12. Respiration

12.1 Introduction

The function of respiration is to ensure that the needs of the tissues for oxygen and for the removal of carbon dioxide - the metabolic demands of the body - are met. Thus it my be said that the lungs exist to ventilate the blood, and their structure is such as to enable blood and gas to come into such a relation with each other that O_2 is transferred from the gas mixture in the lungs to the blood that flows through them and CO_2 is transferred in the opposite direction. The pulmonary capillary bed may act as a filter preventing particles greater than a certain size from reaching the systemic circulation, airborne particles may be cleared by mucociliary action or coughing or phagocytosis and various metabolic operations may take place such as conversion of angiotensin I to angiotensin II and synthesis and removal of prostaglandins.

Gas transfer is only one of the fundamental respiratory processes. Gas is moved in and out of the lungs s a consequence of the action of the muscles of respiration - *pulmonary ventilation* - while at the same time the heart pumps blood through the lung capillaries - *perfusion.* If gas exchange is to be adequate and efficient, ventilation and perfusion, or rather the *ventilation/perfusion ratio,* must be reasonably uniform throughout the lungs. The concentration of O_2 and CO_2 is much higher than would be expected on purely physical grounds. *Carriage of O_2 and CO_2 in the blood* between the lungs and the tissues of the body depends in fact on chemical processes.

The basic respiratory processes may thus be listed in the following order:

(a) Lung mechanics.

(b) Pulmonary ventilation and gas transfer.

(c) Blood gas transport: (i) oxygen carriage.
(ii) carbon dioxide carriage.

(d) Regulation of respiration.

(e) Respiration under abnormal conditions.

Structure of the Lung

Gas exchange takes place cross the *alveolo-capillary membrane* which is on average 1 microm thick and which has a very large total surface area.

After some 23 'generations' bronchioli reach the alveoli. The trachea, and the larger and smaller bronchi (down to the eleventh generation) have, in common, cartilaginous rings and bands of smooth muscle in their walls and a columnar ciliated epithelium with many mucus-secreting cells. The twelfth to sixteenth divisions comprise the *bronchioles* in which cartilage is lacking, smooth muscle is predominant and the lining epithelium is cuboidal. The

remaining bifurcations (*respiratory bronchioles, alveolar ducts, alveolar sacs*) give rise to increasing numbers of alveoli and thus increasingly subserve gas exchange, until finally the alveolar sacs end blindly in alveoli.

The alveolo-capillary membrane may be further subdivided, in terms of the layers through which a gas molecule must pass, into a fluid lining layer, the alveolar epithelium, an interstitial space and the capillary endothelium. The alveolar epithelial cells are of two kinds, type I, comprising the great majority, and type II. Type I are thin flat cells. Type II are cuboidal and are believed to be the source of lung surfactant.

12.2 Lung Mechanics

Gas can only flow along a pressure gradient, developed in the case of the lungs between the alveoli and the airway opening. The amounts of gas which can be moved in and out of the lungs in unit time depend on the force which the muscles of respiration can exert and on the forces which have to be overcome. The latter in turn depend on the stiffness or otherwise of the lungs and chest wall and on the ease with which air can flow through the respiratory passages.

Contraction of the *diaphragm* has the double action of depressing the floor of the thorax and raising the ribcage at its point of origin, thus enlarging the thorax and causing an inspiration. Its motor nerve is *phrenic*, arising from the cervical roots 3 to 5 of the spinal cord. The action of the *intercostal muscles* is primarily to support the chest wall in the intercostal spaces. The contraction of the essentially vertical fibres of the external intercostals favours inspiration and contraction of the more horizontal fibres of the internal intercostals favours expiration. The contribution of these muscles is, however, pronounced only in postural activity, for example, during lateral bending of the trunk. Contraction of such muscles as the *MSCM* raises the ribcage in strenuous inspiration. Contraction of *abdominal muscles* can drive the diaphragm upwards to cause expiration. During quiet breathing, however, expiration is caused by passive *elastic recoil* of elements stretched during the previous inspiration. The duration of expiration is prolonged because of some inspiratory muscle action continuing during expiration. Such an expiratory 'brake' effect is also caused as a result of constriction of the glottis by the laryngeal muscles.

Lung Volumes

The normal subject at rest breathes in and out a volume of gas, the *tidal volume* (V_T), that is very much less than that which can be moved in and out of the lungs with maximal effort. That is to say, there are normally *inspiratory* and *expiratory reserve volumes (IRV, ERV)* of considerable size. The volume of gas that can be exhaled following a maximal inhalation is the *vital capacity (VC).* One cannot, however, expel by voluntary effort all the gas in the lungs. There remains, after a maximal exhalation, a *residual volume (RV)* which can only be got rid if the lungs are made to collapse completely as they do if the chest wall is opened widely. The volume of gas in the lungs following a maximal inspiration, the *total lung capacity (TLC),* is the sum of the VC and the RV. The volume of gas in the lungs at the resting position of the chest after a quiet expiration, is called the *functional residual capacity (FRC).* The *inspiratory capacity (IC)* is the difference between LC and FRC. More

information can be obtained by asking the subject to inspire to the maximum and then to expire as rapidly and completely as possible. This volume is termed the *forced vital capacity (FVC)* and the amount of gas which can be exhaled thus in 1 second, the *forced expired volume in 1 s (FEV_1)*, as a percentage of the FVC is a useful measure of lung function. In healthy subjects the ratio FEV_1/FVC is of the order of 80%.

Pressure-Volume Relationships

If the diaphragm is pulled down the lungs will expand to an extent that depends on their *distensibility*. If the diaphragm is held in the new position, the pressure inside the lungs will be atmospheric and the intrapleural pressure will be less than atmospheric. A transmural pressure gradient has developed across the lung wall.

The *compliance* is the change in volume/unit change in pressure of the system. Most of the 'stiffness' of the lungs *in vivo* is due to the presence of an air-liquid interface - the force of *surface tension.*

Pleural Space

Why is this tendency of the lungs to retract with the consequent generation of a pressure less than atmospheric, not counteracted by the accumulation of gas or liquid or both in the pleural cavity?

Absorption of liquid form the pleural cavity depends on the balance of osmotic and hydrostatic forces across the capillary walls and pleural membranes and on the relative vascularities of parietal and visceral pleurae. Hydrostatic pressure in the systemic capillaries is such that one might suppose filtration to exceed reabsorption through the parietal pleura in the face of a subatmospheric intrapleural pressure. In the pulmonary capillaries, however, the hydrostatic pressure is very low and is substantially exceeded by the plasma colloid osmotic pressure and in addition the visceral pleura is the more vascular. All in all, the balance is in favour of reabsorption of any fluid from the intrapleural space - so much so that total reabsorption is only prevented, and a thin lubricating layer of fluid left, by an increase in the tension and decrease in the permeability of the visceral pleura as the last moiety of fluid is tending to be reabsorbed.

The forces that determine the behaviour of the lungs and chest wall as a respiratory pump owe their existence primarily to the development of an air-liquid interface in the course of the first few breaths at birth, and to the shape of the O_2-dissociation curve, which is an expression of the peculiar relation between O_2 and Hb.

Lung Surfactant

In fact, the force of surface tension is much less than might be expected from the behaviour of a simple air-liquid surface film. If such a film in each tiny alveolus were to obey Laplace's law ($P=2T/r$, where P is the transmural pressure, T is the surface tension and r is the alveolar radius), we would expect (i) the lungs to be much stiffer than they actually are, (ii) that smaller alveoli would transfer their gas to larger, since it may be assumed that not

all alveoli are of exactly the same size, (iii) that on expiration, as alveoli anyhow become smaller, this tendency would be accelerated in the direction of total collapse of the lung, necessitating a corresponding inspiratory effort, and (iv) that fluid would tend to accumulate in the alveoli, because the additional force (20 cm water across the barrier) would now more than balance the excess of osmotic over hydrostatic pressure which would otherwise keep the lungs dry.

