ing to the anode peak, which appeared to be the more active of the two, has been shown to contain either a mucoprotein or a mucopolysaccharide.

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THE DEFINITION AND ASSESSMENT OF RESPIRATORY FUNCTION*

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PART II

FACTORS AFFECTING THE TRANSFER OF
OXYGEN IN THE LUNGS

It has already been emphasized that the main function of the lungs is the transfer of adequate quantities of oxygen to the blood to maintain a normal oxygen tension and content in the blood flowing to the body, no matter what the degree of activity or how great the oxygen utilization of the tissues. The removal of excess carbon dioxide from the blood rarely presents any difficulty in disease, except in a few special circumstances. I will therefore confine my main discussion to the problem of oxygen transfer.

Distribution of Blood and Gas to the Alveoli

The alveolus is the unit of lung anatomy and lung function. All aspects of structure and function are subservient to the proper supply of each alveolus with blood and gas in correct quantities so that an adequate oxygen tension gradient and gas transfer between them is maintained. In a theoretically perfect lung the inspired air that passes the anatomical dead space would be equally divided among all alveoli. In other words, if there were, for argument's sake, one million alveoli, then each would receive one-millionth of the effective inspired air that enters the alveoli. Similarly in such a lung each alveolus would receive one-millionth of the cardiac output. Such a state of affairs would repre-

sent perfect blood and gas distribution and each of the million alveoli would have the same ratio of ventilation and perfusion as all the other alveoli and the total lung itself. The resultant gas and blood tensions in each alveolus would be similar to all other alveoli, and each will be a miniature lung in all respects.

It is easy to imagine various disturbances of blood and gas distribution that could occur. Certain alveoli could receive less than their "share" of ventilation and yet be perfused with their normal "quota" of mixed venous blood. The blood leaving such alveoli and joining the left heart outflow would be inadequately oxygenated.

Next there could be imperfect distribution of blood; this would result in alveoli which are adequately ventilated no longer receiving their quota of mixed venous blood from the right heart. Such blood-distribution defects would not cause any deficiency of blood oxygenation but would manifest themselves in the expired air, which would contain a larger-than-normal percentage of unchanged inspired air.

We shall see later how near normal and diseased lungs come to these entirely theoretical concepts of perfection and imperfection of blood and gas distribution.

Oxygen Transfer (Diffusion) in the Lungs

The diffusion characteristics of a membrane, in regard to a particular gas such as oxygen, can be described by the quantity of oxygen that passes across it in unit time when there is a unit pressure gradient of oxygen across the membrane. This quantity of gas, or the diffusion coefficient, will depend on a number of fairly obvious factors—surface area, thickness, and physical characteristics. If we wish to consider the diffusion characteristics and coefficient of the pulmonary membrane, we must remember that we are dealing with a very complicated structure. It will include all the tissues and fluids between alveolar gas and the haemoglobin molecule in the red blood cells in the pulmonary capillary. It is also possible that the effective area of this "membrane" may vary greatly in the normal lung during various degrees of activity. Marie Krogh (1915) attempted to measure the oxygen diffusion coefficient of the lungs in normal subjects by the use of carbon monoxide. This gas was used because it is taken up by haemoglobin with such avidity that its tension in the pulmonary capillary blood (amount in simple solution) was assumed to be zero at all times. The diffusion coefficient of oxygen was easily determined from these data, as the coefficient of each gas is a simple function of its solubility and molecular weight.

Since that time little definitive work has been done on this subject, but attempts have recently been made to measure the diffusion coefficient of oxygen more directly during normal respiration (Lilienthal *et al.*, 1946). This presents great difficulty even in the normal lung, where it can be reasonably assumed that the alveolar oxygen tension is fairly constant through all alveoli. If the alveolar oxygen tension is known, then the initial pressure gradient between this and the mixed venous blood entering the alveoli can be determined by cardiac catheterization. However, the determination of the final and mean gradient between the alveolus and capillary blood presents more difficulty. These difficulties are even greater in subjects with lung disease, in whom the alveolar oxygen tension may also vary greatly. The diffusion coefficient cannot be measured unless the mean alveolar capillary oxygen tension gradient is known.

