, three of these patients having radiological evidence of fibrosis in addition to infiltration in the lungs.

METHODS

The measurement of the components of gas transfer in these patients was performed in the same way as in the study of pulmonary sarcoidosis (Hamer, 1963b). The single-breath technique described by Ogilvie, Forster, Blakemore, and Morton (1957) was used, with some modifications, to measure the carbon monoxide uptake at two levels of oxygen tension in each subject. After a full but unforced expiration, a

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maximal breath of gas containing approximately 0·2% CO and 15% helium was inspired and held for about 10 seconds. Two gas mixtures were used, one made up in pure O₂ and the other with 20% O₂ and the remainder N₂ (referred to as the ‘air’ mixture). Straining during breath-holding was avoided as much as possible. A single three-way tap was used to reduce the dead space of the apparatus. Rubber bags were applied to the outlet of the tap, using tapered air-tight connectors, and were then evacuated by a suction line. A sample was collected after the expiration of about 1 litre to flush out the dead space. Unduly forceful expiration was avoided, and the sampling time was kept as small as possible. In general, approximately 1 litre of expire was collected in about half a second.

Part of each sample was transferred to a mercury tonometer for the subsequent measurement of O₂ and CO₂ content by the Scholander method. The remainder of the sample was then drawn through a CO₂ absorber to the gas analysers at approximately 0·5 l/min. The gas to be inspired was drawn through a humidifier to the analysers before each estimation. Approximately 0·5 litre of gas was needed for accurate measurement of CO and He. The gas passed first to a Cambridge catharometer set to read He concentrations in moist air. The catharometer readings were corrected for variations in oxygen content on the basis of a reading of 1·9% He with 100% O₂, assuming a linear increase in the reading between 21% and 100% O₂ in the gas carrying the helium. After passing through a water absorber (magnesium perchlorate), the gas passed through a CO analyser (type SCLA). This instrument was calibrated before each study with a standard gas mixture supplied by the makers. One scale, extending from 0·03 to 0·25% CO, was used for measurement of both the inspired and expired gas, and the linearity of the response was confirmed by comparison with the catharometer readings, using serial dilutions of mixtures of CO and He. All measurements were made as soon as CO instruments had reached a steady reading after flow had stopped. The CO and He contents of the expired sample were corrected for the CO₂ absorbed.

The duration of breath-holding and the volume of gas inspired were obtained from the spirometer chart. Breath-holding was measured from the beginning of inspiration to the beginning of sample collection, and the value was corrected as suggested by Jones and Meade (1961), i.e., half the sampling time was added and three-tenths of the inspiratory time subtracted, to allow for variations in the timing of inspiration and expiration. The effective lung capacity during breath-holding was calculated from the dilution of the inspired He, as suggested by McGrath and Thomson (1959), after subtraction of an estimated value for the dead space. The effective capacity calculated in this way is preferred to the total capacity as measured by the closed-circuit method or by body plethysmography as it gives a better estimate of the volume of lung taking part in the absorption of CO from the single breath.

Measurements with the oxygen mixture were performed first in each subject to minimize the correction necessary for the progressive increase in circulating carboxyhaemoglobin. The pulmonary capillary carbon monoxide concentration was estimated by equilibration at high oxygen tensions before and after each study. An equilibrated sample was obtained after a preliminary period breathing oxygen by re-breathing for four minutes in a 6-litre closed circuit filled with oxygen and containing a CO₂ absorber (Siösteen and Sjöstrand, 1951). Values for each experiment were obtained by interpolation and corrected to the appropriate P₀₂ by direct proportion. The estimated pulmonary capillary CO concentration was subtracted from both the initial and final alveolar CO concentrations before calculation of the diffusing capacity. A small further correction was made to the initial concentration for the CO in the residual volume before each experiment.

The rate of uptake of CO by the blood (θ) was calculated for each experiment from the relation

\[
\frac{1}{\theta} = 0.33 + 0.0057 P_{O_2} \text{obtained from Fig. 1 of Roughton and Forster (1957) for } \lambda = \infty, \text{i.e., on the assumption that there is no increase in the resistance to gas transfer at the red cell surface. Recent work shows no evidence of such a resistance in vivo (Thews and Niesel, 1959; Kreuzer and Yahr, 1960; Sirs, 1963). The appropriate P₀₂ was obtained, as suggested by McNeill, Rankin, and Forster (1958), by adding 5 mm. Hg to the P₀₂ of the expired sample to give an estimate of the mean alveolar P₀₂, and subtracting the alveolar-capillary oxygen difference estimated as V₀₂/DL₀₂. Oxygen uptake (V₀₂) was taken from tables, assuming a metabolic rate 20% above basal, and DL₀₂ was assumed to be 1·23 times DL₀₂. The value obtained for \( \theta \) was corrected proportionately for changes in the venous haematocrit.

