5-1-1964

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Hubner, Douglas C., "Diffusion and transport of oxygen at varying atmospheric pressures" (1964). *MD Theses*. 22.
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Diffusion and Transport of Oxygen at
Varying Atmospheric Pressures

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1964

Omaha, Nebraska

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Varying Atmospheric Pressures

Man requires oxygen for proper cellular function and survival maintenance. Increased activity leads to an oxygen debt that can be accumulated but ultimately must be repaid. Muscular activity does occur utilizing anerobic sugar glycolysis with production and accumulation of lactic acid. However, eventually lactic acid must also be oxidized. Therefore, ultimately, oxygen is required for all tissue metabolism. The oxygen available is influenced by the supply and demand of oxygen as well as varying diffusion rates of oxygen. Generally speaking, the oxygen carried by the blood in a bound form is released from hemoglobin, goes into physical solution according to physical laws, diffuses into tissues, and only then becomes available for use by the cells.

Physical Laws. Dalton's law of partial pressure states that each gas in a mixture of gases behaves as if it alone occupied the total volume and exerts a pressure (partial pressure) independently of other gases present. Therefore, total pressure equals the sum of the partial pressures of individual gases.

Lung air contains water vapor in addition to the other gases present. This vapor also exerts a pressure which is independent of the other gases. To calculate the partial pressures of nitrogen, oxygen, and carbon dioxide, it is necessary to subtract the partial pressure of water vapor from the total pressure.[15] Then, according to Henry's law of solubility of gases, the quantity of

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gas physically dissolved in a liquid at constant temperature is directly proportional to the partial pressure of the gas in the gas phase in contact with the liquid. At normal atmospheric pressures, oxygen entering blood from the lungs is carried by hemoglobin mainly. A small amount exists in physical solution in plasma in accordance with Henry's Law:

$$\text{oxygen dissolved} = a \ pO_2$$

where $\underline{a}$ is a constant varying with temperature which for oxygen at 37° C at 760 mm. Hg partial pressure per cc. H_2O is 0.024 cc.[43]

Under normal atmospheric conditions, 100 cc. of blood will carry 19 cc. of combined oxygen with hemoglobin and 0.3 cc. of dissolved oxygen. The pO_2 of arterial blood is approximately 100 mm. Hg at ambient pressures.[43] The amounts of oxygen and carbon dioxide in combination with hemoglobin in circulating blood are much greater than the amounts of these gases that are physically dissolved. The chemical combination with hemoglobin permits efficient exchange without affecting the partial pressure of the physically dissolved gas.

Respiratory Gas Exchange. Oxygen, nitrogen, and water are the components of atmospheric air most important to human respiration. Rare gases (argon, krypton) have not been shown to be biologically significant, and in gas analysis they are included with the values reported for nitrogen. Atmospheric air has remarkably uniform composition with respect to oxygen, nitrogen, and carbon

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dioxide.

The composition of expired air varies, with the depth and frequency of breathing movements. The respiratory mechanisms are controlled so that alveolar air is maintained with minimal compositional changes despite changes in oxygen demand.

The amount of oxygen absorbed is normally larger than carbon dioxide released because oxygen is used to oxidize the carbon and the hydrogen of ingested food; consequently, oxygen is eliminated in expired air as both carbon dioxide and water.[15] The ratio of the amount of carbon dioxide expired to the amount of oxygen absorbed is called the respiratory quotient (R.Q.).

Gas	Atmospheric Air (mm. Hg)	Humidified Air (mm. Hg)	Alveolar Air (mm. Hg)	Expired Air (mm. Hg)
N_2	597.0(78.62%)	563.5(74.19%)	569.0(74.9%)	566.0(74.5%)
O_2	159.0(20.84%)	149.35(19.67%)	104.0(13.6%)	120.0(15.7%)
CO_2	0.15(0.04%)	0.15(0.04%)	40.0(5.3%)	27.0(3.6%)
H_2O	3.85(0.5%)	47.0(6.2%)	47.0(6.2%)	47.0(6.2%)
	760.0	760.0	760.0	760.0

Figure 1.[28] Composition of Atmospheric, Humidified, Alveolar and Expired Air in Man (at Rest and at Sea Level) in mm. Hg and volumes per cent.

Expired air is warmed to the body temperature and saturated with water vapor. During breathing considerable body heat is lost when inspired air is warmed and is saturated with water vapor.

This exchange is one subsidiary means of body temperature regulation accounting for 10 per cent of body heat exchange.

Carlson[15] states that measurements of the pO_2 in air, in alveoli, in the arterial blood and in the tissues demonstrate that the pO_2 decreases as the cells are approached. Oxygen flows down a pressure gradient and at no place in the respiratory system is it necessary to assume active transport against a partial pressure gradient to explain oxygen exchange. Carbon dioxide, like oxygen, also diffuses down a pressure gradient. Accordingly, the pO_2 and the pCO_2 in alveoli, in blood and in tissues determine the quantities of these gases held in physical solution at these sites. These pressures influence the rapidity of transfer across limiting membranes and the extent of completion of important reversible chemical reactions. According to Carlson[15], gas exchange rates across the alveolar surface are governed by several factors: (1) partial pressures of the respiratory gases in the alveoli and in the capillary blood perfusing them; (2) the limiting membrane permeability to oxygen and carbon dioxide -- diffusing capacity of pulmonary capillary membrane; (3) the reaction rate of gases with blood constituents; (4) the absorbing surface area; (5) the contact time of the blood with the breathing surface and, (6) the segment of blood volume exposed to alveolar air.

The respiratory gas exchange across capillary and alveolar endothelium takes place very rapidly. Venous blood enters the al-

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Hg causing oxygen to diffuse rapidly into pulmonary capillary blood.
The average pressure gradient for the diffusion of oxygen through
the pulmonary capillary during normal respiration is, however, a-
bout 11 mm. Hg. According to Guyton[28], this is a "time-integrated"
average, not the average of 64 mm. Hg gradient from the beginning
to end of the capillary. This is because the initial pressure gra-
dient lasts for only a short fraction of the transit time in the
pulmonary capillary, while the low pressure gradient lasts for a
longer time period.

Diffusion of any substance is a function of its solubility,
its molecular weight and the permeability of the membrane. For ex-
ample, carbon dioxide is so highly soluble in the body fluids that
it diffuses through the tissue 25 times more rapidly than oxygen.
This accounts for the exchange of carbon dioxide in the lungs at
a much smaller pressure gradient than that of oxygen.

With exercise, ventilation increases to meet the demands for
increased oxygen. More oxygen is, therefore, taken into the lungs
and more is carried away by arterial blood. According to Carlson[15]
two factors are largely responsible for bringing about increased
removal of oxygen from the lungs. First, increased cardiac output
results in more pulmonary blood flow, allowing a sevenfold increase
in oxygen absorbed. Second, venous blood contains less oxygen
since it loses more to the tissues. Therefore, the pulmonary pres-
sure gradient increases.

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The alveolar air is in gaseous equilibrium with arterial blood and varies in partial pressure of oxygen and carbon dioxide depending on the ventilation of the air sacs.

The manner in which new air reaches the alveolar surface is probably related to the increase in volume and the drop in pressure in the involved areas. The currents set up by the incoming air and the process of gaseous diffusion serve to mix the air in the alveolar sacs and rapidly bring this gas to a uniform composition. More poorly ventilated alveoli approach gaseous equilibrium with the blood adjacent to these alveoli.

According to Carlson[15], at the end of expiration, the air in the anatomic dead space is expelled last from the alveoli. During the interval before inspiration, oxygen continues to diffuse to blood and carbon dioxide to alveoli at rates determined by the blood flow and gas partial pressure. On inspiration, gas in the dead air space enters the alveoli and inspired air enters the lung, diluting the gas already present by mixing with it. Carlson states[15] that the surface area of the alveoli is such that diffusion is not a limiting factor.

Raine and Bishop[42] feel that the measurement of the alveolar to arterial difference in oxygen tension and of the physiological dead air space provides a sensitive indication of a disturbance of ventilation -- perfusion relationships of the lungs. For example, in advance age, lung volumes decrease because of a decrease in

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lung compliance. This is associated with a less even ventilatory distribution and a diminished diffusion capacity of the lung. In a study of compensated and decompensated chronic pulmonary heart disease associated with emphysema of the lungs, Daum et al.[19] found that arterial oxygen saturation was only slightly reduced in compensated pulmonary heart disease despite a marked reduction of oxygen tension. Arterial carbon dioxide content and tension were usually elevated.

Circulatory Gas Transport. Fortunately blood can absorb more carbon dioxide and oxygen than the amount normally carried in physical solution. Hemoglobin (HHb), representing the nonionized hemoglobin and acting as an acid, combines reversibly with both oxygen and carbon dioxide. The affinity of hemoglobin for oxygen allows a circulatory blood volume of one seventy fifth that required if there were no hemoglobin.[15] The pO_2 in blood favors the combination of hemoglobin with oxygen to form oxyhemoglobin. At a partial pressure of 100 mm. Hg in the lungs, the reaction is 97 per cent complete while in the tissues, 60 per cent of the oxygen in the blood is released at a pressure greater than 20 mm. Hg.

With 15 grams of hemoglobin per 100 ml. blood and with 1.36 ml. of oxygen per gram of hemoglobin, approximately 20 ml. of oxygen is transported in 100 ml. of blood.[15] Hemoglobin is not completely saturated until pO_2 reaches 150 mm. Hg. Since pO_2 in alveoli approaches 104 mm. Hg, arterial blood leaving the lungs is

only 98 per cent saturated.