That all these things do not in fact normally happen is due to the presence of an alveolar lining layer of *lung surfactant*, a lipoid substance produced by the type II alveolar epithelial cells. This substance (i) reduces the absolute value of the surface tension to approximately 4 cm water, (ii) behaves anomalously in that its effect becomes greater as the lung surface is reduced in expiration - in other words as the surface energy is concentrated - and conversely on inspiration. Surfactant thus increases not only the compliance but also the stability of the lungs.

Maximal Respiratory Forces

If we breathe maximally in or out against a closed glottis (Muller's and Valsalva's manoeuvres, respectively), then much greater pressures, both positive and negative, are generated in the alveoli and the pleural cavity, but the transmural pressure remains unchanged at any lung volume. Large positive intrapleural pressures impede the venous return to the heart.

Air Flow

We have discussed the effort involved in overcoming purely elastic forces, but under dynamic as opposed to static conditions we must allow for the extra effort necessary to propel gas through tubes.

Flow can be laminar or turbulent or both at the same time in different parts of the respiratory tract. Indeed, the anatomy of the nasal bones is designed to promote turbulent flow. Turbulent flow is also likely to occur if volume per unit time is high, where the tubes are branched or angled, and especially if there is any undue increase in the thickness of the mucous layer in the tubes.

Airways resistance is critically dependent on the internal diameters of the bronchi and bronchioles. Both the tension in their smooth muscle walls and the thickness of the mucous membrane can be affected by circulating catecholamines or autonomic nerves. Sympathetic activity causes *bronchodilatation* which will naturally increase the anatomical dead space. Conversely, parasympathetic activity causes *bronchoconstriction* and decreases the anatomical dead space. The accompanying increase in airways resistance is of little consequence at rest. However, in conditions such as *asthma,* bronchoconstriction, often mediated by histamine acting on the smooth muscle, may cause very high airway resistance. Here the efficacy of inhaled or injected sympathomimetics, as well as antihistamines, may be life-saving.

In normal quiet breathing, however, air flows into the lungs in inspiration along a pressure gradient of approximately -2 cm water. During expiration, this gradient is reversed.

12.3 Pulmonary Ventilation and Gas Transfer

The respiratory process is determined in essence by the metabolic demands of the tissue mass of the body.

Composition of Respiratory Gas Mixture

On inspiration a volume of air from the surrounding atmosphere is taken into the respiratory tract. A portion of it remains in the upper part of the tract, where no gas exchange with the blood takes place (*dead space*), and part of it mixes with the gas that remains in the lungs at the end of the previous expiration. This gas mixture that obtains at any moment in the depths of the lung is called the *alveolar gas.* On expiration a volume of gas equal to that inspired leaves the respiratory tract. The *inspired gas* has a fixed composition from breath to breath. The *expired gas* has different composition if the pattern of breathing changes.

The ratio of CO_2 produced to O_2 consumed is called the *respiratory exchange ratio (R).* In the steady state it is common to use the term *respiratory quotient (RQ)* which depends purely on the chemical nature of the combusted foodstuffs. In theory if pure carbohydrate were being burnt, the value of R would be 1.0, while if pure fat were the fuel the value would be about 0.7. An R=0.82 is often assumed when it is not measured directly. In other words, the volume of O_2 that is taken up into the blood in the lungs is generally rather more than the amount of CO_2 that is excreted.

Conditions of Measurement

Gas in the lungs is at body temperature and pressure and is saturated with water vapour at that temperature (BTPS). Expired gas is measured, however, at room (or ambient) temperature which as a rule is lower than body temperature and so some of the water vapour condenses. The gas is now saturated at ambient temperature and pressure (ATPS). Since we commonly wish to know the volume which a mass of gas occupied when it was in the lung, the measured volume must be corrected appropriately.

On the other hand it is usually necessary to know the volumes of CO_2 produced and O_2 consumed as they would be under standard conditions, that is, dry and under a pressure of 760 mmHg at O °C (STPD) since only then can volumes and moles of gas be related.

Dead Space

Expired gas, collected as is usual in a large bag, has a uniform composition. However, a single expirate V_E, analysed rapidly and continuously as it is expired, has a changing composition. To begin with, there is no CO_2 in the expired gas. A little later the CO_2 fraction rises rapidly and, finally, reaches more or less a plateau. Expired gas is thus a mixture of inspired and alveolar gas and its composition depends on the proportion of the one to the other; that is, on the volume of gas which has occupied the non-exchanging part of the respiratory tract (dead space) relative to that which has come into equilibrium with the blood. *Anatomical dead space* has a value of roughly 150-200 mL and comprises about 0.25 to 0.35 of the tidal volume (V_T). Any increase in (V_D) indicating a dead space greater than that

determined by the structure of the respiratory tract implies in turn *wasted ventilation.* The fraction V_D/V_T may be calculated by the *Bohr equation,* as follows:

$$\mathbf{V_E * F_{ECO2} = V_D * F_{ICO2} + V_{ACO2}.}$$

If we assume that all the CO_2 has come from the alveolar fraction, then, since $V_A = V_E$ (i.e. V_T) - V_D,

$$\mathbf{V_D/V_T = (V_{ACO2} - F_{ECO2}) / V_{ACO2}.}$$

The *alveolar ventilation* (volume/unit time, V_A) is then equal to $f(V_T - V_D)$, where f is the respiratory frequency in breaths/unit time.

Gas Pressures

Gases diffuse down pressure gradients. If temperature is taken as 37 °C, water vapour pressure has a value of 47 mmHg, then pressures of the alveolar gases would be: O_2 100, CO_2 39 and N_2 574. Same pressures are in the end-pulmonary capillary blood. In the systemic arterial blood: O_2 94, CO_2 39 and N_2 574. In mixed venous blood: 40, 46 and 574.

Thus, it is usual to regard alveolar gas and end-pulmonary capillary blood as being in equilibrium. There is a small but distinct difference in the case of oxygen between alveolar gas and systemic arterial blood. This difference arises in part because some of the venous blood from the myocardium and that from the bronchial tree drains back into the systemic circulation and is not oxygenated in the lungs (a *physiological shunt,* normally 1-2% of the cardiac output), and in part because ventilation and perfusion are not in the same proportion throughout the lungs. The total gas pressure in mixed venous blood is a good deal less than that of the corresponding alveolar gases in arterial blood. This is crucial for the maintenance of a subatmospheric intrapleural pressure and therefore for the working of the respiratory pump.

Physiological Dead Space

We must now consider the concept of dead space. It is *end-tidal* rather than alveolar air that has been analysed. In healthy people, the two may be taken as identical, but this is not so in diseased lungs where there may be unequal rates of alveolar emptying or spaces in the lung which are ventilated but not in effect perfused. In the latter case there may be said to be an *alveolar dead space* lying in parallel, so to speak, with the alveolar gas proper. This is in addition to the anatomical dead space, the two together making up the *physiological dead space.* The latter may be calculated by transforming the Bohr equation into the form:

$$\mathbf{V_D = (P_{aCO2} - P_{ECO2}) * V_T / P_{aCO2}}$$

taking the advantage of the equilibrium between alveolar gas and arterial blood in the case of CO_2. The alveolar dead space is then calculated by subtracting an assumed value for the anatomical dead space.