Two or three measurements of DL and θ were obtained at both levels of oxygen tension in most of these subjects, and the mean values were used in the subsequent calculations. The membrane component of carbon monoxide transfer (D₀) and the pulmonary capillary volume (Vc) were obtained from the simultaneous equations

\[
\frac{1}{L_L} = \frac{1}{D_M} + \frac{\theta}{V_C} \quad \text{at each oxygen tension. A standard value for the transfer factor (DL) at an oxygen tension of about 120 mm. Hg was obtained by putting } \theta = 1. \text{ The graphical solution of these equations is shown in Fig. 2 in which } \frac{1}{D_L} \quad \text{is plotted against } \frac{1}{L_L} \quad \text{which is linearly related to } P_{O_2}. \text{ The transfer factors (DL and DM) are expressed throughout in ml./ mm. Hg/min., } \theta \text{ in ml. CO/ml. blood/mm. Hg/min., and capillary volume (Vc) in millilitres. Values more than three standard errors from the regression for age in normal subjects (Hamer, 1962) were regarded}

1 Infra Red Development Co.
**Cause of low arterial oxygen saturation in pulmonary fibrosis**

![Diagram](https://example.com/diagram.png)

**FIG. 2.** Graphical calculation of \( D_M \) and \( V_C \). \( \frac{1}{D_L} \) is plotted against \( \frac{1}{\theta} \) which varies linearly with oxygen tension. As the oxygen tension is increased, \( \frac{1}{\theta} \) becomes larger and \( D_L \) is reduced. The slope of the line joining observations at two different oxygen tensions gives the capillary volume \( (V_C) \). The intercept gives the membrane component \( (D_M) \). A standard value for \( D_L \) is obtained at \( \theta = 1 \).

Lung volumes were expressed as percentages of the values predicted for residual volume and vital capacity in Table X of Needham, Rogan, and McDonald (1954), corrected to B.T.P.S.

Cardiac catheterization was carried out under basal conditions without sedation. Pressure measurements were referred to a base line at the middle of the chest at the level of the fourth costal cartilage. Cardiac output was determined from the Fick principle, using oxygen saturations obtained with a Kipp reflection oximeter and estimating oxygen consumption from tables at 10% above the basal level. The pulmonary vascular resistance was calculated using the pulmonary artery wedge pressure as an estimate of pulmonary venous pressure. In three patients the catheter could not be wedged; the pulmonary venous pressure in these patients was assumed to be similar to that in the other cases studied. The contact time between blood and alveolar gas in the pulmonary capillaries was calculated from the relation between capillary volume and flow \( (t \text{ (sec.)} = \frac{V_c \text{ (ml.)}}{Q_c \text{ (ml./sec.)}}) \).

**RESULTS**

**LUNG VOLUMES** The age and physical characteristics of each patient are described in Table I. All but W. L. and E. F. were non-smokers. The effective lung capacity obtained from the dilution of helium in each single-breath test is shown in Table II. The results obtained using the two different gas mixtures are similar, providing confirmation of the accuracy of the correction of the helium reading for changes in the oxygen content of the gas. The effective lung capacities for a series of tests in any given subject show little variation, the range being less than 15% of the total capacity. The effective residual volume measurements follow a similar pattern.

The patients with pulmonary fibrosis show a considerable reduction of effective lung capacity and residual volume, the average lung capacity being 58% and the residual volume 68% of the predicted value (Table III). The two patients with diffuse carcinomatous infiltration had grossly reduced effective lung volumes, the total capacity averaging 37% and the residual volume 26% of predicted.