The amount of oxygen in blood is not directly proportional to the partial pressures. A plot of the oxygen content against the partial pressures of oxygen takes a distinct S-shaped curve. The equation, $O_2 + HHb \rightleftharpoons HHbO_2$, shifts to the right or left as the pO_2 increases or decreases with corresponding increased saturation of HHb with oxygen and increased dissociation of $HHbO_2$ respectively. This S-shaped curve then indicates the relative amounts of oxyhemoglobin and reduced hemoglobin present at different levels of oxygen tension. The curve is flat above 80 mm. Hg and steep between 20 to 60 mm. Hg. This insures constant composition of arterial blood despite variations in alveolar oxygen pressure as well as delivery of a large amount of blood oxygen to the tissues with reasonable head of pressure. A shift to the right of the oxygen-dissociation curve with subsequent release of oxygen from hemoglobin occurs when carbon dioxide pressure is increased, when the acidity of blood is increased, or with an increase in body temperature. The effect of carbon dioxide is particularly important physiologically, since production of carbon dioxide by tissues will favor the transfer of oxygen to the tissues.[15]

PER CENT SATURATION

GASEOUS PRESSURE OF OXYGEN (mm. Hg)

Oxygenated blood leaving the lungs

Reduced blood returning from tissues
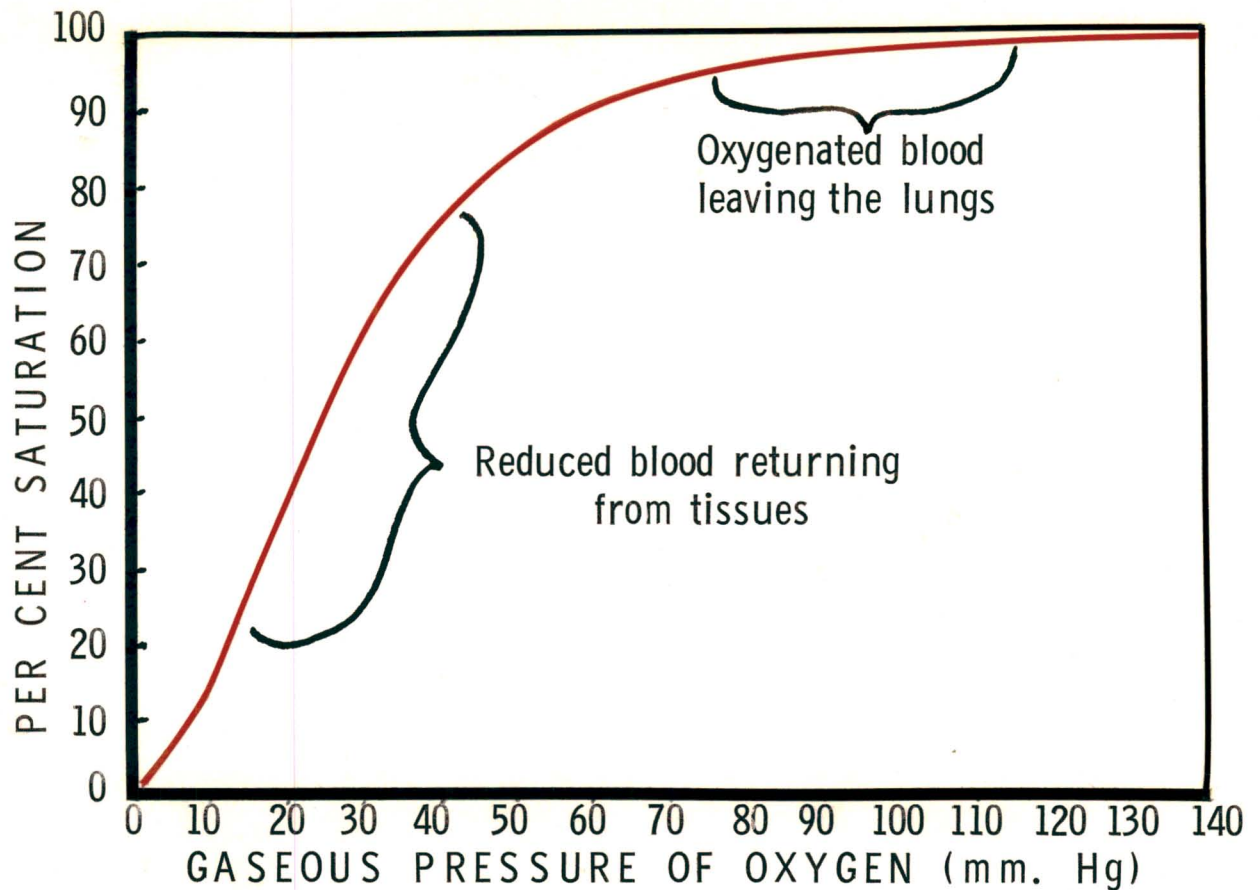
Figure 2. Oxygen–Hemoglobin Dissociation Curve. The oxygen-hemoglobin dissociation curve shows the progressive increase in quantity of oxygen that is bound with hemoglobin as the pressure of oxygen increases. This S-shaped curve, then, indicates the relative amounts of oxyhemoglobin and reduced hemoglobin present at different levels of oxygen tension.

Physiologic mechanisms constantly buffer cellular reactions as a defense against alteration in acid-base balance. Oxygen and carbon dioxide are transported and exchanged in blood with minimal pH changes, the blood becoming only slightly more acid as it passes through tissue.

Respiration acts as the first line of defense against acid-base changes. Rapid adjustment occurs with any variation to preserve the optimal acid-base condition of the body.

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In 1961 Eyzaguirre[23] demonstrated that chemoreceptor mech-
anisms responded in vivo in mammals to decreased oxygen tension
of the plasma rather than to reduced hemoglobin as originally
thought. The carotid body chemoreceptors are capable of respond-
ing to oxygen lack in the total absence of hemoglobin since they
are sensitive to the reduction of plasma oxygen tension.

According to Carlson[15], the action of carbon dioxide in re-
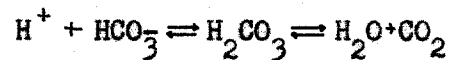leasing oxygen from the blood is twofold. Carbon dioxide increases
the acidity of blood and forms carbamino compounds ($HHbCO_2$) with
the hemoglobin. $HHbCO_2$ has much less affinity for oxygen than
does HHb. This results in a lowering of oxygen that the blood
will hold at a given oxygen pressure and makes oxygen more avail-
able to the tissues.

Like oxygen, carbon dioxide is primarily carried in chemical
combination. Those combined forms known include carbonic acid
(H_2CO_3) and bicarbonate ion (HCO_3^-), present in both cells and
plasma, and carbamino hemoglobin ($HHbCO_3$). These are all in
chemical equilibrium with one another. A dissociation curve
exists for carbon dioxide as well as oxygen and is influenced by
pO_2 in that absorption of oxygen aids in the unloading of carbon
dioxide in the lungs. The absorption of carbon dioxide in turn
then aids in the unloading of oxygen in the tissues.

Reversible chemical reactions take place in the lungs as
oxygen enters blood:

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$$O_2 + HHb \rightleftharpoons HHbO_2 \rightleftharpoons HbO_2 + H^+$$
$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$
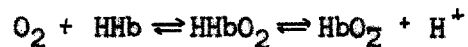
Thirty per cent of the total carbon dioxide in blood is carried as $HHbCO_2$ combining directly with amino groups of the HHb molecules,

$$HHbNH_2 + CO_2 \rightleftharpoons HHbNHCOOH$$
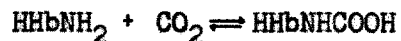
The product formed by the combination of carbon dioxide with hemoglobin is physiologically more important than carbamino compounds because it enters into a reversible reaction with oxygen without marked pH changes,

$$O_2 + HHbCO_2 \rightleftharpoons HHbO_2 + CO_2$$
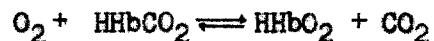
This complex series of chemical reactions occurs in the blood. The oxygen and carbon dioxide transfer is apparently completed while blood is passing through the pulmonary capillaries (0.7 sec.). All reactions are rapid enough to accomplish this and except hydration of carbon dioxide ($H_2O + CO_3 \xrightarrow{slow} H_2CO_3$). This reaction is speeded by carbonic anhydrase, an enzyme, within red cells.

Tissue Gas Exchange. As oxygenated blood reaches the tissues, a reversal of these chemical reactions takes place. Carbon dioxide, which is continually produced in the tissue cells, exist there at the highest partial pressures. Schema summarizing the more important chemical reactions by which tissue oxygenation occur is shown in Figure 3.

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CO$_2$PARTIAL PRESSURE 50 MM.Hg   O$_2$PARTIAL PRESSURE 30 MM.Hg
                        OR MORE   OR LESS
CO$_2$←[TISSUE CELL]→   →[TISSUE CELL]← O$_2$

—————————————— CAPILLARY WALL ——————————————

CO$_2$+H$_2$O (slow) H$_2$CO$_3$ ⇌ HCO$_3^-$+H$^+$
                                    H$^+$+Pr$^-$ HPr   O$_2$

H$_2$O   Na$^+$ (CHLORIDE)
                     SHIFT
                     Cl$^-$
          K$^+$
H$_2$O   Cl$^-$

CO$_2$+H$_2$O (fast) H$_2$CO$_3$ ⇌   HCO$_3^-$+H$^+$
        CARBONIC   H$^+$+HbO$_2^-$ ⇌ HHb+O$_2$
        ANHYDRASE
       →CO$_2$+HbO$_2^-$ ————————→ HbCO$_2^-$+O$_2$ → →
                                          (CARBAMINO-HEMOGLOBIN)

                    RED CORPUSCLE
CO$_2$PARTIAL PRESSURE   PLASMA   O$_2$PARTIAL PRESSURE
    40   46 MM.Hg   100   40 MM.Hg

Figure 3. Forces controlling gas exchange are gradients in par-
tial pressure of carbon dioxide and oxygen between capillary
blood and tissue cells.

Tissues absorb the oxygen necessary for metabolic function
and leave the rest. The amount absorbed per unit time is repre-
sented by the blood flow through the tissue and the tissue oxygen
pressure.

The oxygen in the arterial blood entering the peripheral
capillaries is high and the oxygen in the cells is low. A pres-
sure gradient of about 55 mm. Hg exists which results in oxygen
diffusion into the interstitial fluid. Therefore, again, the
transportation of oxygen and carbon dioxide depend upon both the
process of diffusion and perfusion.