Alveolar Gas Tensions. The Concept of Ideal Alveolar Gas Tensions

The determination of the actual gas tensions in the alveoli during normal respiration presents great difficulties. Without this information the analysis of blood and gas distribution and gas transfer would seem impossible. The Haldane (1915) technique of making a subject expire deeply and collecting the sample at the end of expiration has long been used for this purpose. There is no certainty that the gas obtained in this way is an accurate, statistically repre-

*Adapted from the lectures given in the "Science and Medicine" series, Postgraduate Federation (London University), 1950-1. Part I was published in last week's issue, p. 415.

sentative sample of the gases actually present in the alveoli. Further, this method of sampling interrupts the normal rhythm of respiration and alters the very values it is attempting to determine. Various devices for aspirating a small quantity of gas from the end of each normal expiration over a period have been used; this avoids upsetting the natural respiration and gives far more repeatable results in normal subjects (Rahn *et al.*, 1946). However, the underventilated alveoli will not be adequately represented in such a sample. Recently new concepts and methods have partially solved these difficulties. Fenn *et al.* (1946) pointed out that, in the steady state, the difference of pressure of oxygen and carbon dioxide in the alveoli and the inspired air was a measure of the quantities of these gases being absorbed and excreted by the lungs. Now these quantities of "gases are related, their ratio being the respiratory quotient, which is easily determined by the analysis of expired air collected over a period thus:

$$\text{Respiratory quotient} = \frac{\text{CO}_2 \text{ excreted}}{\text{O}_2 \text{ absorbed}} = \frac{\text{Pressure gradient of CO}_2 \text{ between alveoli and inspired air}}{\text{Pressure gradient of O}_2 \text{ between alveoli and inspired air}}$$

As the pressure of CO₂ in the inspired air is negligible the equation becomes:

$$\begin{aligned} \text{R.Q.} &= \frac{\text{Alveolar pCO}_2}{\text{Insp. pO}_2 - \text{alv. pO}_2} \\ \text{or Alv. pO}_2 &= \text{Insp. pO}_2 - \frac{\text{alv. pCO}_2}{\text{R.Q.}} \end{aligned}$$

It will be obvious that to define the alveolar gas in a single equation, in which the body R.Q. describing total gas exchange is employed, is to assume that all alveoli are equally ventilated and perfused and have the same R.Q. and gas tensions. It would seem that this equation gives little advantage, as the alveolar pCO₂ is now needed to determine the alveolar pO₂.

Riley *et al.* (1946) pointed out that the arterial pCO₂ could be regarded as accurately representing the alveolar tension of carbon dioxide (pCO₂), as, owing to the extremely high rate of diffusion of carbon dioxide in fluids, there must be almost absolute equilibrium of this gas between alveolar gas and blood leaving the alveoli. Again, this would be valid only if the distribution of the blood and gas were perfect. Yet Riley and Courmand (1949, 1951) pointed out that even if there is considerable underventilation of normally perfused alveoli (poor gas distribution) the arterial pCO₂ will differ but little from that which would obtain in a perfect lung with perfect blood and gas distribution. The reason for this superficially surprising fact is that there is only 4-5 mm. difference in the pCO₂ of normally ventilated and of unchanged mixed venous blood, owing to the enormous capacity of the blood for this gas. Thus in most patients with diseased lungs the increase of the arterial pCO₂ above what would be found in the same patient with ideal lungs and perfect gas and blood distribution is rarely significant. This is a most important observation and the key to many advances. It means that the "alveolar oxygen tension" as calculated from the inspired oxygen tension and the arterial pCO₂ and body R.Q. is, even in abnormal subjects, very close to what the alveolar tension would be if the lungs were "ideal" and had perfect distribution of blood and gas and all alveoli had similar gas tensions. It is therefore an easily obtained arbitrary measure of perfection, and the deviation of gas and blood coming from the lungs from this theoretical figure gives much information concerning any departure from complete homogeneity of the ventilation-perfusion relationships of the alveoli.

Venous Admixture Effect

The effect of underventilation of alveoli on the arterial oxygen tension is considerable, as the difference in oxygen tension between mixed venous blood and adequately venti-

lated blood is of the order of 60 mm. Hg. Riley and Courmand (1949) therefore attempted to assess the underventilation of alveoli in the following manner. They studied a normal subject in the steady state and determined the inspired air oxygen tension, the body R.Q., and the arterial pCO₂. From these data they could calculate by the above equation the only alveolar oxygen tension that was possible if all alveoli were homogeneously ventilated and perfused. They then calculated what the percentage oxygen saturation of arterial blood would be if it had all passed through homogeneous "ideal" alveoli. For good reasons, which will be discussed later, they assumed that there was virtual equilibrium of oxygen tension between alveolus and blood in normal subjects when breathing air.

