RESPIRATORY FAILURE IN PULMONARY ANOXAEMIA

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INTRODUCTION

INTRODUCTION

(a) The Ventilation in Pulmonary Hypoxaemia

The role played by chemical constituents of the blood in controlling pulmonary ventilation has been the subject of numerous investigations for over one hundred years since Kussmaul and Tenner in 1857 showed that a chemical stimulus was involved by experiments in which a large increase in ventilation was produced by breathing low oxygen mixtures and by rebreathing from a bag.

The earliest theory which attempted to account for these observations was put forward by Rosenthal in 1862, and again in 1882. He suggested that the oxygen content of the blood determined the ventilatory response. He discounted any place for CO_2 in the regulation of ventilation on the basis of experiments showing that inhalation of high concentrations of CO_2 (20 to 30%) did not affect the breathing.

Pflüger had shown in 1868, however, that both excess of CO_2 provided it was not too great, and oxygen lack stimulated the ventilation.

In a series of brilliant cross circulation experiments on dogs, Frédéricq (1901) appeared to confirm the then prevalent assumption that the influence of these factors was a direct one upon the brain, but the Heymans (1927), father and son, were later to show that there were chemosensitive areas of the aortic arch and carotid sinus capable of responding to alterations in the concentrations of CO_2 and oxygen in the perfusate, and

that these receptors transmitted impulses to the respiratory centres by the vagus nerves. Further studies by Heymans and Riglant (1933) and v. Euler, Liljestrand and Zotterman (1939) showed in anaesthetised cats that the carotid sinus nerves were in a state of continuous tonic excitation. When the oxygen saturation of the blood fell even slightly below the normal of 96% this chemoreceptor discharge of nervous impulses increased.

Gesell, Lapides and Levin showed in 1940 that blocking these sinus nerve impulses in animals by the application of cold to the nerves depressed the ventilation when the animals were breathing room air at rest. These observations were confirmed by Marshall and Rosenfeld (1936).

All of these workers agreed that hypoxaemia was more effective than CO_2 excess in increasing the peripheral chemoreceptor activity, whereas CO_2 excess in the arterial blood was the major factor in stimulating the central respiratory control mechanism.

The relative importance of the central and peripheral mechanisms in maintaining the pulmonary ventilation under varying conditions was estimated in a quantitative way by Gesell et al. (v.s.) using the cold block technique. The part played by the peripheral chemoreceptors in controlling the ventilation in response to a fixed degree of hypoxaemia varied between 0 and 100% according to the concentration of CO_2 which the animals breathed. The greater the amount of CO_2 in the inspirate the less was the effect on

the ventilation of blocking the nerves. When 5 or 6% CO_2 was inspired nerve blocking had no effect, showing that in these circumstances respiration was 100% controlled by a central mechanism which was presumably insensitive to hypoxaemia.

Bjurstedt (1946) and Gernandt (1946) confirmed these observations and found that the greater the acidity of the blood, the less was the effect upon respiration of blocking the sinus nerves. Bjurstedt also showed that in the early stages of acute hypoxia, the peripheral chemoreceptors played a large part in controlling the respiration; but this part gradually decreased with time until, over a period of six to ten hours, it became slight as the pH of the blood fell towards normal. The maximum hypoxaemic stimulus to respiration coincided with the time at which the pH was most raised due to CO_2 washout. The mechanism of the compensatory decrease in plasma bicarbonate which resulted in the return of the blood pH towards normal was assumed to be a renal one due to diminished tubular reabsorption of bicarbonate. This renal compensatory phenomenon had been studied by Haldane (J.S.), Kellas and Kennaway in 1919 and also by Haldane (J.B.S.) in 1921. They observed that the initial alkalinity of the blood upon acute exposure to hypoxia gradually decreased with time, the pH of the blood becoming less upon continued exposure. Y. Henderson in studying the same process in 1919 showed that the "hypocapnia was followed by a hypocarbia."

Winterstein (1956) noted that hypoxaemic human

subjects given 100% oxygen to breath in the early stages of the period of oxygen lack reacted by becoming apnoeic. If the anoxaemia was continued over a longer time the duration of apnoea due to breathing oxygen decreased.

All of these observations point to a direct relationship between the magnitude of the hypoxaemic stimulus to respiration and the pH of the blood. It would appear to be reasonable to test the implication that hypoxaemic emphysematous subjects with marked CO_2 retention and lowered blood pH should show little or no immediate decrease in pulmonary ventilation on breathing high concentrations of oxygen.