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In peripheral tissues the reverse of the same diffusion process occurs as that in the lungs. Interstitial fluid oxygen pressure is about 40 mm. Hg while arterial blood is 95 mm. Hg, representing a pressure gradient of 55 mm. Hg for oxygen diffusion. However, capillary oxygen pressure rapidly approaches the pressure of tissue fluids and consequently, the venous oxygen pressure has essentially equilibrated with tissue oxygen pressure. Tissue pO_2 depends on two factors: (1) the rate of oxygen transport to the tissues, and (2) the rate in which oxygen is utilized by the peripheral tissues.[28] Increased blood flow to a particular area increases the oxygen transported to that area. This results in increasing the potential oxygen availability.

The arteriovenous difference in oxygen concentration divided by the arterial blood oxygen concentration is known as the coefficient of oxygen utilization. According to Carlson[15], brain tissue has a coefficient of 34 per cent while that of muscle is near 100 per cent. The rate of flow of blood is a very important factor in determining not only the way in which oxygen tension falls along the capillary but the level to which it will have fallen by the time the venous end is reached. Usually an arterial oxygen tension of 100 mm. Hg will be associated with a venous oxygen tension of 40 mm. Hg, but if this flow is slowed, it may be considerably less.

When tissue oxygen need increases, additional oxygen is sup-

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plied by increased flow of blood through the tissues, since oxygen content cannot be increased. The pressure gradient between capillaries and the active cells increases because of (1) increase blood flow and (2) increase cellular oxygen utilization. The coefficient of oxygen utilization, then, increases since venous blood contains less oxygen than normal.

Increasing tissue metabolism reduces the interstitial fluid pO_2 by increasing the oxygen consumption.[28] The pO_2 of the intracellular fluid (35 mm. Hg) remains lower than interstitial fluid because cellular oxygen is constantly being utilized. Since 97 per cent of transported oxygen is carried by hemoglobin, reduction in hemoglobin concentration has the same effect on interstitial fluid pO_2 as does a decreased blood flow.

The intracellular pCO_2 is about 46 mm. Hg while that in the interstitial fluids approaches 45 mm. Hg. This is a pressure differential of only 1 mm. Hg. Intracellular carbon dioxide tends to increase but because carbon dioxide affinity for diffusion is 20 times more than oxygen, diffusion of carbon dioxide from the cells to interstitial fluid occurs rapidly and easily.

Arterial blood arrives at peripheral tissues with carbon dioxide pressure approaching 40 mm. Hg. Rapid diffusion of carbon dioxide from the interstitial fluid (pCO_2 of 45 mm. Hg) results in earlier equilibration of arterial pCO_2 (45 mm. Hg) than that of oxygen because of the greater diffusion coefficient of carbon

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dioxide than oxygen.

As mentioned earlier about 97 per cent of the oxygen trans-
ported from the pulmonary system is carried in chemical combina-
tion with hemoglobin while the remaining 3 per cent is transported
in the dissolved state in plasma.

Since the total oxygen combined with hemoglobin in arterial
blood (pO_2 of 95 mm. Hg) approaches 19.4 ml., and since this is
reduced to 14.4 ml. (pO_2 of 40 mm. Hg) after perfusion of peri-
pheral tissues, there is a total oxygen loss of approximately 5 ml.
oxygen from each 100 ml. of blood.

If the normal cardiac output is considered to be approximately
5000 ml. per minute and the oxygen released to tissues to be 5 ml.
volume per cent, then the calculated total oxygen entering tissues
should be 250 ml. per minute.

On the effect of the hematocrit on oxygen transport to tis-
sues, Guyton states that an increase in the blood hematocrit much
above the normal level of 40 reduces the cardiac output because of
increased blood viscosity.[28] The reduction in cardiac output is
more than the oxygen-carrying capacity increase and the oxygen
transport rate is reduced. Therefore, the maximum oxygen trans-
port occurs at a hematocrit of 40 with reduction in carrying
capacity above or below this level.

Although, as stated earlier, the normal alveolar partial pres-
sure of oxygen is 104 mm. Hg at sea levels, this pressure is al-

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tered by changes in elevation with respect to sea level (i.e. high on a mountain or below the sea). According to the oxygen-hemoglobin dissociation curve, when the pO_2 is decreased to as low as 60 mm. Hg, the hemoglobin is still 89 per cent saturated. When above this level, the saturation is never more than 10 per cent below the normal saturation of 97 per cent. The tissues still remove approximately 5 ml. of oxygen from every 100 ml. of blood passing through the tissue capillaries, and to remove this oxygen, the venous pO_2 falls to only slightly less than the normal 40 mm. Hg.

Only 3 per cent of the oxygen transported in the blood is carried in the dissolved state. At the normal arterial pO_2 of 95 mm. Hg, approximately 0.29 ml. of oxygen is dissolved in every 100 ml. of blood plasma.[28] When the pO_2 of the blood falls to 40 mm. Hg in the tissue capillaries, 0. 12 ml. of oxygen remains dissolved. Therefore, 0.17 ml. of oxygen is transported to the tissues in the dissolved state by each 100 ml. of blood.

In the field of oxygen transport Spratt and co-workers [51] have used radioactive oxygen-15 in tracer studies of oxygen transport physiology. The rates and amount of oxygen accumulation in the body parts can be measured directly by this technique. The relative efficiency of pulmonary ventilation and the diffusion of oxygen has been also studied with oxygen-15. This isotope, therefore, has been useful in studying the dynamics of oxygen exchange and transport.

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Diffusion and Transportation of Oxygen in Excess of One Atmospheric Pressure (Hyperbaric Oxygenation, OHP)

History. Shortly after his discovery of oxygen in 1774, Priestly[41] wrote that this newly discovered gas "...might be peculiarly salutary to the lungs in certain morbid cases ... might be very useful as a medicine ... The feeling of it to my lungs was not sensibly different from that of common air; but it fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that, in time, this pure air, may become fashionable article in luxury."

In 1841, Tiger, in France, developed a caisson for bridge pillar construction under water in which pressures up to five atmospheres were used. The condition resulting from too rapid decompression after working in such an atmosphere became known as "caisson disease." In this same era Haldane[53] found it necessary to establish decompression rules to prevent the occurrence of caisson disease.

The physiologic principles underlying the use of hyperbaric oxygen, therefore, have been known since the days of Bert (1870's), Haldane (1895), and Barcroft (1909).

The first studies of hyperbaric oxygenation were done in 1878 by Bert who was interested in the decompression sickness phenomenon. He observed that dogs exposed to oxygen under pressure developed repeated convulsive seizures and he concluded that oxygen was indeed toxic to the central nervous system. Larks that he ex-

posed to 15 to 20 atmospheres of air convulsed and generally died. Bert showed that this convulsant effect was the result of increased oxygen tension.

Then, Lorrain Smith[47] in 1899 demonstrated that animals breathing oxygen over prolonged periods of time at even moderately increased oxygen tensions experienced severe fatal pulmonary damage. The early reports of the 1880's concerning hyperbaric oxygenation led to the belief that increased oxygen tension per se exerted toxic effects on the central nervous system. The blood, according to Smith[4] (1886), was "distributed not in accordance with physiological demands ... but in obedience to overpowering physical force," that compressed air in the blood was squeezed from the peripheral vessels by direct mechanical effect.

For purposes of this review, conditions in which the organism is exposed to oxygen tensions in excess of 760 mm. Hg atmospheric pressure are referred to as those of oxygen at high pressure (OHP).

Circulatory Gas Transport. The normal partial pressure of oxygen in the alveoli approximates 104 mm. Hg at atmospheric pressure but increasing or decreasing this pressure naturally changes the alveolar oxygen partial pressure.

According to the oxygen-hemoglobin dissociation curve, alveolar pO_2 variances above 60 mm. Hg never lower the hemoglobin oxygen saturation level more than 10 per cent below the normal

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saturation of 97 per cent. Peripheral oxygen diffusion continues

to remove 5 ml. per cent of oxygen and in removing this oxygen the

pO_2 of the venous blood falls to only slightly less than 40 mm. Hg.

104 mm. Hg —————————— 97% saturation
80 mm. Hg —————————— 95% saturation
60 mm. Hg —————————— 89% saturation
40 mm. Hg —————————— 73% saturation

Figure 4. Alveolar Partial Pressure as Related to Per Cent of
Hemoglobin Saturation.

When oxygen alveolar partial pressure increases above 104 mm.

Hg the maximum oxygen saturation of hemoglobin never rises above

100 per cent. That is, further increase in alveolar partial pres-

sure above 104 mm. Hg can increase hemoglobin saturation only 3

per cent.

Guyton[28] states that subjecting hemoglobin to alveolar par-

tial pressure of 500 mm. Hg after transportation to peripheral

tissues automatically reduces the pO_2 of venous blood to only a

few millimeters greater than the normal 40 mm. Hg. Therefore,

varying atmospheric oxygen content from 60 to 500 mm. Hg partial

pressure of oxygen results in minimal variance from the normal

tissue pO_2.

As mentioned earlier, when oxygen partial pressure is in-

creased by breathing pure oxygen the hemoglobin cannot carry more

than 20 ml. of oxygen per 100 ml. of blood. The oxygen in physical

solution increases from 0.17 ml. per cent oxygen carried at normal

atmospheric pressure to 2.03 cc. per 100 cc. of blood. This is

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because pressure of oxygen approaches 713 mm. Hg, allowing 47 mm. Hg for water vapor pressure within the lungs.