Alveolar Ventilation

The pulmonary minute volume V_E is equal to f x V_T and an increase in V_E can obviously be brought about by an increase in f or in V_T or in both. But the alveolar ventilation V_A = f x (V_T - V_D) is equally obviously not affected by the breathing pattern and will depend on whether a given increase in V_E has been brought about mainly by an increase in V_T or in f. For example, if at rest f = 12, V_T = 600 mL, then V_E = 7.21 L/min. A 25% increase in V_E can be brought about by increasing f to 15 or V_T to 750 mL, but the increase in V_A is not the same in both cases and it is V_A that matters as far as $P_{A,CO2}$ and $P_{A,O2}$ are concerned. This becomes clear when we consider how these two gas pressures are calculated.

V_{CO2} = V_E x $F_{E,CO2}$. Since there is no CO_2 in inspired air, V_{CO2} = V_A x $F_{A,CO2\ t}$ then $F_{A,CO2}$ = V_{CO2} / V_A then $P_{A,CO2}$ = (V_{CO2} / V_A) x (P_B - P_{H2O}).

Thus for any steady rate of production of CO_2, $P_{A,CO2}$ is inversely proportional to V_A and is independent of P_B.

The case of O_2 is less simple because the gas is present in both inspired and expired air but one can see that for any given V_{O2}, $P_{A,O2}$ must approach $P_{I,O2}$ as V_A increases, that is,

$$\mathbf{P_{PI,O2} - P_{A,O2} = 0.863 \times (V_{O2}/V_A)}$$

but V_{O2} = V_{CO2}/R so $P_{A,O2}$ = $P_{PI,O2}$ - ($P_{A,CO2}$/R).

However, it must be remembered that V_A calculated from V_E is not the same as V_A calculated from V_I unless R=1. When the correction is made, one form of the so-called *alveolar air equation* is:

$$\mathbf{P_{A,O2} = P_{I,O2} - (P_{A,CO2}/R) + (F_{I,O2} \times (P_{A,CO2}/R) \times (1-R).}$$

The alveolar gas mixture is not just a random matter, but is determined by (i) $P_{I,O2}$, (ii) the value of R and (iii) the ratio V_{CO2}/V_A.

Ventilation and Perfusion

No matter what the alveolar ventilation may be or how much blood is sent by the right ventricle to the lungs, unless the two phases, blood and gas, come into effective contact, the arrangement is useless for the business of respiration. We need only think of the extreme example of a block in one main bronchus and a block in that branch of the pulmonary artery supplying the other lung. It is necessary that ventilation, V_A, and perfusion, Q, be reasonably matched in each exchanging unit throughout the lungs.

In normal man at rest a V_A of about 4.5 L/min is matched with a cardiac output of about 5 L/min giving a V_A/Q of approximately 0.9. However this ratio does vary substantially in different parts even of the normal lung when the subject is in the upright position. Indeed it is not to be expected that all the 300 x 10^6 exchanging units should behave in exactly the same way. Such variation in ratio as occurs even in normal people is sufficient to account for at least half of the admittedly rather small difference between P_{AO2} and P_{aO2}.

The reasons for the variations are as follows. The apex of the lung in the erect position is less well perfused than is the base of the base because of the low pressures that obtain in the pulmonary circulation. This fact, combined with the collapsible nature of the pulmonary vessels, means that at times pressures outside may be greater than those inside the apical vessels and perfusion may be at best intermittent.

Ventilation also falls off from the base to apex of the lung because, strictly speaking, the lung has weight and contrary to what is usually assumed for simplicity's sake, intrapleural pressure is more subatmospheric at the apex than at the base. Consequently the apex of the lung is working, so to say, on a 'stiffer' part of the compliance curve and so for a given expanding force the base fills more easily than does the apex. These discrepancies between base and apex are more marked in the case of perfusion than in that of ventilation so that the ration V_A/Q is appreciably higher at the apex than at the base.

Units that are well-perfused but ill-ventilated contribute to the systemic circulation blood that is not fully arterialized. Because the dissociation curve at oxygen pressures greater than approximately 100 mmHg is virtually flat blood from these units is not compensated for by blood from units where ventilation is more than adequate to arterialize the blood. Moreover, in absolute terms the contribution from the lung bases is greater than that from the apices. And so a spread of V_A/Q throughout the lung leads to a measurable difference. In many lung diseases such inequalities are greatly magnified.

The same argument of course holds in theory for CO_2, but because the CO_2-dissociation curve is, in the physiological range, virtually a straight line with a slope much steeper than that of the O_2-dissociation curve, and because also of the Haldane effect, hyperventilation can reduce $P_{a,CO2}$ to compensate or even more than compensate for any increase in blood P_{CO2} leaving units that are relatively poorly ventilated. Moreover, any tendency for $P_{a,CO2}$ to rise leads reflexly to an increase in ventilation.

There is some automatic compensation for the V_A/Q mismatching, in that in over-ventilated zones there will be a tendency for the blood vessels to dilate in response to the high P_{O2} and low P_{CO2}. The bronchioles will tend to constrict in the same circumstances. The reverse applies to hypoxic, hypercapnic zones. This compensation can only partially counter mismatching, but is of great consequence when the whole lung is hypoxic and hypercapnic: then the whole pulmonary vasculature will constrict!

Diffusion

The amount of a gas that will diffuse in unit time across a barrier such as that separating alveolar gas from blood (strictly, from the interior of the red blood cell) depends on the area and thickness of the barrier and on the pressure difference across it. By Fick's law, $V_X = A/T * D(P_1 - P_2)$ where A is the alveolar surface area and T is the thickness of the air-to-blood barrier. The diffusion constant D is for any gas proportional to the absorption coefficient alpha (mL gas/mL solution/760 mmHg gas pressure), the value of which depends on the temperature, and is inversely proportional to the M_r. At 37°C, with plasma as solvent, alpha has a value for O_2 of 0.023 and for CO_2 of 0.51. Thus the relative diffusibilities of CO_2 and O_2 are given by

alpha1/alpha2 * sq root (32/44) = 20.

The high diffusibility of CO_2 is balanced by the rather small pressure gradient between mixed venous blood and alveolar gas, if we bear in mind that similar amounts of O_2 and CO_2 have to be exchanged in the same time.

Because of difficulties in measurement it is usual to lump A/T and D together as the *diffusion capacity (D_L)* of the lung for, say, O_2. Thus

$$\mathbf{D_{L,O2} = V_{O2} / (P_{A,O2} - P_{c,O2})}$$

Since $P_{c,O2}$, the average O_2 pressure in the lung capillaries, cannot really be measured, the diffusion capacity for carbon monoxide is measured instead, because P_{cO2} can be taken as zero on account of the very high affinity between CO and haemoglobin. Thus, $\mathbf{D_{LCO} = V_{CO} / P_{ACO}}$**.** To obtain D_{LO2} we could multiply by 1.23 but in practice clinicians simply compare the measured with the predicted D_{LCO}. This account of diffusion and its calculation in clinical practice takes no account of the fact that part of the 'resistance' to the passage of O_2 (or CO) from gas to final combination with Hb lies in the rate of reaction itself which, though rapid, is not indefinitely so. What we measure as D_L has thus a chemical as well as a physical component.

12.4 Blood Gas Transport

The amount of O_2 or CO_2 taken up or excreted from the alveolar gas must equal that taken up from or added to the blood by the tissues in the same time. In other words, for O_2:

Vol O_2/min = Volins x Fins - Volex x Fex = Volblood (Ca- Cv)

In the normal adult male at rest volume of inspired O_2 is roughly 300 L/min. If O_2 were carried in the blood only in physical solution its solubility is such that concentration in arterial blood would be 100/760 x 0.023 x 10^3 = 3 mL/L, so that even if concentration in venous blood were zero, volume flow of blood would have to be impossibly high to provide necessary O_2 to the tissues. In fact the amount of O_2 normally carried in arterial blood is of the order of 200 mL/L, as a result of its combination with haemoglobin.