**TABLE I**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Height (in.)</th>
<th>Weight (lb.)</th>
<th>B.S.A. (m²)</th>
<th>Haemoglobin (g./100 ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C.M.</td>
<td>25</td>
<td>M</td>
<td>67</td>
<td>119</td>
<td>1-62</td>
<td>13-9</td>
</tr>
<tr>
<td>R.G.</td>
<td>30</td>
<td>M</td>
<td>68</td>
<td>177</td>
<td>1-96</td>
<td>14-4</td>
</tr>
<tr>
<td>J.D.</td>
<td>72</td>
<td>M</td>
<td>71</td>
<td>186</td>
<td>2-04</td>
<td>14-8</td>
</tr>
<tr>
<td>W.L.</td>
<td>59</td>
<td>M</td>
<td>70</td>
<td>145</td>
<td>1-82</td>
<td>14-9</td>
</tr>
<tr>
<td>A.L.</td>
<td>71</td>
<td>F</td>
<td>62</td>
<td>105</td>
<td>1-45</td>
<td>12-8</td>
</tr>
<tr>
<td>M.G.</td>
<td>47</td>
<td>F</td>
<td>59</td>
<td>120</td>
<td>1-48</td>
<td>12-7</td>
</tr>
<tr>
<td>E.F.</td>
<td>63</td>
<td>M</td>
<td>67</td>
<td>125</td>
<td>1-64</td>
<td>15-1</td>
</tr>
<tr>
<td>Diffuse carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.C.</td>
<td>62</td>
<td>M</td>
<td>67</td>
<td>175</td>
<td>1-91</td>
<td>15-5</td>
</tr>
<tr>
<td>W.C.</td>
<td>56</td>
<td>M</td>
<td>59</td>
<td>120</td>
<td>1-48</td>
<td>12-7</td>
</tr>
</tbody>
</table>

* Diffuse systemic sclerosis.

**GAS TRANSFER** The values obtained for the transfer factor \( (D_L) \) and the corresponding measurements of \( \theta \) in each subject are shown in Table II, and the calculated values for the transfer factor \( (D_{L1}, \theta = 1) \), the membrane component \( (D_M) \), and the pulmonary capillary volume \( (V_C) \) are given in Table III. In the patients with pulmonary fibrosis, the transfer factor \( (D_L) \) was more than three standard errors below the normal for the patient's age (Hamer, 1962). The membrane component \( (D_M) \) was similarly reduced in all cases, but the capillary volume \( (V_C) \) was less affected, being in the normal range in two subjects. The patient (E.F.) with the largest capillary volume appeared to be less severely affected than the other patients in this group, as the radiographic changes were minimal. There was no clear relationship between the changes in gas transfer and the severity of the disease as judged from the reduction in lung volume. The two patients with diffuse carcinoma had a gross reduction of both components of gas transfer.
The average values in each group, together with the average findings in 25 normal subjects (Hamer, 1962) and in three groups of patients with pulmonary sarcoidosis (Hamer, 1963b), are shown in Table IV. The results of the present study resemble those reported in the more severely affected patients with pulmonary sarcoidosis. Similar findings have been reported by McNeill et al. (1958) in five patients, and by Bates, Varvis, Donevan, and Christie (1960) in four patients using a slightly different technique.

PULMONARY CIRCULATION Cardiac catheterization was performed in four patients with diffuse

<table>
<thead>
<tr>
<th>Patient</th>
<th>Air Mixture</th>
<th>Effective Lung Volumes</th>
<th>Oxygen Mixture</th>
<th>Effective Lung Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I 0 D.</td>
<td>T.L.C. (ml.) R.V. (ml.)</td>
<td>I 0 D.</td>
<td>T.L.C. (ml.) R.V. (ml.)</td>
</tr>
<tr>
<td>C.M.</td>
<td>0.66 1.10</td>
<td>1.800 2.10</td>
<td>6.8 1.870</td>
<td>6.7 1.670</td>
</tr>
<tr>
<td>R.G.</td>
<td>0.76 0.97</td>
<td>3.200 1.93</td>
<td>5.1 3.220</td>
<td>5.0 1.640</td>
</tr>
<tr>
<td>J.D.</td>
<td>0.83 1.10</td>
<td>5.700 2.33</td>
<td>9.6 5.760</td>
<td>9.0 2.430</td>
</tr>
<tr>
<td>W.L.</td>
<td>0.95 1.06</td>
<td>5.700 2.38</td>
<td>8.9 5.530</td>
<td>8.5 2.350</td>
</tr>
<tr>
<td>A.L.</td>
<td>0.83 1.08</td>
<td>1.810 1.98</td>
<td>3.7 1.740</td>
<td>3.6 1.080</td>
</tr>
<tr>
<td>M.G.</td>
<td>0.95 1.06</td>
<td>3.150 2.90</td>
<td>9.1 3.070</td>
<td>9.0 1.230</td>
</tr>
<tr>
<td>E.F.</td>
<td>0.91 1.06</td>
<td>5.460 2.76</td>
<td>10.7 5.570</td>
<td>10.4 1.880</td>
</tr>
<tr>
<td>L.C.</td>
<td>0.73 1.06</td>
<td>2.420 1.94</td>
<td>3.1 2.260</td>
<td>3.0 0.760</td>
</tr>
<tr>
<td>W.C.</td>
<td>0.71 1.06</td>
<td>2.520 1.23</td>
<td>6.2 2.330</td>
<td>6.0 1.500</td>
</tr>
</tbody>
</table>