According to Attar et al.,[2] the amount of oxygen dissolved in plasma is directly proportional to the partial pressure of oxygen (i.e., 0.003 ml. of oxygen per 100 ml. of blood per millimeter of mercury pO_2). At three atmospheres oxygen, or 2280 mm. Hg pressure, the dissolved oxygen is 6.6 ml. per 100 ml. of blood. Because the tissues first utilize that oxygen in physical solution, tissue partial pressure of oxygen rises and carbon dioxide transport is altered since there is no reduced hemoglobin to carry the carbon dioxide.
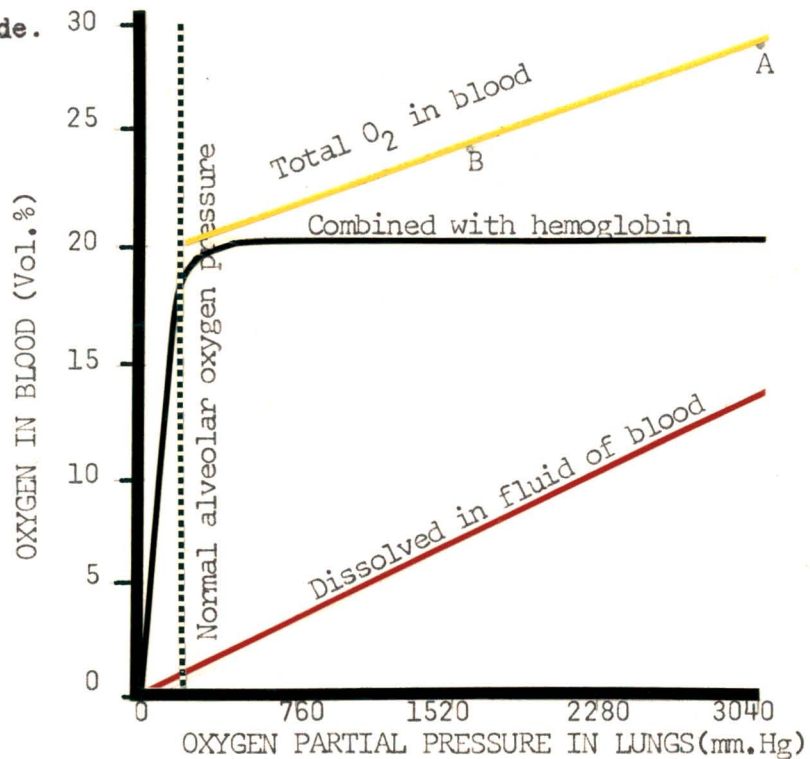

Figure 5.[28] Quantity of Dissolved Oxygen in Plasma and Oxygen Combined to Hemoglobin at High Oxygen Pressures.

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Figure 5 above illustrates the quantitative relationships of that oxygen transported in the dissolved state to that bound by hemoglobin. The figure shows that the total oxygen transport in blood under normal conditions is carried almost entirely by oxygen-bound to hemoglobin.

The amount of oxygen in solution in the blood conforms to Henry's Law which states that the solubility of the gas in plasma depends upon its partial pressure in the gaseous mixture with which the blood is in equilibrium (i.e. the pulmonary alveolar content).

Bohr[31] showed as far back as 1905 that with pure oxygen at one atmosphere pressure approximately 2.2 ml. oxygen will be taken up by 100 ml. blood at body temperature. When the ambient pressure is doubled, the amount of oxygen in solution is raised about 4.2 ml. which is nearly enough to supply oxygen requirements of resting mammals without hemoglobin.[31]

Using the diagram above and assuming that oxygen is administered under four atmospheres pressure so that the partial pressure of oxygen in the lungs is 3000 mm. Hg, this would represent a total oxygen content of 29 volume per cent. As the blood passed through the tissue capillaries and as the tissues utilized the normal requirements (approximately 5 ml. of oxygen per 100 ml. blood), the total quantity of oxygen leaving the tissue capillaries would be 24 volume per cent, a pO_2 of 1200 mm. Hg. It will be re-

called that venous oxygen pressure is nearly equal to the pO_2 of peripheral tissue. High pulmonary pO_2, therefore, can also cause high tissue pO_2 if these pressures are high enough for transport of excessive quantities of oxygen in the dissolved state.

Therefore, the raised oxygen tension resulting from this more than fifteen-fold rise in the plasma content not only increases the amount of oxygen immediately available to the tissues but also increases the transfer rate of oxygen through the capillary wall to tissue fluid and cells.

It is comparatively easy to alter the oxygen tension on the arterial side of the capillary loop according to Sanger[44] for it is similar to that in the arteries and closely approximates that in alveolar air. Breathing pure oxygen will raise it from about 100 mm. Hg to 500 mm. Hg, and breathing pure oxygen at three atmospheres will raise it to nearly 2000 mm. Hg.

Figure 6.[44] Oxygen Content of Arterial Blood during Respiration of Air, 100 Per Cent Oxygen and 100 Per Cent Oxygen at Three Atmospheres. Nearly all the Extra Oxygen is Carried in Simple Solution in the Plasma.

Under conditions where oxygen is breathed under increased atmospheric pressure the oxygen partial pressure of arterial blood increases tremendously. Therefore, if a part of the body is deprived of a portion of its blood supply there develops a steep partial pressure gradient between the increased plasma partial pressure and the reduced pressure of hypoxic tissue. An increased diffusion rate results.

Trapp[53] discusses the observations made by Boerema and his associates at Wilhelmina Hospital of the University of Amsterdam in which pigs' circulating blood was diluted using plasma under three atmospheres pressure until only 0.4 per cent of the original

hemoglobin remained; a normal electrocardiogram was maintained throughout the procedure. The blood had been diluted to nearly clear fluid and the animals were apparently abnormally pale in color. Under 100 per cent oxygen at atmospheric pressures the hemoglobin could be reduced only to 11 or 12 per cent if a normal ECG was to be preserved.

Circulatory Changes. Attar et al.[2] produced vascular collapse by bleeding 30 dogs to an arterial pressure of 30 mm. Hg and maintaining it for $2\frac{1}{2}$ hours. They found that an average quick rise in blood pressure was noted in dogs treated with OHP. It is also interesting to note that all the dogs that died within 48 hours of treatment with OHP either maintained a low mean arterial pressure or dropped 15 to 20 mm. despite an initial rise.

Although oxygen at atmospheric pressures induces a slight vaso-constriction, experimental data shows that breathing OHP does not cause vasoconstriction, and if anything, causes dilatation of the cerebral vessels because of the accumulation of carbon dioxide.[2]

Attar et al.[2] observed, as have numerous other investigators, that the pulse slows upon exposure to OHP because of central vagal stimulation.

Attar et al.[2] in their observation of 35 dogs subjected to hyperbaric oxygenation after controlled hemorrhagic shock found that the arterial pH, which in the control group dropped to acidotic levels, was improved. Venous pH becomes slightly more acidotic

(Attar, Behnke). This was accounted for by the decrease in buffer base. Attar[2] then found that lactic acid showed a steady rise during the controlled hemorrhage of the dogs under OHP. Assuming that OHP provides enough oxygen to the tissues, the anaerobic glycolysis which prevails in shock should be curtailed and lactic acid formation diminished.[2] Since this is not the case, the increase in lactic acid may be accounted for by accumulation in tissues undergoing vasoconstriction, released upon peripheral vasodilation. Eichenholz[22] relates the lactic acid increase to a decreased arterial pCO_2 produced by hyperventilation. Venous pCO_2 under OHP is significantly elevated, representing an increased pCO_2 tension of tissues.

Gessel,[25] Guyton,[28] and others have postulated that since the dissolved oxygen under OHP is sufficient for metabolic needs, part of the dual function of hemoglobin is lost since hemoglobin is not reduced and oxyhemoglobin circulates through the tissue unchanged. Consequential interference with hemoglobin reduction and failure of hemoglobin to release base impairs the normal carbon dioxide transport mechanism with subsequent tissue and venous pCO_2 elevation.[25] The reduction of hemoglobin in the tissues ordinarily permits carbon dioxide to be removed readily from tissues, but under hyperbaric oxygenation, tissue oxygen tension remains so high that hemoglobin remains completely oxygenated and tissue carbon dioxide retention occurs.

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Inspired OHP (3 atmospheres)

Increased tissue O_2 ← Increased Physically Dissolved O_2 (6.6 cc./100 cc. arterial blood)

Cardiac Output
$A - \overline{V}O_2$
O_2 Consumption
} no significant change

Increased Venous O_2 Saturated

Increased Tissue Acidity ← 100% Hemoglobin Saturation and Decreased Hb Affinity for CO_2

Inhibition of $HgbO_2$ Buffer System

Increased Sensitivity of the Respiratory Center ← Increased Venous pCO_2 (Increased ventilation)

Increased Respiratory minute volume

Increased CO_2 Elimination and Decreased Arterial pCO_2
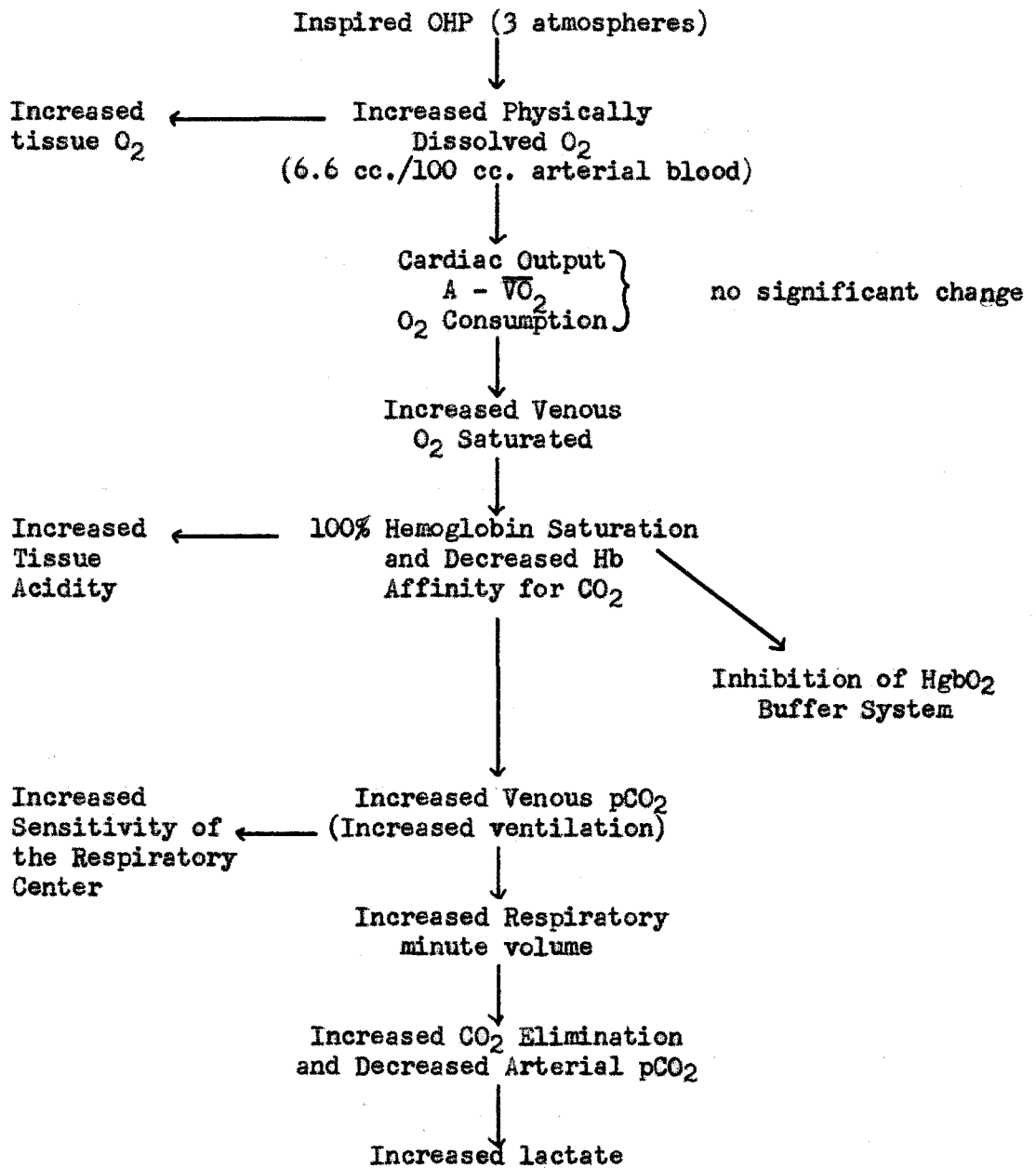
Increased lactate