Oxygen Carriage

Because O_2 combines with the haemoglobin in the red blood cells, the amount of O_2 carried in any volume of blood is much greater than one would expect on physical grounds. The O_2 combines with the iron-porphyrin complex or haem part of the haemoglobin molecule to form oxyhaemoglobin. The association is easily reversible and is termed an *oxygenation.* It is not an oxidation. Oxidized haemoglobin is useless for the biological carriage of O_2. From the molecular weight of haemoglobin and the fraction of iron in it one would expect 1 g of Hb to combine at a maximum with 1.39 mL O_2. Actual measurement shows that 1.34 mL is a more realistic value. Haemoglobin combined with this amount of O_2 is said to be fully saturated with O_2 and thus the *O_2 capacity of blood* depends on its Hb concentration. The O_2 concentration in any blood sample will depend on the extent to which the Hb is saturated, i.e., on the *percentage saturation, S,* and will also include the small amount of O_2 that is

physically dissolved. Both depend in turn on the pressure of O_2 with which the blood has come into equilibrium. Thus

Percentage saturation (S) = (total O_2 - O_2 in solution)/O_2 capacity

The relation between O_2 bound to haemoglobin and pressure of O_2 is given by the *oxyhaemoglobin dissociation curve.* Such a curve is constructed by equilibrating a series of blood samples with gas mixtures over a range of oxygen partial pressures, the temperature, pH and P_{CO2} being the same for each. The bound O_2 (i.e., total O_2 concentration - O_2 in physical solution) per unit volume of blood, or the percentage saturation, is then plotted against O_2 pressures. If we take 150 g/L as a reasonably normal Hb concentration then the bound O_2 concentration at full (100%) saturation, i.e., the oxygen capacity, will be approximately 200 mL/L. Blood from an anaemic patient will be fully saturated at the same P_{O2} as is required to fully saturate normal blood, but the O_2 concentration will be correspondingly less.

The shape of the oxygen dissociation curve depends on a number of factors. The Hb molecule has four iron-binding haem groups and its combination with O_2 takes place in four stages. The stages are not, however, independent of each other. In particular the last of these reactions proceeds at a high velocity which counteracts the tendency of the whole process to slow down as the number of oxygen-binding sites on the Hb molecule diminishes and so oxygenation proceeds more or less uniformly until it is virtually complete.

The combination of O_2 and Hb depends, too, on the precise shape of the haemoglobin molecule. This is influenced by such factors as temperature, pH and P_{CO2}, so that the iron-containing haem groups with which the O_2 combines may become more or less accessible. This is the basis of the *Bohr effect*, the term applied to a shift of the dissociation curve following a change in any of the above factors. Thus a decrease in temperature or in P_{CO2} or an increase in pH will increase the affinity of Hb for O_2 and thus will shift the curve to the left. Such shifts are greater in the middle part of the curve than at either end. The shape of the Hb molecule and therefore the position of the dissociation curve is also greatly influenced by the concentration in the red cells of the substance 2,3-diphosphoglycerate (2,3-DPG), which is formed in the course of red cell metabolism as a deviation from what in other cells is the main glycolytic path. An increase in 2,3-DPG concentration decreases the affinity of Hb for O_2 and moves the curve to the right.

The rather peculiar shape of the dissociation curve has a number of important biological implications:

(i) Above O_2 pressure of 100 mmHg the curve is almost flat. At that O_2 pressure, which is more or less what we would expect to obtain in normal alveolar gas, the Hb is approximately 97% saturated and a further increase in P_{O2} will make little difference to the O_2 concentration in the blood. The last little moiety of Hb is very hard to saturate and requires a P_{O2} of approximately 300 mmHg. Beyond that the O_2 concentration in the blood will increase at a rate of approximately 3 mL/L per 100 mmHg P_{O2}, purely as a result in the physically dissolved O_2.

(ii) There is little tendency for the Hb to desaturate until P_{O2} has fallen to around 60 mmHg. In biological terms there is thus a considerable reserve, so that despite a fall in P_{AO2}, the saturation of Hb in arterial blood within limits remain high.

(iii) Below 60 mmHg desaturation is rapid so that O_2 is readily given off to the tissues with little further fall in P_{O2}. Thus when we compare with normally oxygenated blood, blood that has been exposed in the lungs to a P_{AO2} substantially lower than normal, the difference in P_{vO2} is surprisingly small.

It is useful to be able to describe the O_2 affinities for shifts in the dissociation curve and for different haemoglobins. This is done by finding the *P_{O2} at which the Hb is half-saturated (P_{50})*. Normal adult Hb has it at 25 mmHg. Haemoglobin with a greater O_2 affinity will have a dissociation curve with a lower P_{50} that lies to the left of the normal curve. Fetal Hb has a curve that lies to the left of that for maternal Hb, i.e., it has a greater affinity for O_2.

If we now consider the uptake of O_2 in the lungs and its transfer to the tissues we see that these processes are aided by the reciprocal movements of CO_2 as a result of the Bohr effect. The decanting of CO_2 from the mixed venous blood in the lungs assists the uptake of O_2 from the alveolar gas. Conversely, in the tissues, as CO_2 is loaded on to the blood, O_2 is more easily released from the Hb.

The P_{O2} within the individual cells of the tissue mass is hard to measure but is assumed to be very low - at the mitochondria, the actual point of utilization of the transferred O_2 molecules, perhaps 1 mmHg.

Haemoglobin can combine with gases other than O_2, for example CO_2. Very importantly it can combine with CO to form *carboxyhaemoglobin.* This combination, with the ferrous iron, is similar to that of Hb and O_2 except that the affinity of CO and Hb is very much greater, of the order of 250 times, than that of Hb and O_2. Thus a pressure of CO of only 0.1 mmHg will serve to half-saturate the Hb so that it takes only a small fraction of CO in the inspired air to reduce drastically the ability of the blood to carry O_2. Moreover, as far as the remaining Hb is concerned the oxyhaemoglobin dissociation curve is shifted to the left so that a subject suffering from CO poisoning is much worse off than an anaemic patient with a comparable reduction in the O_2 capacity of his blood.

Carbon Dioxide Carriage

There is a discrepancy between what we might expect to find on purely physical grounds and what we actually do find when blood is analysed.

In arterial blood we might expect in *physical solution $39/760 \times 0.5 \times 10^{-3}$* = 26 mL/L, and a little more in mixed venous blood, whereas we commonly do find something of the order of 500 mL/L.

(i) Physically dissolved CO_2 is a sizeable proportion of the total CO_2 in contrast with O_2.

(ii) There is no obvious upper limit to the amount of CO_2 that can be taken up and therefore there is no sense in talking of 'percentage saturation'.

(iii) If red cells and plasma are separated from each other, about one-third of the total CO_2 is found to be in the red cells and about two-thirds in plasma, whereas nearly all the O_2 is in the red cells in combination with Hb.

(iv) If a dissociation curve is constructed for plasma, which has been separated from its red cells, the curve is noticeably different from that for whole blood of that for plasma samples separated anaerobically from the red cells after equilibrium has been reached. It is much flatter on the right and does not come down to the origin of the graph on the left. Indeed there is a substantial proportion of the total CO_2 which can only be obtained from such equilibrated separated plasma following the addition of a strong acid. Thus, despite the fact that most of the CO_2 in whole blood is in fact in the plasma, the presence of the red cells during the equilibration process is clearly essential. Whole blood can, equally clearly, take up a given increment of CO_2 with a smaller rise in P_{CO2} than can plasma separated from the red cells.