TABLE III
RESULTS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Effective Lung Volumes</th>
<th>Gas Transfer Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T.L.C. (ml.) R.V. (ml.)</td>
<td>Dθ (ml.mm. Hg.min.) Dw (ml.mm. Hg/min.) Vc (ml.)</td>
</tr>
<tr>
<td>C.M.</td>
<td>1.810 26 770 38 8.3 11 33</td>
<td></td>
</tr>
<tr>
<td>R.G.</td>
<td>3.180 48 1.610 89 7.5 18 33</td>
<td></td>
</tr>
<tr>
<td>J.D.</td>
<td>5.880 89 2.120 89 13.1 31 30</td>
<td></td>
</tr>
<tr>
<td>W.L.</td>
<td>3.090 45 2.480 83 13.2 20 38</td>
<td></td>
</tr>
<tr>
<td>A.L.</td>
<td>1.780 43 1.100 56 4.3 7 15</td>
<td></td>
</tr>
<tr>
<td>M.G.</td>
<td>3.030 73 1.260 87 15.3 26 29</td>
<td></td>
</tr>
<tr>
<td>E.F.</td>
<td>5.400 84 2.000 67 14.2 18 72</td>
<td></td>
</tr>
<tr>
<td>L.C.</td>
<td>2.330 30 730 30 4.2 8 10</td>
<td></td>
</tr>
<tr>
<td>W.C.</td>
<td>2.350 34 650 21 7.0 13 15</td>
<td></td>
</tr>
</tbody>
</table>

* Within three standard errors of normal for age.

TABLE IV
AVERAGE VALUES FOR THE COMPONENTS OF GAS TRANSFER

<table>
<thead>
<tr>
<th></th>
<th>Dθ (ml/mm. Hg/min.)</th>
<th>Dw (ml/mm. Hg/min.)</th>
<th>Vc (ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 normal subjects (Hamer, 1962)</td>
<td>29.4</td>
<td>52</td>
<td>75</td>
</tr>
<tr>
<td>Pulmonary sarcoidosis (Hamer, 1963b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal findings, 7 subjects</td>
<td>27.7</td>
<td>49</td>
<td>68</td>
</tr>
<tr>
<td>Low Dw only, 16 subjects</td>
<td>16.6</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Low Dw and Vc, 7 subjects</td>
<td>10.8</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Present study</td>
<td>10.9</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Pulmonary fibrosis, 7 subjects</td>
<td>10.9</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Diffuse carcinoma, 2 subjects</td>
<td>5.6</td>
<td>11</td>
<td>13</td>
</tr>
</tbody>
</table>
pulmonary fibrosis and in four with sarcoidosis (Table V); the gas transfer measurements in the patients with sarcoidosis have been reported elsewhere (Hamer, 1963b). There was only slight elevation of pulmonary artery pressures in most of these patients, with a corresponding slight increase in pulmonary vascular resistance. In two cases the pulmonary hypertension was appreciable, and the resistance exceeded 10 units (expressed in terms of body surface area). The cardiac output was normal or slightly reduced, and there was no evidence of cardiac failure though some patients showed a prominent 'a' wave in the right atrial pressure-pulse. The arterial oxygen saturation was reduced at rest in all but one patient, and in this subject there was a clear fall in saturation on effort.