Figure 7.[2] Effects of Oxygen Breathing at Three Atmospheres (modified from Attar, Esmond and Cowley.)

According to Guyton[28] as long as pO_2 in the lungs remains above 1500 mm. Hg essentially no oxygen will be released from the hemoglo-

bin as it passes through the tissue but only from the dissolved plasma. Hemoglobin saturation will remain near 100 per cent inhibiting the hemoglobin - oxygen buffer system from maintaining acid-base balance. Therefore, if all the oxygen needed by the tissues can be transported in the dissolved state, "oxygen poisoning" will usually result. That is, under conditions of OHP, oxygen is forced upon the heme molecule, hydrogen is displaced and the total quantity of reduced heme is diminished. This diminution, the increase in hydrogen ion concentration, and the combined effect upon the bicarbonate system all tend to result in a reduced buffering capacity of the blood during hyperbaric oxygenation.

Metabolic Changes. In 1955 Haugaard[30] proposed that there is oxidation of essential metabolities, such as co-enzymes containing sulfhydrl groups, rather than inactivation of enzymes directly during OHP.

Richards et al.[43] have more recently noted (1963) that oxygen inhibits certain enzymes involved in the tricarboxylic acid cycle, particularly those containing sulfhydryl groups. According to studies in vivo, reduced glutathione yields some protection against oxygen poisoning, and cupric ions, which are a catalyst for the oxidation of sulphydryl groups by oxygen, accentuate oxygen toxicity.

Oxygen has also been postulated to be directly toxic to the central nervous system, particularly through the liberation of ex-

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cess free radicals capable of oxidizing sites similar to those mentioned above.[43]

As to the effect on metabolism, various investigators consider metabolism to be decreased under OHP, judging the metabolic alterations by changes in body temperature. Behnke[2] (1934) measured the total oxygen consumption using the basal metabolism apparatus technique. After an initial rise which he related to tissue oxygen solubility, oxygen consumption stabilized at about the same level as at sea level.

Under conditions of OHP with associated oxidized hemoglobin, the tissue acidity rises somewhat, resulting in a small amount of released oxygen from hemoglobin. However, with the passage of time, the amount of physically dissolved oxygen in the body must be slowly altered, and the oxygen stores increased. As the tissue oxygen tension rises, and the entire body ultimately becomes a potential bank of deposited oxygen, the stored oxygen in solution becomes available for tissue utilization and cellular metabolic functions. Richards[43] states that there would be a three-to-four-fold increase in the oxygen content per kilogram of tissue stores at three atmospheres of pure oxygen pressure as compared to ambient pressure.

Pulmonary Changes. Finally, concerning pulmonary physiology in OHP, it is important to note that an average sized man submitted to two atmospheres pressures contains approximately three

liters of gas in his pulmonary system. As atmospheric pressure
increases to four atmospheres the lungs vital capacity for gas ap-
proaches the patient's residual volume. The lungs can collapse no
further and even greater pressure does not effect the lung gas
volume. However, increased atmospheric pressures cause a rise in
pulmonary circulation pressure creating a gas tension differential.
At first, fluid would pass from the alveolar capillaries in the
form of pulmonary edema to be followed, if the difference continued,
by ruptured vessels and pulmonary hemorrhage.[38] It would be pos-
sible in the extreme case for the ribs to crack and the chest wall
to cave in. Increasing the atmospheric pressure in an obstructed
patient to more than four atmospheres pressure would be disastrous
to the involved lung.

Levy and Richards[35] demonstrated (1962) the effects of com-
bining pressure oxygenation at three atmospheres on asphyxial sur-
vival of rats following tracheal occlusion. Exposure to 100 per
cent oxygen at OHP increased survival times about 55-80 per cent
over animals breathing 100 per cent oxygen at atmospheric pres-
sure. Addition of carbon dioxide to the inspired oxygen under
pressure apparently afforded additional protection.[35]

Utilization of Hyperbaric Oxygenation

History. Medical uses of OHP appeared first in 1955 when Churchill-Davidson, Sanger and Thomlinson suggested that radio sensitivity of tissues might be enhanced by irradiation utilization hyperbaric oxygenation.[17]

Then in 1956 Boerema of Amsterdam stimulated interest in the application of hyperbaric oxygen in surgery and was the first to indicate the possible uses of operating rooms maintained at three atmospheres ambient pressure to carry physically dissolved oxygen to hypoxic tissue.

A systematic approach to the therapeutic use of OHP may be proposed bearing in mind the ability of body cells to use oxygen to support normal function. Inability of these cells to utilize oxygen for cellular demands has been defined as anoxia.[15] The use of OHP is indicated for clinical hypoxias which may be differentiated into four general types: (1) stagnant hypoxia, (2) anoxic hypoxia, (3) histotoxic hypoxia, and (4) anemic hypoxia.

Stagnant Hypoxia. Stagnant hypoxia arises when the flow of blood through a tissue is reduced. Reduced flow may occur locally as a result of interference with peripheral circulation (eg. arterial spasm, embolism, or thrombosis). Generalized reduced flow may occur in shock, cardiac insufficiency and vasomotor collapse.

The use of oxygen in shock was studied by Wood et al.[57] in 1940. They showed that the amount of oxygen reaching peripheral

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tissues was increased by pure oxygen inhalation at one atmosphere pressure. In 1941 Orr and Schnedorf found that oxygen at this pressure was beneficial to dogs in shock and increased their survival time. These findings were not confirmed, however, by Frank and Fine[24] who obtained no benefit from the administration of oxygen at three atmospheres in the treatment of hemorrhagic shock in dogs. Similar results were obtained by Burnett and co-workers[14] in 1959 who induced shock in rats by trauma. Failure to demonstrate beneficial results in these experimentations with OHP is explained by the fact that circulating fluid loss was too extensive to support oxygen transport to tissues even under high pressure conditions. This was shown in 1959 when Burnett and associates demonstrated notable improvement in survival rates of rats in glycerol-induced hemolytic crisis when placed under two atmospheres absolute oxygen pressure for two hours.

Illingsworth et al.[31] have had extensive experience in the management of acute arterial injuries and chronic peripheral vascular occlusion both experimentally and clinically using a pressure chamber at two atmospheres pressure.

In two cases of arterial injury of limbs treated in the chamber, they felt that massive gangrene of the affected part was prevented. These patients breathing oxygen through a face mask at two atmospheres pressure for forty-eight hours continuously experienced increased skin temperature and normal color in the in-

volved foot. Three months later the toes were gangrenous but the greater part of the foot was viable. In occlusive peripheral vascular disease, striking relief of pain was noted in five elderly patients and healing of ulcerations was noted. These patients received three hours of OHP daily for two weeks without development of oxygen toxicity.

Illingsworth and associates[31] have also had experience in treatment of arterial thrombosis. They reported one patient who developed necrosis of most his small intestine after a superior mesenteric thrombosis. Reanastomosis of the remaining, questionably viable, bowel under OHP management resulted in the return of normal coloring and healing. Unfortunately the patient developed a generalized staphylococcal infection from which she eventually died.

The effect of OHP in coronary artery occlusion has been observed by Smith and Lawson[31] also from Glasgow in 50 healthy dogs. The effects of acute coronary artery obstruction were studied under OHP and significant decrease in ventricular fibrillation and grossly smaller infarcts were noted histologically.

An interesting experiment on myocardial infarction was carried out by Illingsworth and his associates[31] in which one patient, who had experienced a severe myocardial infarction involving 75 per cent of the left ventricle, was restored to a feeling of well being from a previous unconscious state under OHP. Enough improvement

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occurred that he was able to read a newspaper while in the chamber. Although the high-pressure management failed to raise his systolic pressure of 60 mm. Hg, his previously anuric state was restored to a normal output. Attempts, however, to maintain this patient at atmospheric pressure was unsuccessful and he developed fatal fibrillation.

Striking benefits of OHP in cerebral vascular occlusion was observed by Smith et al.[48] This supports the opinion that the pressure chamber may be of value during operations on the cerebral circulation in man.