(v) Just as in the case of the combination of O_2 and Hb the P_{CO2} had to be defined, so with CO_2 carriage P_{O2} and thus S has to be stated. Whole blood in which the Hb is completely desaturated can carry more CO_2 at a given P_{CO2} than can fully oxygenated Hb. This is known as the *Haldane effect.*

While blood, or plasma, is mildly alkaline, CO_2 reacts with water to form H_2CO_3, a weak acid. It then dissociates in H+ and HCO_3-. The hydration process is a slow one and without catalyst there would be insufficient time available for the necessary on- and off-loading if it must include such a process.

When CO_2 is added to whole blood we observe that:

1. Bicarbonate increases in both red cells and the plasma.

2. pH decreases in both the red cells and the plasma.

3. Cl- increases in the red cells and decreases in the plasma.

4. The water content of the red cells increases.

These observations can be explained if we note in detail what happens. At a molecular level, when CO_2 is added, the reaction $CO_2 + H_2O$ <==> $H+ + HCO_3$ takes place. In the plasma this is slow, but it does take place to some extent whereupon the H+ is buffered by the plasma proteins which have a net negative charge within the relevant pH range, thus

$$\mathbf{H^+ + HCO_3^- + Na^+ + Prot^{n-} <==> Na^+ + HCO_3^- + HProt^{(n-1)-}}$$

CO_2 also readily diffuses into the red cells in which K^+ is the predominant cation. These contain an enzyme, *carbonic anhydrase,* which catalyses the hydration process, which

thus takes place very much more quickly. The H^+ is now buffered largely by the globin moiety of the Hb; thus

$$\mathbf{O_2Hb^- + K^+ + H_2O + CO_2 <==> O_2 + HHb + HCO_3^- + K^+.}$$

The red cell membrane is very much more permeable to anions than to cations. The continuing formation of HCO_3^- establishes an electrochemical gradient down which bicarbonate moves from the red cells to plasma. Since the K+ cannot move in association, electrical balance can only be maintained if anions move in, and so Cl-, the only obvious candidate, moves from plasma to cells. This is known as the *chloride shift* or Hamburger phenomenon. However, although this serves to maintain electrical equilibrium, the total red cell osmolar content has been increased by the gain of chloride anions, really at the expense of polyvalent Hb-, and so water moves from plasma into the red cells to restor osmotic balance. The red cells thus increase in volume and the haematocrit increases.

Thus CO_2, or rather H_2CO_3, is buffered by the formation of a weak acid, HHB, so that the H+ load results in a much smaller change in pH than would otherwise be the case. Furthermore, HHb is a weaker acid than is $HHbO_2$ and so the concomitant loss of O_2 from combination with Hb aids the buffering of CO_2. Nevertheless venous blood is a little more acid (pH 7.37) than arterial blood (pH 7.4).

Because of its concentration in the red cells and their content of carbonic anhydrase, Hb is much the most important of the substances responsible for the minimal change in pH that occurs with the uptake of CO_2. Its importance is enhanced by the fact that it also combines directly with CO_2 to form a *carbamino-complex.*

This reaction is inherently rapid and does not depend on enzyme activity. It also takes place more readily with desaturated than oxygenated Hb. Although this direct combination with Hb comprises a smaller fraction of the total CO_2 in whole blood than was originally thought, it accounts for a substantial proportion of the Haldane effect when the CO_2 concentration of the blood flowing through the tissues is increased at the same time as the O_2 concentration is decreased (Table).

Table: Proportions in which CO_2 is transported in the blood

	% Arterial (a)	% Venous (v)	% (v-a)
Physically dissolved 5.5	5.8	8.0	
Bicarbonate	89.6	87.0	62.0
Carboxyhaemoglobin	4.9	7.2	30.0

So far, CO_2-carriage has been described in terms of its uptake from the tissues into the blood. In the lungs the various processes are reversed as the CO_2 is given off. The Haldane and Bohr effects taken together form a very beautiful example of biological organization. Both depend essentially on the spatial configuration of Hb molecule and the forces which hold it together.

The usual increment of CO_2 can be taken with a much smaller increase in P_{CO2} than would ensue were there no concomitant desaturation of the Hb. Nevertheless, it should not be thought that this partial desaturation of Hb is absolutely essential for CO_2-carriage. If we consider the circumstances, unusual but not unheard of, in which a patient may be exposed to very high pressures of pure O_2, for example in conjunction with radiotherapy, then it can easily be calculated that at a P_{O2} of about 3 atmospheres the usual resting demands for O_2 can be satisfied by the O_2 in physical solution. In this case CO_2-carriage has to take place without the assistance of desaturation of Hb. The price to be paid is a rise in P_{CO2}, as arterial becomes venous blood, of about three times the usual rise. The P_{CO2} matters because of its critical involvement in the acid-balance of the body.

Acid-Base Balance

From the law of mass action and the behaviour of buffer solutions, one can derive the expression

$$\mathbf{pH = pK' + \log(HCO_3^-/SxP_{CO2}).}$$

In this equation HCO_3^- is expressed in mmol/L and S in this case is a solubility factor converting P_{CO2} to mmol/L. It has a value of 0.03 at 37 °C.

This is known as Henderson-Hasselbalch equation. The equation makes it clear that pH depends on a ratio rather than on the absolute amount of any particular substance. If we bear in mind the relation of CO_2 to H_2CO_3, we see that the terms of the ratio comprise a 'buffer pair', quantitatively the most important mechanism for buffering of all acids stronger than H_2CO_3 and bases stronger than HCO_3^-.

It may seem strange from the point of view of the chemist that the most important buffer system in the body should have a pK' (6.1) so far removed from that pH at which it is desirable the body fluids be stabilized. The explanation lies in the fact that both bicarbonate and carbon dioxide are under physiological control by the kidneys and the lungs respectively, so that a primary change in the one is compensated for by a secondary change in the other in the appropriate direction.

It should be appreciated that the carriage and buffering of CO_2 in vivo is a good deal more complicated that the preceding account might suggest, and is by no means yet fully understood. For one thing the total amount of CO_2 in the body is very large, over 100 litres, much of which is dissolved in fat or stored in the bones. These tissues are relatively poorly perfused with blood and their CO_2 levels can only change slowly so that a new steady state is reached only after a considerable elapse of time. Secondly, buffering does occur, although again slowly, in cells other than red cells, whereas in the laboratory when dissociation curves are being constructed all the bicarbonate formed is obviously confined to red cells and

plasma. Finally, within the blood itself where time for equlibration is not unlimited, changes in bicarbonate, chloride, etc. are the results, really, of two equilibration processes taking place at very different rates, one in the red cells and one in the plasma.

12.5 Regulation of Respiration

Breathing occurs rhythmically. The rhythmicity is generated within areas of the brain-stem referred to as the *respiratory centres.* Respiration is reflexly regulated by specific *chemoreceptor* and *mechanoreceptor* inputs to the respiratory centres. This results in a level of V_E that is appropriate to the O_2 requirements of the moment and to the maintenance of arterial P_{O2}, P_{CO2} and acid-base homeostasis. Superimposed on this are short duration reflexes initiated by, for example, irritants as in coughing or sneezing. The effects of some stimuli, i.e. temperature, are mediated by *higher brain centres* which then influence the respiratory centres. Respiration is also under appreciable *voluntary control* from the cerebral cortex as in breath-holding, taking large breaths or speaking. The cortex can for a short time dominate respiratory centre reflexes but eventually the reflex control takes precedence.