There is no correlation between the severity of the respiratory disease, as judged from the reduction in effective lung capacity, and the vascular changes. Although the pulmonary vascular resistance and capillary volume were abnormal in all but two patients (R.G. and K.S. respectively) there was no definite relation between these two factors within the group (Fig. 3). Similarly, changes in the cardiac output and the arterial oxygen saturation appeared to be independent of the other parameters studied. The contact time was considerably reduced in most patients but was largely determined by the changes in capillary volume, as the pulmonary capillary blood flow was relatively unchanged. The average contact time was 0.3 sec.

**DISCUSSION**

Idiopathic pulmonary fibrosis was first described in an acute form by Hamman and Rich (1944). Baldwin, Cournand, and Richards (1949) studied the functional changes produced by pulmonary fibrosis and found a reduction in the volume of the lungs, a low arterial oxygen saturation, and evidence of hyperventilation. Austrian et al. (1951) suggested that the abnormality in these patients was due to 'alveolar-capillary block', i.e., impairment of diffusion of gases from the alveoli to the pulmonary capillaries. Subsequent work extended the definition of idiopathic pulmonary fibrosis to include chronic cases (Rubin and Lubliner, 1957; Scadding, 1960; Livingstone, Lewis, Reid, and Jefferson, 1964). It appeared to confirm the hypothesis of a diffusion defect (Marks, Cugell, Cadigan, and Gaensler, 1957) both in the idiopathic cases and in pulmonary fibrosis due to sarcoidosis (Marshall, Smellie, Baylis, Hoyle, and Bates, 1958) or scleroderma (Catterall and Rowell, 1963), and also in diffuse carcinomatous infiltration of the lungs (Baldwin et al., 1949).

The suggestion that a diffusion defect was responsible for the low arterial oxygen saturation in pulmonary fibrosis was first seriously
challenged by Swiss workers (Rossier, Bühllmann, and Luchsinger, 1954; Luchsinger et al., 1957; Luchsinger, Katz, McCormick, Donohoe, and Moser, 1959). They pointed out that the hypoxaemia was associated with a rise in the pulmonary vascular resistance and suggested that a critical reduction in the pulmonary vascular bed was responsible for both changes. A small pulmonary capillary bed in the presence of a normal cardiac output would be expected to reduce the contact time between the red cells and the alveolar gas so that equilibrium could not be attained before the red cells reached the end of the capillary.

The work of Roughton and Forster (1957) has allowed a more accurate assessment of the importance of changes in the pulmonary capillary bed. They demonstrated the importance of the rate of combination of the gas with blood (θ) and showed that the capillary volume could be calculated using carbon monoxide. Unfortunately, the study of oxygen transfer is more difficult as there is no simple relation between θ for oxygen and the oxygen tension (Staub, Bishop, and Forster, 1962). Recent calculations, however, confirm the importance of a reduction in the contact time in the production of low arterial oxygen saturations, and suggest that in normal subjects equilibrium with alveolar gas is reached before the end of the capillaries except on exercise breathing a hypoxic gas mixture (Staub, 1963). These estimates are based on the assumption that the capillary volume calculated using carbon monoxide is also applicable to oxygen transfer. However, it has been suggested (Turino, Bergofsky, Goldring, and Fishman, 1963) that the capillary volume for oxygen may be smaller than for carbon monoxide as slow-moving oxygenated blood will take up carbon monoxide but not oxygen. However, this effect is unlikely to be large enough to affect the argument, and Staub (1963) estimates that a reduction in contact time to one-fifth of normal is necessary to produce any measurable difference in oxygen tension between alveolar gas and the blood at the end of the capillaries at rest. Measurements of the contact time in the present study showed changes of this degree only in the more severely affected patients, suggesting that restriction of the pulmonary vascular bed is not the major determinant of the low arterial oxygen saturation in pulmonary fibrosis, though it may be a contributory factor.