The so-called "irreversible" cerebral anoxia which occurs as an operative anesthetic complication does not respond to conventional methods of treatment because of the barrier to diffusion of oxygen presented by the edema fluid. Only by increasing the gradient across the edema barrier (ambient pressure of two atmospheres) can the anoxic depression of the respiratory center be relieved.[40]

Experimentation in the total circulatory arrest also have been carried out by the Glasgow researchers to test the hypothesis that tissues under OHP may withstand total circulatory arrest for longer periods than normal and to determine the maximum safety period of arrest when combined with moderate hypothermia.[31] In successive experimentation on dogs the maximum safe period of arrest permitting survival without sequelae was 35 minutes.

The initial basic pathology in vascular collapse is generalized

tissue stagnant anoxia. Attar, Esmond and Cowley[2] have produced vascular collapse in dogs and found that the improved tissue oxygenation provided by OHP presumably protected the animal during vascular collapse and shock. According to Richards et al.,[43] the use of hyperbaric oxygen chambers for the treatment of shock and vascular collapse in man has been suggested in the form of modified recovery rooms but this has not yet actually been practiced or reported upon.

In 1960, Boerema, Meijne and Vermeulen-Cranch[57] operated for the first time upon cyanotic children in a pressurized chamber utilizing the Pott's anastomosis. Then, in 1961, Boerema[9] reported that circulatory arrest was possible twice the normal time at moderate hypothermia of 29° C. at three atmospheres absolute pressure. He stated that circulating hemoglobin was unnecessary for short periods of time under OHP. He has also noted other clinical applications for OHP, among which are: the treatment of ileus, the reduction of incarcerated inguinal hernia and prolonged atriotomy and ventriculotomy at hypothermic levels of 16° to 19° C. permitting opening of the heart with only occasional extrasystoles.

Meijne et al.[22] (1962) also noted that surface cooling to temperature below 28° C. for cardiac surgery could be performed under OHP (three atmospheres) more safely than under normal atmospheric pressures.

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Complete occlusion of pulmonary artery and aorta circulation was possible for at least ten minutes without hypothermia under OHP by Boerema in 1962 when he operated on a child with congenital heart disease.[10] Shunt construction was notably facilitated in this state in that the patient's condition was ideal as far as the oxygen saturation of his blood is concerned.

Concerning the use of OHP with heart-lung by-pass apparatus, Weale[56] in 1961 initiated a pilot program designed to test the practicability of (a) pressurizing blood with oxygen in an oxygenator (b) pre-cooling the blood. The combined use of by-pass, hypothermia and pressurized heart-lung machine together reduced the quantity of the priming blood necessary for sufficient perfusion in cardiac operations, although oxygen levels were not appreciably elevated. Boerema[11] noted of this experimentation that low oxygen levels resulted from failure to pressurize the surrounding atmosphere. According to Boerema[11] apparent pressurization of heart-lung machine alone was of no value when administered to patient at normal ambient atmospheric pressure.

Bernard and Tank[8] at present are utilizing hyperbaric oxygenation (3.0 to 3.6 atmospheres absolute) in cardiac surgery on cyanotic infants. Transient improvement in the metabolic status of patients, as characterized by an increase in arterial pH, was noted during the period of oxygen administration. Since the improvement in tissue oxygenation rapidly disappeared after the use

of compression, Bernard and Tank suggested that the prime indication for hyperbaric oxygenation in the management of patients with cyanotic congenital heart disease was the performance of palliative or corrective operations during the time that the temporary improvement occurred in the chamber.

Experimentation done by these men indicate that simultaneous decrease of tissue needs for oxygen consumption by lowering body temperature and concurrent increase in body oxygen stores with OHP prolong periods of "safe" circulatory and respiratory arrest which are not feasible at normal atmospheric pressure. These concepts have been explored in rats by Levy and Richards[35] who found hypothermia additive to survival time of rats under OHP.

The expected use of the pressure chamber for open-heart surgery is approaching realization. Moderate hypothermia and pressurized oxygen will permit up to 30 minutes of cardiac arrest with total circulatory occlusion with less complications than the cardiac by-pass.

The physiologic principles are rather complex because hypothermia increases the affinity of oxygen for hemoglobin and shifts the oxyhemoglobin-dissociation curve to the left. Carbon dioxide accumulation and blood acidity increase. This shifts the curve to the right aiding in oxygen release from oxyhemoglobin. Increased venous carbon dioxide increases cerebral flow through vasodilatation with subsequent increased cerebral oxygen diffusion.

Dogs at normal ambient pressures and temperature survive about three minutes in circulatory-respiratory occlusion, while dogs breathing OHP (three atmospheres) under normo-thermic conditions survives ten minutes. Dogs under conditions of OHP and hypothermia (29° C.), however, were able to tolerate complete respiratory and circulatory occlusion for periods of 45-64 minutes.[43]

Anerobic infections such as clostridia, anaerobic streptococci and tetanus are surgical entities seen periodically in stagnant anoxias today. Oxygen inhibits the growth of many anaerobes if present in high concentration. Success with the use of OHP in combating anaerobic infections was noted by Boerema in 1961. In 1962 Smith et al.[50] reported on OHP at two atmospheres utilized over twenty-four hour period in three patients with success in two. The other patient went into the pressure chamber (two atmospheres) shortly after the onset of gas infection, but three hours later required leg amputation because of progression of the infection.

Brummelkamp (1962)[12] reported a series of twenty-one patients with Clostridial infections successfully treated with under three atmospheres pressure. To avoid oxygen toxicity staging of the OHP exposure was divided so that in the first twenty-four hours there were three treatment periods of two hours each, followed by four sessions of two hours each over the next forty-eight hours. In all there were a total of seven treatments in a course of three

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days. No deaths were attributed to gas gangrene or to complication of oxygen therapy at high pressure.

Most recently, Brummelkamp et al.[13] have noted successful results with the use of hyperbaric oxygenation in treatment of Clostridial infections. They noted that operation after treatment had several advantages: (1) the patient is non-toxic, (2) operation can be limited to excision of necrotic tissue avoiding radical limb amputation and (3) the period of delay allows demarcation of necrotic tissue to take place.

In May 1963 Maudsley and co-workers[36] described the use of a small mobile oxygen chamber in a case of lower extremity ischemia following an open fracture of the tibia and fibula. The clinical response to OHP was dramatic. The subsequent recovery after open reduction was uneventful.

Relief of pain has been afforded to a number of cases of chronic occlusive vascular disease complicated by ischemic neuropathy. These elderly patients have spent 2-3 hours daily in the chamber for periods up to 30 days.[31] Although such treatment appears less effective in chronic ischemia due to occlusive vascular disease, several patients with ischemic pain had relief when breathing oxygen in the pressure chamber.

Anoxic hypoxia. Anoxic hypoxia results from the interference with the exchange of oxygen across the pulmonary membranes or other preceding steps in respiration causing a reduction of the

pO_2 in arterial blood. The effects are general and may be caused
by any condition reducing the amount of oxygen available for for-
mation of oxyhemoglobin. This situation is encountered in pneu-
monia, drowning and respiratory muscle paralysis as well as de-
creased atmospheric pO_2. Hyperbaric oxygenation (OHP) in these
cases would be beneficial but probably unnecessary since pure oxy-
gen might be more practical. However, Illingsworth et al.[31] re-
ported an incident of medullary depression secondary to barbiturate
poisoning (20 nembutal capsules) when normal resuscitation was
without response. OHP (two atmospheres) was beneficial in this
case by bringing about normal vital signs and general improvement,
which were maintained after removal from the pressure chamber.

Experimentation in treating premature infants with hyaline
membrane disease has been carried out in Glasgow. Initially the
results were impressive. Cyanosis was rapidly corrected and re-
spiratory distress relieved. Although biochemical control remains
the mainstay of treatment, OHP is maybe beneficial and used when
available. The mortality in cases of hyaline membrane disease
has been reduced from 66 per cent to 33 per cent according to the
Glasgow group.

More recent experimentation in the field of OHP by Kylstra,
Tissing and Van der Maen[33] include the attempt to keep mice alive
while submerged in a balanced salt solution to which trisaminome-
thane (T.H.A.M.) was added to minimize hypercapnic acidosis due to

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deficient elimination of carbon dioxide. In these experiments a-
dult mice continued breathing fluid up to 18 hours -- that is ap-
proximately 1000 times as long as controls.[32] Goodlin in 1962 re-
ported on his experimentation with newborn mice and three human
fetuses (11 to 15 weeks) which were maintained in an immersion
chamber of Hanks' basic salt solution under conditions of OHP for
prolonged periods of time. Although he ascribed prolonged sur-
vival of human and mice fetuses in hyperbarically oxygenated salt
solution to cutaneous respiration, Klystra noted that in his opin-
ion survival time increased primarily due to gas exchange occurring
in the lungs rather than cutaneous respiration.[32]

Histotoxic Hypoxia. Histotoxic hypoxia occurs when the tissue
cells cannot efficiently use the oxygen available to them. Alco-
hol, narcotics, and such poisons as cyanide interfere with the a-
bility of cells to utilize oxygen even though the supply is entirely
adequate. The blood passing through the tissues does not lose oxy-
gen since the oxidative system of the cells cannot accept it.
Therefore, hyperbaric oxygenation administered to a patient in
histotoxic anoxia would be to no avail since oxygen supply to tis-
sues was adequate but unusable -- "poisoning" of the cellular
respiratory enzymes inhibits the oxidation.

Drill[21] stated that there is no indication that increased
blood oxygen content can relieve histotoxic anoxia, but he also
says, "If the patient is breathing poorly, oxygen inhalation and

other supportive measures such as blood transfusions should be instituted.

Cope,[18] however, demonstrated in 1961 that oxygen is of paramount importance in the immediate treatment of cyanide poisoning. After reviewing the literature and animal experimentation he concluded that oxygen exerts a protective effect against cyanide toxicity at the cellular level and that this property could be used to counteract fatal doses of cyanide poisoning. The exact biochemical mechanism responsible for this effect has not yet been elucidated. Cope[18] reviewed experimentation by a Russian, K. Ivanov, in which OHP (2.8 atmospheres) was used to rapidly restore normal electrical activity to the mouse cerebrum depressed by near-lethal doses of cyanide.