They then compared this arterial percentage oxygen saturation with that actually found in the subject. Any passage of blood through underventilated alveoli or systems unrelated to air spaces would cause the arterial saturation to be lower than the calculated ideal figure. They then expressed the drop of percentage oxygen saturation from the ideal as a certain percentage of unaltered mixed venous blood being added to ideally ventilated blood. This figure, stated as *percentage venous admixture*, is a measure of perfusion of poorly ventilated alveoli or of direct venous addition (bronchial veins, thebesian veins, etc.) to the blood in the left heart. It is in fact an integration of all degrees of imperfection of ventilation of blood passing through the lungs into ideal ventilation and complete lack of ventilation. In normal subjects studied the arterial oxygen tension is only a few millimetres below the "ideal" figure and the percentage venous admixture is usually well below 5%, over 95% of the cardiac output being perfectly oxygenated. This emphasizes how remarkably near to perfection the distribution of blood and gas is in the normal lung. It is not yet known whether the "venous admixture" is due to anatomical venous admixture, to a slight degree of alveolar underventilation, or to a combination of the two.

Dead-space Effect

Just as poor gas distribution, or alveolar underventilation, is studied by its effect on the arterial blood, so inefficient blood distribution, or alveolar underperfusion, can be assessed by the analysis of expired air. It is now well established that in a normal person two-thirds or more of the tidal air passes the conducting air passages in which significant gas exchange does not occur and enters the alveoli. As all the gas leaving the alveoli has been in virtual carbon dioxide equilibrium with the blood leaving the alveoli, then this gas will have a similar carbon dioxide tension to the arterial blood. In an ideal lung, which the normal closely approaches, all alveoli will be equally ventilated and perfused and thus the expired gas will have a carbon dioxide tension which is at least two-thirds of the arterial carbon dioxide tension, as two-thirds will be from the alveoli and not more than one-third returned unchanged from the anatomical dead space. The small amount of air leaving poorly ventilated alveoli will, for reasons already given, have a pCO₂ very close to the arterial pCO₂ and have little effect on the expired pCO₂. However, if there is poor distribution of blood to alveoli and a number are well ventilated but not perfused with venous blood, then the gas leaving these alveoli will be unchanged inspired air. Similarly, if the blood perfusing ventilated alveoli is reduced then less oxygen will be extracted and less carbon dioxide will be added to the alveolar gas. This will result in the gas leaving the alveolus being nearer in composition to inspired air than that from normally ventilated and perfused alveoli.

Now, many studies in various lung diseases have shown no significant increase of the anatomical dead space. Thus if the pCO₂ of the expired air is less than two-thirds of the arterial pCO₂ then this is regarded as good evidence of the ventilation of unperfused and poorly perfused alveoli. The overventilation of normally perfused alveoli will also add to this so-called "dead-space effect." This is an extension of Bohr's concept of the physiological dead space, which

*Corrected for change in volume as in oxygen-consumption determination from analysis of expired air.

again integrates the various degrees of imperfection of distribution into absolute lack of alveolar perfusion and ideal ventilation and perfusion. The dead-space effect can be stated as a percentage of tidal air or of total ventilation. It is estimated as follows:

$$\text{Dead-space effect (as \% tidal air or total ventilation)} = \frac{\text{Arterial } p\text{CO}_2 - \text{Expired } p\text{CO}_2}{\text{Arterial } p\text{CO}_2} \times 100$$

Diffusion Gradients in the Alveolus

It will be remembered that so far in this discussion it has been assumed that when a normal subject breathes air the transfer of oxygen across the pulmonary membrane is so efficient that there is no appreciable oxygen tension gradient between the alveolar gas and the blood leaving the alveolus, and that the diffusion factor did not contribute in the normal subject to the slight depression of arterial oxygen tension below the theoretical ideal. Let us return to the question of whether it is reasonable to assume that this depression of the arterial oxygen tension is due only to so-called "venous admixture" or distribution disturbance.