Uneven distribution of ventilation and perfusion in the lung is responsible for most of the difference between alveolar and arterial oxygen tensions in normal subjects (Briscoe, 1959; Asmussen and Nielsen, 1960 and 1961). These effects are greatly accentuated in pulmonary fibrosis by focal involvement of airways and blood vessels, and many investigators have concluded that the low arterial oxygen saturation in this condition can be accounted for by the distribution disturbances (Motley, 1958; Holland and Blacket, 1960; Finley et al., 1962; West, 1963). The changes in the components of gas transfer reported here must be interpreted in the light of these findings. The single-breath method used to measure the transfer factor for carbon monoxide is influenced by uneven ventilation, and in addition local variations in capillary volume are probably produced by uneven blood flow in the lungs (Hamer, 1963b). These distribution effects reduce the transfer factor by limiting the contact between alveolar gas and capillary blood (Burrows, Niden, Mittman, Talley, and Barclay, 1960). If the effect is similar at all levels of oxygen tension, both the components of gas transfer (DM and VC) will be similarly reduced. However, Burrows et al. (1960) suggest that the effect may be less at higher oxygen tensions. Breathing air, the carbon monoxide concentration will fall to low levels during breath holding in alveoli with a rapid uptake. At higher oxygen tensions, the reduced uptake will maintain higher carbon monoxide levels in these alveoli throughout breath holding, so the transfer factor will be greater than

FIG. 4. Suggested mechanism by which a reduction in DM can be produced by uneven distribution in the lungs. If distribution effects are similar at all oxygen tensions, both DM and VC are reduced. However, if the effects are less at higher oxygen tension, as suggested by Burrows et al. (1960), only DM is affected.
expected. If this mechanism reduces the changes due to uneven distribution by approximately one third at high oxygen tensions, the effects of uneven distribution will be confined to the membrane component \((D_M)\) (Fig. 4).

In many patients with pulmonary sarcoidosis of relatively short duration (Hamer, 1963a), and in two patients with mild idiopathic pulmonary fibrosis reported here, the membrane component \((D_M)\) was found to be significantly impaired but the capillary volume \((V_c)\) was normal. These findings might at first sight be taken to indicate interference with diffusion across the alveolar-capillary membrane, either by sarcoid deposits or diffuse fibrosis, but they can also be explained on the basis of uneven distribution of ventilation and perfusion. Even in normal subjects, measurements of the membrane component \((D_M)\) probably overestimate the resistance to diffusion across the alveolar-capillary membrane as uneven distribution effects are included in the measurement. Experimental studies of the effect of anaemia on perfused dog lungs (Burrows and Niden, 1963) and of movement of gases of different molecular weights (Chinard, Enns, and Nolan, 1961) confirm that there is in fact little resistance to diffusion. Although thickening of the alveolar walls in pulmonary fibrosis must greatly increase the diffusion pathway (Meessen, 1961; Schulz, 1962), Staub (1963) has estimated that the resistance to diffusion must be more than five times the normal value to produce any detectable fall in arterial oxygen tension. Changes in the membrane component \((D_M)\) of this order were frequent in the present study but are probably in the main a reflection of ventilation-perfusion disturbances. It seems unlikely that thickening of the alveolar-capillary membrane is playing more than a minor part in producing the low arterial oxygen saturations in these patients.

The small capillary volume \((V_c)\) found in most patients with pulmonary fibrosis or longstanding sarcoidosis (Hamer, 1963b) may also in part be due to distribution disturbances. However, the changes in the membrane component \((D_M)\) are similar to those found in patients with a normal capillary volume (Table IV), suggesting that the effects of uneven distribution are not grossly different in the two groups. A fall in the membrane component might be expected to accompany a reduction in capillary volume as the area available for diffusion is diminished. The relative constancy of the membrane component in these patients, and in physiological changes in capillary volume (Cotes, Snidal, and Shepard, 1960), gives further support to the suggestion that the resistance to diffusion does not play an important part in determining the membrane component of gas transfer.

**SUMMARY**

The components of the pulmonary gas transfer \((D_L)\) were measured in seven patients with diffuse interstitial pulmonary fibrosis and in two with carcinomatous infiltration of the lungs.

The membrane component of gas transfer \((D_M)\) was considerably impaired in all cases. This is interpreted as evidence of disturbances of distribution in the lungs rather than of a diffusion defect.

The pulmonary capillary volume \((V_c)\) was also markedly diminished in most of these patients. However, cardiac catheterization confirmed that the changes were not sufficient to produce a serious reduction in the contact time between the blood and the alveolar gas.

The results are consistent with the suggestion that the fall in arterial oxygen saturation in diffuse pulmonary fibrosis is due to uneven distribution effects. The concept of ‘alveolar-capillary block’ should be discarded.

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Cause of Low Arterial Oxygen Saturation in Pulmonary Fibrosis

John Hamer

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