Levine[34] substantiated Copes work on use of oxygen in cyanide poisoning in experiments on sublethal intoxication of rats by intravenous potassium cyanide. He noted that slightly more cyanide was required to induce brain lesions if oxygen was administered. He attributed its beneficial effect to augmentation of that small proportion of cellular respiration which is independent of cytochrome oxidase (the enzyme inhibited by cyanide). Levine[34] noted that even if the metabolic effect of oxygen was small, it may prolong life enough to give detoxification mechanisms a chance to operate.

Anemic Hypoxia. Anemic hypoxia follows reduction of the oxy-

gen carrying capacity of the blood. This capacity may decrease because hemoglobin has been modified so that it can no longer transport oxygen or because hemoglobin is deficient quantatively. The effects of such anemia are general. Causes are shown below:

1. Primary HHb Loss: (a) anemia, (b) hemorrhage.

2. HHb modifications: methemoglobin (nitites and chlorates)

3. Blocking reactive groups of HHb with which oxygen combines: carbon monoxide poisoning.

The end result of insufficient oxygen transportation, therefore, might easily be corrected in a pressure chamber containing high partial pressure oxygen. In this way a large quantity of oxygen could be carried to the tissues in the dissolved state rather than combined with hemoglobin. In experimentation with dogs[2] it has been possible to transport enough dissolved oxygen to supply more than 60 per cent of the quantity of oxygen needed by peripheral tissues.

The utilization of OHP in anemic anoxia, however, must proceed with caution since administration of oxygen under extreme pressure to an anemic patient may lead to death, not because of failure in oxygen transport, but because of the failure of the oxygen buffer function of hemoglobin. Carbon dioxide tensions rise to near toxic levels.

In 1950, Pace, Strajman and Walker[39] demonstrated the acceleration of carbon monoxide elimination in man under high pressure

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oxygen therapy. Richards et al.[43] show the efficiency of OHP

therapy in carbon monoxide poisoning and barbiturate poisoning

in man.

Illingsworth et al.[31] (1961) reported 18 cases of carbon mon-

oxide poisoning which had been treated successfully with OHP. In

these cases OHP served a double purpose: (1) to increase oxygen in

blood to maintain life during the critical phase, while (2) in-

creasing blood oxygen tension to drive off the carbon monoxide

from hemoglobin. The most recent report from Glasgow by Smith[49]

substantiates the belief of Illingsworth that OHP revival procedure

is superior to all the more usually available techniques of resus-

citation. No deaths occurred with the use of OHP in 32 cases of

carbon monoxide poisoning, whereas, carbon monoxide poisoning

treated by conventional methods in Glasgow did carry a considerable

mortality rate.

Radiation Therapy. In 1953, Gray demonstrated that sensitivity

of cells to irradiation was related to the oxygen concentration in

their environment.[27] Churchill-Davidson et al.[17] utilized OHP

(three atmospheres) in irradiation of selected cancer patients in

London. The initial results were encouraging and conclusion was

made in 1959 that irradiation under hyperbaric oxygenation was

effective technique of carcinoma management.

Seaman et al. (1961) noted that an increase in the radio-

sensitivity of a tumor occurred only if there were tumor cells

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that were growing at decreased oxygen tension.[45] Cater et al.[16] more recently measured the effect of breathing oxygen at high pressure on the oxygen tension of tumors and found that the maximum radio-sensitivity was not achieved with less than five atmospheres of pressure.

Adams et al.[1] recently (1963) described a series of six patients with advanced malignant disease in which the effect of combined nitrogen mustard and hyperbaric oxygen therapy was observed. There was no evidence that the addition of OHP therapy was of significant clinical benefit in terms of potentiating the tumoricidal effects or of reducing the side-effects of nitrogen mustard therapy.

Experimentation on mice by Back and Ambrus[3] concerning the relationship of oxygen tension to the therapeutic and toxic actions of alkylating agents has led these authors to the conclusion that changes in oxygen concentration from one to five atmospheres did not alter the effect of nitrogen mustard. Survival time or tumor growth decrease in mice innoculated with Ehrlich adenocarcinoma, Sarcona 180 and Leukemia L1210 showed no significant change, substantiating earlier studies.

Complicating Variables Introduced by Hyperbaric Oxygenation

Various Systemic Effects of Increased Pressure. Two Germans,
Bornstein and Stroink[43] in 1912 first demonstrated the existence of
oxygen toxicity in humans. While breathing oxygen at three atmos-
pheres at rest for 45 minutes, no ill effects were noted. However,
clonic spasms of legs were observed by Bornstein at 51 minutes
while exercising.

In 1935 confusion and amnesia were attributed to oxygen intake
in deep-sea divers breathing air at 300 feet in a study done by
Haldane and Priestly.[29] Later that year Behnke and co-workers[7]
demonstrated that the confusion, irritability and unresponsiveness
of deep-sea divers was the result of the intoxicant effect of
nitrogen at high pressure. In these same studies, Behnke[7] showed
that subjects breathing pure oxygen at three atmospheres for three
hours noted no ill effects but that after the fourth hour there
was an abrupt onset of dizziness, vertigo, nausea and impending
collapse. At four atmospheres pressure, oxygen breathing produced
convulsions at about 15 minutes but without permanent sequelae
on reduction of oxygen tension. These observers realized that
oxygen poisoning was a definite hazard in man and deserved fur-
ther study since in underwater diving each 33 feet of diving depth
increased the atmospheric pressure approximately one atmosphere,

When tissue oxygen tension rises too high, it has a tendency
to change reaction rates within the cells, sometimes producing

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cellular injury. The tissues most likely to be "poisoned" are those involved with high metabolic rates. The most sensitive cells are those of the central nervous system; oxygen poisoning in its early stages, therefore, may cause severe convulsions and later actual destructive lesions.

Residual damage has not been detected clinically or electrically providing the subject returns to normal oxygen tension immediately following the onset of seizures. The cardiac effects have been transient and likewise without permanent damage. The pulmonary effects witnessed in animals are pneumonia, atelectasis, edema or hemorrhage. These have not been observed in man, possibly because man's central nervous system is so sensitive to oxygen toxicity that he is removed from high ambient pressures before pulmonary changes occur.

It has been postulated that exposure of animals to oxygen at increased tension caused cerebral vasoconstriction and, therefore, protection from the adverse effects of high oxygen pressure. However, Bean[5] in his study of anesthetized dogs and rats breathing OHP increased oxygen to the brain at levels maintained throughout the exposure and brain vasculature did not react en mass to stimulation. Cerebral vasoconstriction which may have occurred in OHP was apparently insufficient to prevent pronounced deviation of cerebral oxygen or to protect against oxygen toxicity represented by precipitation of the typical convulsive seizures.

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Increased oxygen tension has been reported to produce a variety of symptoms depending upon exposure time, concentration and pressure. This phenomenon was designated by Bert as "oxygen poisoning", a general term applied to any deleterious change from the normal organ structure or function attributable to a higher than normal oxygen concentration. Treﬁiokas,[54] in examination of normal and "oxygen poisoned" lung tissue under electron microscopy, found no alternation in the active respiratory centers, of the alveolar cells, or of the mitochondria. He, therefore, concluded that mitochondrial and respiratory enzyme system damage was not involved in oxygen toxicity.

There is little doubt that in animals 65 per cent oxygen concentrations at atmospheric pressures for more than 12 hours results in some pathologic changes, especially in the lungs. According to Richards and co-workers,[43] pulmonary changes in animals include inflammation, congestion, edema, atelectasis, fibrin formation, pneumonia, and subsequent cardiac involvement with cor pulmonale.

The periodic use of 100 per cent oxygen for several hours a day followed by breathing oxygen at normal pressures has been well tolerated in animal experiments. Oxygen tolerance in this manner is apparently indefinite and the pathology characteristic of acute and chronic oxygen poisoning has not been defined.

Exposure to oxygen tension above 155 mm. Hg for five to six

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hours results in acute oxygen poisoning characterized by convul-
sions. Neuromuscular coordination also became impaired after sev-
eral hours of pure oxygen breathing. Behnke et al.[7] concluded that
healthy men could breathe pure oxygen at one atmosphere without
ill effects for only four hours. Longer periods resulted in car-
diac, pulmonary and central nervous system changes with fever,
leukocytosis, dyspnea, tachycardia and paresthesias.

Thomson[52] reported oxygen poisoning in breathing compressed
air at increased ambient pressure (four atmospheres absolute) in
naval officers. These officers suffered convulsive symptoms after
approximately 14 minutes breathing time.

Behnke and co-workers[7] (1935) found that human subjects after
breathing oxygen at four atmospheres experienced convulsive seizures
only after as long as 44 minutes and at three atmospheres exper-
ienced ill effects during the fourth hour.

In 1947 Donald[20] demonstrated the marked variations of oxygen
tolerance in man and concluded that:

1. 70 feet diving depth - 3.7 atm, 95% oxygen tolerated approxi-
   mately 55 minutes.

2. Toxicity occurred earlier in underwater experiments than com-
   pressed air at same pressure.

3. Oxygen tolerance time greatly shortened above 3.7 atmospheres.

4. Oxygen tolerance reduced by exercise.

To summarize, the extent of the practical use of OHP, the
limits of pure oxygen tolerance time should be held at three hours

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at three atmospheres absolute pressure and to thirty-six hours of continuous administration at two atmospheres pressure. No administration of pure oxygen, therefore, should be used above three atmospheres absolute because of the known variability of oxygen tolerance.

Donald[20] in his 1947 study found certain recurring complications during OHP utilization. The symptoms, in order of their occurrence and incidence were lip twitching, dizziness, nausea, choking sensation, dyspnea, tremor and followed by convulsions (not unlike a grand mal seizure) with confusion, amnesia, vomiting and headache.

Miles in Underwater Medicine[38] also mentioned occurrence of adrenal cortex hypertrophy in experimental animals under conditions of OHP.