Lilienthal *et al.* (1946) studied the alveolo-arterial oxygen tension gradient in normal subjects breathing low percentages of oxygen. Under these conditions the effect of alveolar under-ventilation becomes insignificant and the whole of the alveolo-arterial oxygen tension gradient can be safely assumed to be due to the final alveolo-capillary gradient in the alveoli (final diffusion gradient). This allowed the mean oxygen tension gradient between the alveolus and capillary to be calculated, and from this the diffusion gradient (O_2 uptake per minute mean diffusion gradient). By applying this diffusion coefficient to the data obtained while the subjects were breathing air, they showed that under these conditions the mixed venous blood reaches oxygen tension equilibrium with the alveolar gas when it is about halfway through the alveolar capillary. They were thus able to state that the slight alveolo-arterial oxygen tension gradient in normal subjects when breathing air was due to slight distribution disturbances—that is, venous admixture.

The application of this "two-level" technique to abnormal patients presented many great difficulties. A smaller degree of anoxia was advisable, and it could not be assumed that distribution or diffusion gradients were negligible at any particular level of oxygen breathing. These difficulties were overcome (Riley *et al.*, 1951), and the resultant studies (Donald *et al.*, 1952) have allowed the disturbances of blood and gas distribution and of alveolo-capillary oxygen diffusion, and their role in arterial desaturation, to be more precisely assessed in various lung diseases. The most important findings can be briefly outlined.

Two main groups of patients were studied by this technique. Those in the first group were suffering from pulmonary disease in which the pathological processes involved the alveolar walls and in which interference with the diffusion of oxygen across the pulmonary membrane was suspected (Baldwin *et al.*, 1949a). The second group consisted of patients with pulmonary emphysema in whom impairment of the efficient distribution of blood and gas to the alveoli was thought to be the main disability.

Pulmonary "Infiltration," or "Pneumonitis"

These patients complain of severe shortness of breath on very slight exertion. All show radiological evidence of widespread pulmonary infiltration. Although the physiological findings are remarkably constant, there is a very wide range of diagnoses. These include beryllium granuloma, asbestosis, scleroderma, Boeck's sarcoid, reticuloses, "interstitial pneumonitis," and various unclassified granulomata. In those patients coming to necropsy the occurrence of pathological tissue in the alveolar walls can be demonstrated. All the patients studied had no spirometric evidence of ventilatory obstruction, and the residual volumes were equal to or less than the predicted normal range. The normal or nearly normal ventilatory capacity (M.B.C.)

in all cases was further evidence that emphysema was not present. At rest the arterial blood saturation was normal or only very slightly depressed, whereas on very mild exercise marked arterial blood desaturation associated with considerable dyspnoea occurred, despite the unimpaired ventilatory capacity.

In some of these patients, studied at rest, the gas and blood distribution in the lungs was normal, as shown by the normal dead space (33%) and the normal venous admixture effect (6%). Yet the mean oxygen diffusion gradient (mean alveolo-capillary oxygen tension gradient) was about twice that found in normal subjects (normal, 20 mm. Hg), the diffusion coefficient being abnormally low (normal, 15 ml./mm./minute). Thus the interference with the transfer of oxygen across the alveolar membrane, despite the relatively efficient distribution of blood and gas to the alveoli, which had been previously suspected in these cases, was now definitely demonstrated. This interference with the oxygen diffusion necessitated an increased oxygen tension gradient between alveolus and capillary to maintain the transfer of even the resting oxygen requirements.

Let us contrast these patients with normal subjects. It has been pointed out already that, under resting conditions, the blood in the normal alveolar capillary reaches almost complete oxygen equilibrium with the alveolar gas in just over half the capillary length. Further, when a normal subject exercises there is probably a considerable increase in the diffusing capacity of the lung due to this expansion of the alveolar capillaries or the opening up of new capillaries. Even if this mechanism is greatly limited the "reserve" distal half of the lung capillaries will allow a large increase in capillary blood velocity, even with the same or increased mixed venous blood desaturation, without any risk of incomplete oxygenation of the blood leaving the alveolus.

In this group of patients a measurable oxygen tension gradient between the alveolar gas and the blood leaving the alveolus could be demonstrated when air was breathed in the resting state. Thus the normal reserve of lung capillary was no longer available. It is probable that the ability to expand the pulmonary capillary bed and increase the diffusing capacity was also much impaired. More important is the fact that any increase in the velocity of blood through the lung capillary will inevitably increase the final alveolo-capillary oxygen tension gradient, and thus the blood leaving the lungs and entering the systemic circulation will be considerably desaturated. In more simple terms these patients show marked cyanosis and distress on exercise because they have no reserve diffusing capacity.