Respiratory Centres

In the early 1920s Lumsden performed brain-stem transections and concluded that the respiratory centres were composed of a *pneumotaxic centre* in the upper pons, an *apneustic centre* in the lower pons and an expiratory centre and a gasping or inspiratory centre in the medulla oblongata. The latter two centres were postulated because after removal of the pontine influence breathing was dominated either by expiratory spasms or by a pattern of irregular gasping. More refined neurophysiological techniques have demonstrated since then that the medulla when separated from the pons does maintain a relatively normal rhythmic respiration. Rather than an inspiratory and expiratory centre, this medullary centre is composed of two bilateral aggregations of respiratory neurones known as the *dorsal respiratory group* and the *ventral respiratory group.* Breathing is abolished only by a transection between the medullary centres and the spinal cord.

The *dorsal respiratory group (DRG)* is close to the nucleus of the tractus solitarius from which it receives and integrates afferent information from respiratory mechano- and chemoreceptors. It is composed entirely of inspiratory cells which are upper motor neurones projecting via the ventrolateral column of the cord to the lower motor neurones of the contralateral phrenic nerve which innervates the diaphragm. Respiratory rhythmicity is thought to originate in the DRG. One suggestion is that the inspiratory cells have pacemaker properties and spontaneously discharge in a phasic manner.

The *ventral respiratory group (VRG)* is composed of both inspiratory and expiratory upper motor neurones. When the cells of the DRG are firing in inspiration, they excite VRG inspiratory cells and inhibit VRG expiratory cells. The VRG is located rostrally in the nucleus ambiguus and caudally in the nucleus retroambigualis. The rostral group innervates the ipsilateral accessory muscles of respiration and the caudal group projects via the ventrolateral column of the cord to the contralateral expiratory intercostal and abdominal lower motor neurones and ipsilaterally and contralaterally to the lower motor neurones of the inspiratory intercostal muscles.

The expiratory lower motor neurones in the spinal cord are inhibited during inspiration and vice versa. This prevents reflex contraction of antagonist muscles when agonist muscles actively contract. This *reciprocal inhibition* originates in the DRG and VRG and is not mediated via muscle-spindle reflexes as in other skeletal muscle systems. However, muscle spindles are present in intercostal muscles and modulate lower motor neurone discharge to the same muscle throughout contraction. Thus the strength of contraction can be adjusted to achieve a certain V_T whatever the airway resistance.

The activity of the DRG is modulated by the two centres in the pons. The *pneumotaxic centre (PNC)* is found in the nucleus parabrachialis and contains both inspiratory and expiratory cells. Its function is to finely tune the f/V_T pattern by influencing the switch-over from inspiration to expiration. Without the PNC breathing is slower and deeper because inspiration proceeds for longer. If removal of the PNC is combined with a bilateral vagotomy, breathing shows a pattern of prolonged inspirations interspersed with brief expirations. This is known as apneustic breathing and led to the postulation of the *apneustic centre (APC).* No specific neuronal population has been identified yet in the APC but it thought that it is the location of the inspiratory cut-off switch to which project both axons from the PNC and vagal afferents carrying information about lung volume.

Voluntary control of respiration from the cortex bypasses the respiratory centres and travels in the dorsolateral column of the cord directly to the lower motor neurones. There is also involuntary tonic control from higher centres influencing the respiratory centres. Inhibitory pathways from the cortex and hypothalamus and excitatory pathways from the diencephalon and hypothalamus have been demonstrated. The cortical and diencephalic pathways may also operate during responses to altitude and the hypothalamus is involved in the respiratory responses to pain, emotion, temperature and exercise.

Respiratory Chemoreceptors

The receptors for respiratory control are classified usually into chemoreceptors and non-chemical or mechanoreceptors. However, as some of the mechanoreceptors can also respond to certain chemical stimuli, the term chemoreceptor will be reserved for those monitoring directly or indirectly blood gas pressures. Chemoreceptors maintain homeostasis of arterial P_{O2}, P_{CO2} and pH and assist in ensuring that V_E is appropriate for the level of metabolism. They are stimulated by a rise in $P_{a,CO2}$ and arterial H^+ and a fall in $P_{a,O2}$ and reflexly cause an increase in V_E. Since V_E is more sensitive to increases in $P_{a,CO2}$ and arterial H^+ than to decreases in $P_{a,O2}$, the controlling link between V_E and the metabolism is the CO_2 produced rather than the O_2 consumed. The precision of chemical control is such that in healthy individuals the alveolar and arterial P_{CO2} remain remarkably constant over a wide range of metabolic rates. On the other hand, if the $F_{I,CO2}$ is raised or the $F_{I,O2}$ is lowered the reflex increase in V_E is such that the initial increase in $P_{a,CO2}$ (hypercapnia) and arterial H^+ or decrease in $P_{a,O2}$ (hypoxia) is minimized and a new steady-state is maintained.

The steady-state responses in hypercapnia show that the V_E is linearly related to $P_{a,CO2}$. However at lower $P_{a,CO2}$ values V_E is relatively intensive to $P_{a,CO2}$ and at higher $P_{a,CO2}$ values sensitivity is reduced due to CO_2 narcosis of the brain and respiratory centres. By comparison V_E is inversely related to $P_{a,O2}$ with a curve that steepens progressively as the hypoxia becomes more severe. At $P_{a,O2}$ values below 30 mmHg the hypoxia severely depresses the

brain and decreases $V_{E.}$ Note that, since an increase in V_E per se will lower $P_{a,CO2}$ and elevate $P_{a,O2}$, the $F_{I,CO2}$ and $F_{I,O2}$ have to be manipulated experimentally to maintain a normal $P_{a,CO2}$ of 40 mmHg during the hypoxic tests and a normal $P_{a,O2}$ of 100 mmHg during the hypercapnic tests. When the $P_{a,O2}$ is held constant at say 50 mmHg, the V_E response line to not only shifts upwards but also steepens. This increased V_E sensitivity is referred to as a multiplicative or potentiating interaction between hypoxia and hypercapnia and apparently is only well developed in man. This interaction can also be demonstrated by holding $P_{a,CO2}$ at say 50 mmHg whilst the sensitivity to $P_{a,O2}$ is tested.

There are two groups of chemoreceptors. The first group, the arterial or *peripheral chemoreceptors,* are located in the *carotid* and *aortic bodies* and are stimulated by arterial hypoxia, hypercapnia and acidity. After removal of the peripheral receptors, all V_E responses to acute hypoxia, approximately 20% of the V_E response to hypercapnia and nearly all the V_E response acute metabolic acidosis are lost.

The *carotid bodies* are small nodules of tissue found bilaterally at the bifurcation of the internal and external carotid arteries. The vast capillary network of each carotid body is supplied by a branch from the external carotid artery and the venous blood drains into the jugular vein. The blood flow of 20 mL/min is so great that the V_{O2} of the carotid body causes only a tiny arterial-venous O_2 difference. Thus capillary gas tensions are very close to arterial values and the carotid bodies are said therefore to monitor arterial P_{O2}, P_{CO2} and pH. The change in the arterial stimulus reaches equilibrium in the carotid body within seconds because of the massive blood flow. Changes in the blood flow to the carotid body alter its apparent sensitivity to arterial gases. For instance, a reduction in blood flow, caused by local sympathetic vasoconstriction or by a large drop in blood pressure, increases the P_{CO2} and decreases the P_{O2} in the capillaries and stimulates the carotid body without any change in arterial gas tensions. There may also be a parasympathetic vasodilatory control of blood flow.