Concerning anesthetics in OHP, Van der Brenk[55] in 1962 noted from his experience with exposure of animals to high oxygen pressures a paradoxical action of anesthesia in accentuating delayed damage to the central nervous system due to oxygen poisoning, while protecting against acute damage. Van der Brenk concluded that chemical protection against the acute effects of high-pressure oxygen poisoning was largely due to a lowering of metabolic rate or possibly a reversal in tissue redox potential changes which may result from OHP exposure. However, he noted that organic nervous system damage due to exposure to high-pressure oxygen ap-

peared refractory and possibly was related to increased carbon dioxide tension in the cerebrum and its effect on cerebral vascular calibre and cerebral oxygen tension.[55]

Etiology of the Reactions. There is no agreement in the literature today as to the exact cause of oxygen toxicity. The factors potentially involved in oxygen poisoning are known: (1) carbon dioxide retention, (2) increased tissue acidity, (3) enzymatic inactivation, (4) hormonal involvement, (5) direct central nervous system effects, and (6) eventual decrease of metabolic rate.

Bean,[4] in a review of the literature prior to 1945 concerning the effects of oxygen at increased pressure, concluded that the increased carbon dioxide tension constitutes an important, but not only, etiological factor in poisoning by OHP. Bean[4] reported that the increased carbon dioxide tension and its acid properties resulted in tissue acidity with secondarily depressed tissue oxidation and cellular respiration with subsequent decreased cellular metabolism. Richards et al.[43] discounts significant increase in tissue acidity, however, to account for toxic symptoms.

Tissue and venous carbon dioxide tensions have been shown to increase in recent experimentation (Richards,[43] Attar[2]) because of failure of oxyhemoglobin to reduce under OHP and become available for carbon dioxide transport. Richard[43] has stated that although carbon dioxide tension does rise with hyperbaric oxygenation, the

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increase is not sufficient to account for toxic symptoms.

Hormonal mechanisms, although involved in oxygen toxicity as demonstrated by hormonal ablation on oxygen poisoning cannot sufficiently explain the nature toxicity either.

At the present time the most plausible theory indicated by OHP investigators seems to involve the enzymatic effects of high oxygen tension on body cells, especially the central nervous system. Oxygen is known to inhibit enzyme activities notably in the tricarboxylic acid cycle. Through the liberation of excess free radicals capable of oxidizing sites such as sulfhydryl groups from enzymes, oxygen may act as a directly toxic substance to body cells, especially those of the central nervous system.

In conclusion the direct toxic action of OHP on respiratory enzymes, the influence of increased carbon dioxide tension and the acid effect of carbon dioxide retention together tend toward an increased tissue acidity and decreased metabolism, subsequently ending in cellular toxicity -- "oxygen poisoning".

Mechanical Effects of Increased Pressure. Besides the effects associated with the rise in oxygen tension, it is necessary to consider the effects resulting from rise in barometric pressure. In this group the only effect of importance is the possibility of damage to the ear drums or middle ear by pressure differentials. This can easily and safely be overcome if necessary by myringotomy.[44] Other consequences of increased barometric pressure are the pressure

differentials produced in the sinuses and intestinal lumen which may give rise to discomfort in the conscious individual. Also to be considered are the increase in blood gas solubility, the increase in the viscosity of inspired gases, some impairment of carbon dioxide elimination and possible changes in temperature. Sanger[44] states that "bends", or "caisson disease", is not a problem with oxygen owing to its being rapidly metabolized. When present, however, decompression sickness is represented by slowly developing dull ache in or near the joints with a general feeling of exhaustion, chills or fever.

Finally, an individual entering the pressure chamber should be free of the common cold, catarrh or upper respiratory tract infection which might preclude equalizing the air pressure of both sides of the tympanic membrane.

Summary

Research in the field of hyperbaric oxygenation has already revealed a revolution in the treatment of a wide variety of medical and surgical conditions associated with tissue hypoxia as the common factor of pathologic processes -- all benefited by hyperbaric oxygenation.

Under one atmospheric absolute pressure, once oxygen has diffused from the alveoli into the pulmonary blood it is normally transported through the plasma bound to hemoglobin, goes into physical solution according to physical law, diffuses into the tissues and is utilized for the majority of metabolic processes in man by the tissues for proper function and maintenance.

As noted in Chapter 1, tissue oxygen tensions vary throughout the system because of variations in both oxygen supply and demand, flow rate differences to various body tissues, and differences in diffusion distances between capillaries and tissues.

Oxygen carriage in the body is by (1) chemical combination with hemoglobin, and (2) simple solution in plasma. Under normal conditions the hemoglobin plays the greater role in oxygen transport. Blood leaving the heart does so with hemoglobin 95 per cent saturated and with nearly twenty volumes per cent oxygen carriage. However, oxygen in simple solution in the plasma, on the contrary, amounts only to 0.25 volume per cent but is important because it represents the gas immediately available to the tissues.

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By increasing the oxygen tension in the plasma the oxygen transfer rate through the capillary wall to the tissue fluid is increased.

Oxygen carriage by hemoglobin can be increased by only 5 per cent, but dissolved oxygen is capable of greater increase, since in obeying Henry's Law, the solubility of oxygen increases as the partial pressure of that gas increases. Under normal atmospheric conditions 0.25 volumes per cent of oxygen dissolves in plasma, while at two atmospheres 2.2 volumes per cent dissolves, and at three atmospheres the same volume of plasma will dissolve 4.2 volumes per cent.

This 16-fold oxygen increase in solution in plasma after inhalation of pure oxygen at three atmospheres pressure represents the physiologic rational for hyperbaric oxygen therapy which is based on the ability to force oxygen into physical solution in the extra-cellular fluid.

With tissue hypoxia occurring at one part of the body or another, there will, therefore, be an increased gradient between the depressed partial pressure in the anoxic tissue and the blood under OHP. Resulting will be an acceleration of the oxygen diffusion rate into the anoxic tissues. OHP, then, may be utilized for disease processes characterized by impaired oxygen-carrying capacity of the blood, as well as by markedly reduced peripheral arterial flow. The advantates of augmenting the oxygen stores of the body

are quickly seen under circumstances of peripheral ischemia, vascular occlusion and collapse, anaerobic infections, cardiac surgery, respiratory and pulmonary diffusion impairment, anemia as well as many chemical poisonings.

Oxygen toxicity has been well known since the great physiologist, J. S. Haldane, produced the decompression tables which revolutionized diving techniques during the 1890's.

Signs and symptoms of oxygen poisoning as discussed in Chapter IV, are extremely variable. Symptoms usually noted were those of twitching, dizziness, nausea, choking sensation, dyspnea and tremor. Convulsions, by EEG methods not unlike grand mal seizures, usually followed if the subject was not removed from the hyperbaric environment. The pulmonary effects seen in animals generally were not observed, probably because the central nervous system in man is so sensitive to oxygen toxicity that he must be removed from OHP prior to the onset of pulmonary change. Most recent research concerning oxygen poisoning seems to associate the enzymatic effects of high oxygen tension on tissue cells with oxygen toxicity although carbon dioxide retention and increased tissue acidity are certainly also involved.

Conclusion

1. <u>Oxygen Transport at One Atmosphere</u>. Oxygen carried in chemical combination with hemoglobin represents nearly 20 volumes per cent of oxygen at 95 per cent saturation. Oxygen in dissolved state amounts to only 0.25 volumes per cent but may be important because it represents that part of the oxygen immediately available to the tissues.

2. <u>Oxygen Transport under Conditions in Excess of One Atmosphere</u>. According to Henry's Law, dissolved oxygen increases with elevated partial pressure of the gas. Plasma at two atmospheres will dissolve 2.2 volumes per dent, while at three atmospheres pressure the same volume of plasma will dissolve 4.2 volumes per cent.

3. <u>Rate of Diffusion into Tissues</u>. The 16-fold increase in the volume of oxygen carried in solution at three atmospheres represents an increase in pO_2 in the blood which results in an increased pressure gradient at the capillary level. An acceleration of the oxygen diffusion rate results at normal as well as hypoxic tissue levels.

4. <u>Utilization of OHP.</u> Since tissue hypoxia is the physiologic rational for hyperbaric oxygen therapy, experimental work with OHP has centered around oxygen requirements of resting body, total circulatory standstill in dogs, infections with anaerobic bacteria, cerebrovascular and coronary artery occlusions in dogs,

carbon monoxide poisoning treatment and immersion experiments in mice. Clinical applications of OHP were reviewed including injury to main artery of a limb, peripheral vascular disease, carbon monoxide poisoning, barbiturate poisoning, radiation therapy for malignancy, and treatment of anaerobic infections. Utilization in surgical operations was initiated by Boerema and treatment of shock, vascular collapse, anoxia, overwhelming stress, and use with hypothermia have been studied by Sharp, Attar, Richards and associates.

5. Oxygen Tolerance. Until more extensive clinical research is carried out, many questions involving human oxygen tolerance will be left unanswered. However, at present it is generally recommended that the limits to pure oxygen tolerance time be held at three hours at three atmospheres pressure and to 36 hours of continuous administration at two atmospheres absolute pressure. Pure oxygen should presently not be administered above three atmospheres pressure.

6. Oxygen Toxicity. Signs and symptoms of oxygen toxicity were found to vary according to authors but the most frequent findings represented were twitching, dizziness, nausea, choking, dyspnea and tremor followed by convulsions. Oxygen was found to produce toxicity either acutely or chronically. Acute changes responded to removal from OHP conditions. Chronic effects involved pulmonary changes especially in animals.

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The factors involved in oxygen poisoning were notes as (1) increased tissue acidity, (2) carbon dioxide retention, (3) enzymatic inactivation, (4) hormonal involvement, and (5) direct central nervous system effects. Recent studies seemed to indicate that the most probable theory to account for oxygen toxicity was the enzymatic effects of high pO_2 on tissue cells, although the other above factors are undoubtedly also involved.

7. <u>Future Experimental Projects</u>. Present research has opened up an entirely new field of treatment for a multitude of medical and surgical problems. Hyperbaric oxygen therapy can be used whenever hypoxia is involved in a disease process. Authors such as van Zyl and Maartens have suggested new uses in shock (olegemic, toxemic and irreversible), vascular occlusions and acute respiratory insufficiency. Other possible uses might include utilization in severe cranial injuries, in tissue transplantation, in obstetrics, hepatic disease and cardiac arrest.

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