In the more severely affected patients not only was the diffusion of oxygen even more impaired but the dead-space and venous admixture effects were greatly increased. It was considered, in the absence of emphysema, that this was probably due to such severe involvement of the alveolar membrane in certain portions of lung that no significant gas exchange was possible, and that gas and blood were returned unchanged from such areas.

Pulmonary Emphysema

The patients investigated all had clinical and radiological evidence of emphysema. Lung-volume studies showed the usual increase of residual volume and decrease of maximum breathing capacity. A number of these patients showed moderate arterial blood desaturation at rest and considerable desaturation on exercise. Raised arterial blood carbon dioxide tensions were found in some cases.

It has been demonstrated in many ways that the distribution of inspired air throughout the lungs is exceedingly uneven and inefficient in this disease. The uniform distribution of blood is probably also impaired in emphysema owing to the damage to the finer branches of the pulmonary vascular tree; but there is so far only indirect evidence of this, such as histological and injection studies, and haemodynamic studies of the pulmonary circulation during rest and exercise.

In this investigation considerable increase of the dead-space effect (ventilation of underperfused and unperfused alveoli) and of venous admixture effect (perfusion of under-ventilated or unventilated alveoli) was demonstrated. In some patients the dead-space effect was well over 60% of the tidal air, the upper limit of normal dead space due to the conducting passages being about 33% of the tidal air. Similarly, venous admixture effects of nearly 50% of the cardiac output were found. Such findings indicated gross upset of the normal distribution of blood and gas to the alveoli and of the efficient correlation of alveolar ventilation and circulation. It must be remembered that, as it is impossible to describe the almost infinite variations of ventilation-perfusion relationships, the present method integrates all departures from homogeneity into ideal ventilation-perfusion relationship and into the return of unchanged gas and blood from the lungs.

It was also found that an increase of dead-space effect was not always associated with a similar increase of the venous admixture effect, and vice versa. This is an important finding, as it means that emphysema may interfere predominantly with alveolar ventilation in certain cases and with alveolar circulation in others. It may also explain the remarkable variation in disability and prognosis in this disease.

A somewhat unexpected finding in a number of these patients was a greatly increased oxygen diffusion gradient (mean alveolo-capillary oxygen tension gradient) and a decreased diffusion coefficient. Histological studies in emphysema do not suggest any structural interference with the diffusion of oxygen across the alveolar membrane. However, it must be remembered that lung which is ventilated but not perfused, or perfused but not ventilated, is as functionless as lung that receives neither blood nor air. Thus these distribution disturbances will render large amounts of lung quite functionless, and the effective blood-gas interface where blood and gas meet and there is an adequate gas gradient between them will become less and less as these disturbances increase.

In confirmation of this, the most pronounced impairment of diffusing capacity was found in those patients with the largest combined venous admixture and dead-space effects. Just as the area of the pulmonary membrane and the diffusing capacity will become less and less in patients whose lungs are being progressively destroyed by infection or cystic disease, so increasing disturbances of alveolar ventilation and perfusion will also reduce the amount of effective lung and diffusing capacity.

The findings further suggested that deficient arterial blood oxygenation at rest in emphysema is mainly due to alveolar underventilation, whereas marked arterial desaturation on exercise, as in the previous group described, was due to the limited diffusing capacity of the lung.

Practical Considerations

The methods required in such studies need a large trained team and generous facilities. These studies are necessary for furthering our knowledge of lung function but are quite impracticable as routine investigations. However, without such experiments the value and significance of the more simple tests which can be used in clinical medicine will remain obscure.

Arterial Blood Studies

In routine clinical work the commonest cause of severe cyanosis is severe congestive cardiac failure due to rheumatic heart disease. These patients have greatly reduced cardiac outputs, and their cyanosis is caused by the inevitable extraction by the body tissues of an unusually large percentage of oxygen from the reduced amount of circulating blood. Yet they have normal or nearly normal arterial blood oxygenation. Again, many patients with congenital heart disease and arterial blood desaturation have considerable polycythaemia, and their cyanosis is further increased because of this.