The capillaries of the carotid body are surrounded by *glomus cells* and sensory nerve endings of cranial nerve IX (*glossopharyngeal nerve*). The latter are believed to be the chemosensitive structures because the neuroma that eventually forms on the stump of the IX nerve after the carotid body is removed shows some chemosensitivity. The glomus cells are high in dopamine and are thought to be inhibitory interneurones modulating the responses of the sensory nerve endings.

The *aortic bodies* are scattered over the aortic arch and the main arteries of that area and are anatomically very similar to the carotid bodies. The sensory nerve is cranial nerve X (*vagus nerve*). Their reflex effect on respiration is weak or non-existent during hypoxia, hypercapnia or acid conditions. However, as they appear to have a low blood flow and to be very sensitive to changes in blood flow, they may have important reflex effects on V_E during anaemia, carbon monoxide poisoning and hypotension.

The second group of chemoreceptors comprises the intracranial or *central chemoreceptors* located superficially at a depth of about 500 microm in discrete areas on the *ventrolateral surface* of the *medulla oblongata*. Within these areas no precise structure has yet been identified anatomically but it is presumed that nerve endings here monitor the brain interstitial fluid (ISF). The central chemoreceptors are stimulated by arterial hypercapnia and

are responsible for about 80% of the V_E response to hypercapnia but are only slightly stimulated by acute increases in arterial acidity and are insensitive to hypoxia. The presence of a blood-brain barrier, which greatly restricts movements of ions (but not of O_2 and CO_2), affects the extent to which arterial H^+ can influence the brain ISF. Since H^+ and bicarbonates do not readily cross this barrier, most of the arterial H^+ changes in acute metabolic acidosis and alkalosis are not reflected in the brain ISF. During chronic metabolic acidosis or alkalosis, there is a slow leak of bicarbonates down its concentration gradient between blood and ISF but equilibrium is never reached.

An increase in blood P_{CO2}, on the other hand, immediately increases P_{CO2} in the brain ISF although, since the relative blood flow to the brain is about forty times less than that to the peripheral chemoreceptors, it takes 5-10 min to reach equilibrium. This ISF CO_2 is then hydrated to carbonic acid which dissociates to bicarbonate and hydrogen ion and it is believed that hydrogen ion rather than P_{CO2} is the actual stimulus to the central chemoreceptors.

The pH of brain ISF is influenced mainly by the composition of the arterial blood but also by the rate of cerebral blood flow and the metabolism of the brain cells. It is also influenced to some extent by the slowly flowing cerebrospinal fluid (CSF) on the surface of the medulla. Since the location of the central chemoreceptors was first identified by applying acidic CSF to the brain surface, it has been implied that the receptors monitor CSF pH. However, CSF pH is dependent on ISF pH, on blood P_{CO2} and on the proximity of the CSF to a blood vessels, and it can only be a modified reflection of the ISF pH at the site of the receptor.

An increased ISF P_{CO2} during hypercapnia will also cause an increase in brain cell P_{CO2} leading to a very rapid hydration of CO_2 (catalysed by cellular carbonic anhydrase) and H^+ and bicarbonate formation. The hydrogen ion is buffered by cellular proteins but over some hours bicarbonate leaks out of the cells into the ISF. This will slowly reduce the acidity of brain ISF pH and under *chronic hypercapnia* the long-term compensation is to restore brain ISF pH towards normal. This process is also aided by the fact that hypercapnia causes brain cells to reduce their basal anaerobic metabolism and hence to release less lactic acid into the brain ISF. In chronic hypercapnia restoration of brain ISF pH obviously minimizes the acute V_E response.

In *chronic metabolic acidosis* the initial acute stimulation of the carotid bodies will have led to an increase in V_E and a lovered $P_{a,CO2}$. This will decrease brain ISF H^+ and decrease stimulation of the central chemoreceptors. Bicarbonate will move slowly from ISF to brain cell and to a small extent to plasma whilst the hypocapnia will increase lactic acid production from the brain cells. All this will restore brain ISF pH towards normal. The converse happens in *chronic metabolic alkalosis.*

Acute hypoxia in the absence of the carotid bodies can lead to a delayed increase in V_E if the reduced O_2 level does not depress the CNS too much. It does so by increasing brain cell lactic acid production and making ISF pH acidic. Normally acute hypoxia will stimulate the carotid bodies and hence increase V_E leading to hypocapnia and an alkaline ISF pH. Acclimatization to *chronic hypoxia* involves restoration of ISF pH by pathways described for chronic metabolic acidosis and aided by both hypocapnia and hypoxia stimulating brain cell lactic acid production. This leads to a progressive increase in V_E.

Respiratory Mechanoreceptors

Mechanoreceptors having reflex effects on respiration are found in the nose, epipharynx, larynx and trachea of the upper airways, and in the lower airways and alveoli there are *lung stretch receptors, lung irritant receptors* and *juxtacapillary* or *J receptors.* All of these mechanoreceptors provide protective reflexes affecting both V_E and bronchomotor tone but some are involved also in determining the f/V_T pattern of breathing. *Limb proprioception* appear to cause some of the V_E increase occurring in exercise.

Nerve endings of the olfactory and trigeminal nerves in the nasal mucosa are excited by chemical and mechanical irritants and reflexly cause a *sneeze* and broncho-laryngeal constriction. A sneeze is a number of superimposed inspirations followed by a strong and rapid expiration and then a short pause in expiratory position.

Glossopharyngeal nerve endings in the epithelium of the epipharynx are excited by chemical and mechanical irritants such as a blockage and this results in the *sniff* or aspiration reflex and bronchodilatation. The sniff is a large slow inspiration followed by rapid and powerful expirations. Mild stimulation of these receptors causes slow, deep breathing.

Lung stretch receptors (LSR) are vagal nerve endings in the smooth muscle of the trachea and lower airways that are stimulated by the increase in airway pressure accompanying lung inflation. The nervous discharge shows little adaptation and is proportional to the degree of inflation. A sustained inflation followed by occlusion of the airways reflexly causes cessation of further inspiratory efforts before the next inspiration is attempted. The duration of the pause is proportional to the degree of inflation. This response is called the *Hering-Breuer reflex* and demonstrates that the LSR shorten the inspiratory duration, restrict the depth of V_T and lengthen the expiratory duration by inhibiting via the APC the inspiratory cells of the DRG. LSR stimulation also cause bronchodilatation. These reflex effects also occur during normal breathing as the LSR nervous discharge increases and decreases in phase with inspiration and expiration. In the resting V_T range of man but not of other animals the LSR reflex is weak but at higher V_T of exercise or of breathing driven by hypoxia or hypercapnia, the LSR reflex in man becomes apparent. The inhibitory effects of LSR on V_T may be reduced in hypercapnia because increased airway P_{CO2} has been shown to depress LSR activity.

Lung irritant receptors (LIR) are vagal nerve endings in the epithelia of the trachea and lower airways that are stimulated by mechanical or chemical irritants. The reflex initiated is an increase in f and V_T together with broncho-laryngeal constriction. Histamine released in *asthma* probably stimulater the LIR. These receptors can also be stimulated by large deflations and large inflations but the response rapidly adapts. The significance of this sensitivity to volume is not clear but it may be part of the known role of LIR in triggering the augmented breaths or *sighs* that punctuate normal breathing. Evidence suggests that the resting discharge of LIR shortens the expiratory duration and that this is stronger that the lengthening effect of the LSR. Thus a vagotomy removing both LSR and LIR inputs causes an increase in V_T and a lengthening of both inspiratory and expiratory duration resulting in a decrease in f.