In most patients with lung disease the cardiac output is normal and marked polycythaemia is not present. In such patients it is most difficult to assess the degree of arterial blood oxygenation by visual inspection, and they may be dangerously anoxaemic with only what seems to be very slight cyanosis. Although the difference between "peripheral" and "central" cyanosis has been long appreciated, the difficulty of assessing the latter, particularly if acute, and its sinister import if marked, is not so clearly understood. In all cases of respiratory disease, whether acute or chronic (apart from pneumonia responding rapidly to treatment), the determination of the arterial blood oxygenation is as essential and obvious an investigation as the determination of the blood urea in kidney disease.

With practice arterial puncture is a smooth, easy, and painless procedure. The brachial artery is almost always used in respiratory studies, as most patients are conditioned to assault in this region and are not disturbed. It is not justifiable to risk damaging the femoral artery in middle-aged and elderly patients, as the circulation is always more precarious in the leg than in the arm. Further, the patient can be exercised without disturbing the needle. The best needle for this type of work is the Riley modification of the Courmand indwelling arterial needle, although, if only a single sample is needed, any medium-sized needle can be used, providing the bevel is kept short. The arterial blood is collected into a heparinized syringe and sealed after a drop of mercury has been added to facilitate mixing. It is quite incomprehensible why a number of workers continue to transfer these beautifully sealed blood samples to another vessel under oil. It is not only messy but an unnecessary additional manipulation. Further, the carbon dioxide diffuses through the oil at a high rate and is lost to the atmosphere. There is therefore a variable loss of this gas and change in the pH of the blood. Even more serious is the fact that when the sample is left to stand sedimentation of red cells occurs. Most vigorous stirring under oil will not give homogeneous red cell distribution, and thus samples taken for analysis may vary considerably and contain a greater concentration of red cells than in the original sample (Donald and Wade, 1952). A sealed syringe can be placed on a conical roller and the blood will remain well mixed until the analysis.

The most accurate method of determining the oxygen and carbon dioxide content of blood is the Van Slyke and Neil manometric technique (Peters and Van Slyke, 1932). The Haldane blood-gas analysis method is also satisfactory for determining the oxygen content if the Courtice and Douglas (1947) modifications are used. It takes less time than the Van Slyke method. However, the reliability of all methods is checked against Van Slyke determinations, and if several of these instruments are used, and all concerned are trained in its use, then the more reliable and accurate method can be employed without undue loss of time. An important point is that the oxygen capacity of arterial blood varies in different states and exercise will cause it to rise considerably. The use of a resting capacity in exercise studies may cause considerable errors.

If more precise and fundamental work is being done then it is necessary to measure the arterial blood-gas tensions. This procedure, although not yet suitable for routine clinical studies, is essential in the study of blood oxygenation in lung diseases. A glance at the oxyhaemoglobin dissociation curve will show why tension studies are so necessary for more precise work. It will be seen that, provided the blood pH does not alter, a fall in blood oxygen tension from 100 to 62 mm. Hg involves a drop of haemoglobin saturation of only 97 to 90%. Thus disturbances in alveolar ventilation or oxygen transfer have to be quite gross before pronounced arterial blood desaturation is obtained.

The bubble equilibration method of Riley, Proëmmel, and Franke (1945), although not perfect and demanding great skill, is an essential weapon in modern respiratory research. Without it, as already emphasized, only the most severe disturbances in blood oxygenation can be demonstrated. It is unwise to attempt to develop this technique without first seeing it done by a worker who is trained in the method.

When arterial blood is being taken for gas-tension studies it is necessary to collect the expired air at the same time,

so that the expired-gas tension and respiratory quotient can be determined. This allows the ideal alveolar oxygen tension to be calculated and thus the gradient between this and the arterial oxygen tension. This is the most accurate and delicate method of expressing how far arterial blood oxygenation falls short of perfection.

Finally, let us consider the value of studying the oxygen and carbon dioxide content of arterial blood in various lung diseases.

Resting Studies

The arterial blood desaturation in emphysematous subjects at rest is never of the extreme order seen in many cases of congenital heart disease, unless there is extreme interference with alveolar ventilation due to acute bronchitis, severe asthma, or pneumonia. Figures below 85% saturation are unusual, but even this is roughly equivalent to 40% of the blood from the right heart passing through the lungs unchanged. This would again emphasize how relatively insensitive arterial blood saturation is as a measure of defective alveolar ventilation. It may also explain why marked polycythaemia is not often encountered in this disease. In fibrosis and pathological infiltrations of the lung there is rarely any significant arterial desaturation at rest.

Speaking in general terms, the arterial desaturation at rest is due to the venous admixture effect from under-ventilated alveoli and is not caused by any limitation of the diffusing capacity, which is adequate in the resting state even in patients with severe diffusion disturbances.

Patients may suffer severe anoxaemia after intrathoracic operations. This is due to acute and severe interference with alveolar ventilation caused by oedema, bronchial irritation and blockage, collapse, and effusions. Such patients are usually obviously cyanosed, and oxygen therapy is given until cyanosis is relieved. However, precise measurement of the arterial blood saturation in these patients can be of great help in the conduct of such cases. More studies of post-operative arterial oxygenation are needed to increase the knowledge of the hazards of various surgical procedures.

Again, arterial blood studies are most useful in the treatment of patients with chronic respiratory diseases who are suffering from acute pneumonic infections. The carbon dioxide content or tensions are particularly valuable in helping to assess the risk of carbon dioxide retention when oxygen therapy is given (Donald, 1949).

Finally, the only method of demonstrating deficient blood oxygenation at rest in early and moderate emphysema is that of measuring the alveolar-arterial oxygen tension gradient. This is greatly increased even in patients with what seems to be relatively normal arterial blood saturation (90-94%).

Exercise Studies

The fact that considerable alveolar underventilation or limitation of the oxygen diffusing capacity causes only very moderate depression of the arterial blood saturation at rest would appear to make this approach unfruitful if blood-tension studies are not available. However, it is fortunate that limited diffusing capacity can be demonstrated by increasing the oxygen demands of the body by brisk exercise. Any inability to increase oxygen transfer in the face of increased oxygen demands will cause dramatic arterial-blood desaturation. This inability to transfer increased quantities of oxygen to the blood is due to a decreased effective blood-gas interface or, more rarely, interference with oxygen diffusion into the alveolar capillary. Thus marked arterial desaturation on exercise may be due to faulty gas or blood distribution, rendering large amounts of lung relatively functionless (emphysema, bronchial obstruction), by disease destroying large amounts of lung tissue (extensive tuberculosis, cystic disease, etc.), or by pathological infiltration of the alveolar wall. The ability to maintain normal arterial oxygenation in the face of increased oxygen demands is therefore a remarkable test of overall respiratory effi-

ciency and actual amount of functioning lung. Arterial blood studies are carried out during various standard exercises (walking, step-test, treadmill), but this relatively simple method of assessing overall lung function is still in its infancy. As in this method study is made of the change or otherwise of arterial saturation, it is likely that oximetry may be of great help and render the test even more accessible to the practising physician.

Finally these various functions of the lungs can now be studied and to some extent assessed quantitatively. Nevertheless, although great progress has been made, mainly by academicians, the true value of these various concepts and methods of assessment of respiratory function will not be known until they are understood and used by practising chest surgeons and physicians, who can then reject, endorse, and advance in the light of real practical experience.

General Summary

The function of the lungs is defined. The importance of lung ventilation and circulation bringing blood and gas in close contact in all alveoli so that efficient gas exchange occurs is emphasized.

The various methods of assessing ventilatory function are discussed. The determination of the lung volumes and ventilatory capacity is described and the greater value of the more dynamic measurements emphasized. The relationship of the volumes ventilated to the ventilatory capacity present in the causation of ventilatory discomfort or dyspnoea is discussed.

The important features of the pulmonary circulation are detailed and the disturbances of this circulation in lung disease, and their effect upon the right ventricle, are described.

Finally, the problem of oxygen transfer and blood oxygenation is considered. It is emphasized that this depends upon the efficient distribution of gas and blood and the proper correlation of alveolar ventilation and circulation throughout the lungs. The diffusion of oxygen across the pulmonary membrane is considered. The theoretical concept of ideal distribution of blood and gas is elaborated and the application of this concept to the measuring of the efficiency of the lungs in this respect, both in health and in disease, is described. The diffusion gradients in the alveoli and the diffusing capacity of the lungs are also considered in both normal and abnormal subjects. The value and future of arterial blood studies in pulmonary disease is discussed.