J receptor are vagal nerve endings thought to be in the interstitium between alveolar epithelium and capillary endothelium. They are stimulated by an increase in interstitial fluid pressure such as occurs in pulmonary congestion and oedema and by large inflations but the response rapidly adapts. The reflex initiated is broncho-laryngeal constriction and apnea followed by rapid, shallow breathing. It is not known what role, if any, the J receptors play in the regulation of normal respiration.

12.6 Respiration Under Abnormal Conditions

Individuals with partial pressure of O_2 lower than the usual 100 mmHg (give or take 10 mmHg) are said to be *hypoxic* and they will also show *arterial hypoxaemia* even if there is complete equilibration between blood and gas. The term *hypoxia* can be a source of some confusion inasmuch as it is also used to denote an insufficient supply of molecular O_2 to the tissues, irrespectively of the cause.

A patient who is hypoxic will exhibit signs and symptoms which are a mixture of:

(a) The direct effects of a poor O_2 supply to the tissues.

(b) The attempts of the body to compensate for this.

(c) Possibly, primary and secondary effects of the pathological process which are unrelated to the hypoxia.

Hypoxia in its purest form has long been studied on individuals acutely and chronically exposed to low O_2 pressure at altitude.

Decrease in Barometric Pressure

Height (f)	Height (m)	Pressure	PIO_2	PAO_2
8500	2591	550	103	80
14000	4267	450	84	59
21000	6401	350	63	38
28000	8534	250	42	17

Acute Hypoxia

1. *Respiratory function:* There is hyperventilation and respiratory alkalosis. Hypoxia directly depresses the respiratory centres but stimulates ventilation via the peripheral chemoreceptors. In so far as this increases ventilation, CO_2 will be blown off in excess of its rate of production. Thus the subject will become *hypocapnic* and pH will rise. This in turn will inhibit ventilation. The net effect at moderate altitude at rest is commonly an approximate doubling of ventilation, but individual responses vary.

2. *Cardiovascular function:* There is tachycardia and an increase in cardiac output, while arterial blood pressure usually remains about normal or is even decreased.

3. *Cerebral function:* This is acutely sensitive to the severity and to the speed of onset of hypoxia. Severe and sudden hypoxia will result in rapid loss of consciousness. Moderate hypoxia of relatively gradual onset may cause only such changes as lack of judgment and psychomotor disturbance.

4. *The blood itself:* The degree of deoxygenation of the blood in the small vessels affects skin and mucosal colour. In moderate hypoxia the darkening of the blood may be detectable as a change in colour, termed *cyanosis.*

These manifestations, combined with dizziness, headache, vomiting, nausea, dyspnoea (difficulty in breathing), incoordination, and so on, constitute the picture of *acute mountain sickness.*

Acclimatization

Acclimatization means the sum of those processes by which the body tries to compensate for the conditions which would otherwise result in a substantial degree of impairment of O_2 supply to the cells. It is what the patient is trying to achieve while burdened with pathology often of long standing. It can be studied 'pure' in those who live for long periods at high altitude.

1. Hyperventilation continues, indeed tends to increase for the next 5-10 days after acute exposure, despite the systemic alkalosis, and it is no longer abolished by breathing O_2. Cyanosis may be absent at rest but recur on exercise.

2. Cardiac output and heart rate tend to come back to normal at rest, but the maximum work-load is decreased.

3. The kidneys excrete bicarbonates with eventual correction of the systemic alkalosis. This takes 2-3 weeks.

4. Changes develop in the pulmonary vascular bed. Increased muscularity of arterioles and hypoxic vasoconstriction lead to pulmonary hypertension and right ventricular hypertrophy.

5. Over 4-6 weeks there develops an increase in blood volume and bone marrow hyperplasia with increased RBC count (haematocrit 0.60 or more; Hb 200 g/L or more). The increased blood viscosity further increases cardiac work.

6. An increase in 2,3-DPG production shifts the O_2 dissociation curve to the right so that O_2 is given up to the tissues a little more easily than would otherwise be the case.

7. There are increases in capillarity and other changes at tissue level, but these are much less well understood.

Over days, weeks and months most people acclimatize and remain so while at altitude, provided the height is not too great. No human communities live permanently above about 18000 ft. Above that there is a slow deterioration in all aspects of performance.

Some individuals, apparently acclimatized, gradually or even suddenly fail in their responses. Their ventilation falls, with dyspnoea and cyanosis. There may be clubbing of the fingers. Haematocrit and pulmonary arterial blood pressure increase still further, leading to right heart failure. This is the picture of *chronic mountain sickness.* In sudden failure, acute pulmonary oedema may be dominant. In either case the only course of action is to remove the subject to a lower altitude.

As we might expect many of the above features may occur in patients who have been hypoxic for a long time.

Increased Ambient Pressure

A dive may be:

(i) Short enough to be accomplished on such air as can be inhaled at the surface - 'single-breath' diving. This is, basically, breath-holding with the additional complicating factor of submersion. Suppose one takes a deep breath and goes down to 10 m. The partial alveolar pressures of O_2 and CO_2 will approximately double. Not quite, because both gases will pass along their gradients into the blood. After brief period (20-30 s) the combined effect of rising partial pressure of CO_2 and falling of partial pressure of O_2 and decreasing lung volume is sufficient to force the diver to the surface. The danger lies in the temptation to hyperventilate before submerging in an attempt to prolong the dive. The initial hypocapnia may permit a much longer stay at depth by which time partial pressure of O_2 has reached a low level. On ascent this is very rapidly lowered to levels at which unconsciousness is likely to supervene.

(ii) Carried out at little depths by maintaining connection with the atmosphere through a tube - 'snorkel' diving. Here the problem is essentially one of lung mechanics. The subject is breathing to and from the atmosphere. Alveolar pressure is therefore, on average, atmospheric pressure. The pressure on the chest wall is greater than atmospheric by an amount that depends on the depth. This must be counteracted by the action of the respiratory muscles if the chest is not to collapse. The maximum subatmospheric intrapleural pressure that can be generated is, however, of the order of 100 mmHg (about 1.2 m). When we consider that maximum muscular effort can in general be expected only for short periods, and when we further take into account the increased dead space and some increase in resistance to air-flow provided by the tube, we see that the 'snorkel' diver is, over any appreciable period of time, confined to a depth of about half a metre under the surface.

(iii) Sufficiently long to demand a maintained supply of air, in which cases the latter must be supplied at ambient pressure - 'conventional' and 'free (or scuba)' diving. Where the diver is required to function at depth for relatively long periods, he must be provided with a respirable gas mixture at ambient pressure. Technical difficulties apart, the problem is now one of the effects of breathing N_2 and O_2 at pressures greater than atmospheric, and is thus similar to breathing in compression chamber.

Nitrogen breathed at a pressure greater than about 4 atm (about 30 m below the surface) results in narcosis. The effects is very similar to that of N_2O at atmospheric pressure. This difficulty cannot be circumvented by substituting O_2 because it also is toxic under pressure. The breathing of pure O_2 even at atmospheric pressure for long periods (days) leads to pathological changes in lung structure, while O_2 at pressure greater than about 3 atm for much shorter periods affects predominantly the CNS to cause convulsions.

Exposure to N_2 pressures on the safe side of those causing narcosis puts he diver at risk not at depth but as he ascends. Nitrogen dissolves physically in the body fluids and especially in the fatty tissues in proportion to the pressure. If this is decreased too quickly, the nitrogen comes out of solution with the formation of tiny bubbles causing *decompression sickness.* If these bubbles form emboli in the cerebral, myocardial or pulmonary circulation, or in the substance of the CNS, severe effects may follow such as coughing and dyspnoea ('the chokes'), paralysis, and where bubbles have formed in the joints severe pain ('bends'). Treatment is by recompression in a pressure chamber followed by slower decompression.