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THROMBO-ANGIITIS OBLITERANS

CLINICAL DIAGNOSIS AND CLASSIFICATION OF CASES

BY

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"Thrombo-angiitis obliterans is a segmental, inflammatory obliterative disease of the arteries and veins which occurs almost exclusively in young men, involves the extremities, and rarely the viscera also, and produces ischaemia of tissues and frequently gangrene."—Allen, Barker, and Hines (1946).

In 1908 Buerger suggested the name thrombo-angiitis obliterans for a disease of the peripheral arteries which he had studied in eleven lower limbs amputated for "pre-senile spontaneous gangrene." He did not claim that he had described a new disease, but gave due credit to earlier writers, notably von Winiwarter (1879), who had described the condition under other names. Nevertheless it was largely due to Buerger's (1908, 1924) publications that the disease became a recognized clinical entity, and the name which he suggested, or its eponymous alternative "Buerger's disease," came to be generally used. Since 1908 the literature on thrombo-angiitis obliterans has become extensive; among the more important contributions are the American monograph by Brown and Allen (1928) and, in this country, the papers by Parkes Weber (1916), Telford and Stopford (1924, 1935), and Telford (1937).

As a result of the attention thus focused on the disease it has become customary to classify patients with symptoms of occlusive disease of the arteries of the limbs into two groups: (1) a group of young patients in whom the diagnosis is thrombo-angiitis obliterans, and (2) an older group in whom the arterial occlusion is thought to be secondary to atheroma (arteriosclerosis obliterans). Although the patient's age is regarded as an important factor in deciding his grouping, it is recognized that there are other fundamental differences between the two conditions (Table I). There is, however, no unanimity

TABLE I.—*Differential Diagnosis of Thrombo-angiitis Obliterans and Arteriosclerosis Obliterans*

Feature	Thrombo-angiitis Obliterans	Arteriosclerosis Obliterans
Age at onset of symptoms	Usually under 35 years; rare over 40 years	Usually over 50 years
Sex	Almost exclusively males	Preponderantly males, but not rare in females
Distribution	Upper limbs often involved	Upper limbs seldom involved
Venous involvement	Superficial phlebitis in about 40% of cases	Rare
Blood pressure	Normal	Frequently elevated
Association with diabetes	Rare	Frequent
Radiography	Vessels seldom calcified	Vessels often calcified
Biochemistry	No constant abnormality	Blood cholesterol and total fats often high
Pathology	Acute or subacute "inflammatory" lesions	Degenerative lesions with benign thrombosis

regarding the age which separates the two groups. Buerger (1924) described thrombo-angiitis obliterans as a disease which begins in the twenties or early thirties, and the average age at the onset of the disease in his cases was 32 years and 5 months. Brown and Allen (1928) stated that 90% of cases of thrombo-angiitis obliterans occurred between the ages of 20 and 50 years. The average age in Telford and Stopford's (1935) series of 48 cases was 45 years, and Telford (1937) said, "A diagnosis of thrombo-angiitis obliterans may be made with some confidence in patients up to 45 years or even 50." Lewis (1936) thought that the onset of thrombo-angiitis usually occurred in the thirties, Homans (1939) stated that the disease occurred in young men between the ages of 20 and 40 years, and Wright (1948) said that all patients have symptoms before 55 and most before 45. The opinion of Allen *et al.* (1946) was that "it is fairly safe to consider that if the symptoms of chronic occlusive arterial disease begin after the patient is 50 years of age the lesion is arteriosclerosis, and if they begin before the age of 40 years the lesion is thrombo-angiitis obliterans."

Current views regarding the differential diagnosis between the two groups may be summarized as follows: a diagnosis of thrombo-angiitis obliterans may be made with some certainty in the case of a male patient suffering from occlusive arterial disease who was under the age of 35 years at the time of his initial symptoms, gives a history of superficial phlebitis, and has involvement of the arteries of the upper limbs; if the patient is over 50 years, if the disease is confined to the lower limbs, if there is some degree of hypertension, and if radiographs of the affected limbs reveal calcification in the walls of the arteries, then arteriosclerosis may be diagnosed confidently. There are many patients with occlusive arterial disease in whom the clinical picture is not sufficiently clear-cut to permit of these definite diagnoses. These patients are in the age group between 35 and 45 years; although their blood pressure is normal and they do not have calcified vessels, they do not give a history of