(b) Altered Ventilatory Responses to Chemical Stimuli.

(i) Emphysema

The increased anatomical and physiological dead space of the respiratory system which results from the structural abnormalities of the lung in chronic bronchitis and emphysema, is responsible for a deficient gas exchange between the lungs and the blood. This is corrected, in the early stage of the disease process, by an increase in the minute ventilation. As the structural defects of the lungs progress in severity the work of breathing, at first on exercise and latterly even at rest, becomes excessive if a normal blood gas status is to be maintained. Some arterial blood oxygen deficiency and CO_2 retention then appears during exercise and later persists at rest.

This process, described by Donald in 1953 and Cohn, Carroll and Riley in 1954, indicates that an adaptation occurs which allows an increase in CO_2 tension to occur in the blood without too great an alteration in the reaction of the blood. This is achieved by a renal tubular reabsorption of increased amounts of bicarbonate as a direct function of the increased arterial CO_2 tension as described by Brazeau & Gilman (1953).

Donald and Christie (1949) showed that there was a diminished ventilatory response to the breathing of CO_2 mixtures in subjects with emphysema and CO_2 retention. There was a significant negative correlation in a group of these subjects between the amount of the alkali reserve and the ventilatory response to CO_2. They suggested that

many of these individuals would have shown a normal response if the period of observation had been sufficiently prolonged.

This diminished responsiveness to CO_2 was first demonstrated in 1912, by a German medical student (Reinhardt) and confirmed by Scott in 1920, who suggested that the increased buffering power of the blood and tissue fluids as a result of the bicarbonate retention, might account for the diminished response to added CO_2.

Since then many authors have considered this hypothesis in the light of more recent investigations. Schneider (1931) thought it adequate to explain the observations in this and in other conditions of altered ventilatory sensitivity to chemical stimuli; since in a condition where the buffering power of the blood is altered, the pH change produced by a given increment of CO_2 would vary accordingly. (See Fig. I).

Tenney (1954) thought that it was clear that a large part of the decreased response to CO_2 in emphysema was a simple physico-chemical consequence of an increase in the buffer base of the blood in that condition, but pointed out that it was not certain that this was the sole mechanism.

Prime and Westlake (1954) suggested that the increase in the blood buffers could not be the whole explanation of the decreased CO_2 sensitivity in Chronic CO_2 retention, because of the independant effects of hydrogen ion concentration and CO_2 on the respiratory

centre as demonstrated by Gray (1950). No explanation was offered for this statement.

A more important objection by Prime and Westlake (v.s.) to the idea that varying buffering capacity of the blood might influence, in a major way, the ventilatory response to CO_2 and hydrogen ion, is based on their calculation that the total effective respiratory stimulus is reduced by only 7% when the formulae derived from Gray's multiple factor theory of respiratory control (1950) are applied to the blood gas figures found in a subject with emphysema and a plasma CO_2 capacity of 80 vols.%. This theoretical decrease in ventilatory response to CO_2 was less than that actually observed in such a case.

It is possible that the discrepancy might be accounted for if the following points are taken into consideration:-

(A) There are grounds, to be discussed later in this introduction, for the belief that a factor in respiratory control is not included in Gray's formulae. This is the effect upon respiration of a varying blood level of fixed acids.

(B) The apparent sensitivity of the respiratory control mechanism is decreased when oxygen enriched CO_2 mixtures as opposed to air mixtures are breathed by subjects who are chronically anoxaemic. This observation of Brodovsky, Macdonnel and Cherniack (1960)

(B contd.)

is relevant to the results of Prime and Westlake (v.s.) who used CO_2 and oxygen mixtures. Since in many cases of chronic anoxaemia a mixture of CO_2 in air will increase the ventilation sufficiently to achieve normal oxygen tensions in the arterial blood, the further depressing effect of CO_2 in oxygen mixtures must depend in some way upon the greatly increased oxygen tensions which will be produced.

Alexander, West, Wood and Richards (1955) showed a diminished response to CO_2 of the ventilation of six patients with emphysema and cor pulmonale, and three with emphysema alone. Two subjects with chronic metabolic alkalosis showed the same phenomenon. An increase in respiratory sensitivity was noted in three patients with chronic anoxaemia due to cyanotic congenital heart disease, and in three cases of chronic metabolic acidosis.

They concluded that the respiratory centre became altered in some way so that it's sensitivity to CO_2 varied in these conditions.

(ii) Experimental CO_2 retention.

Normal subjects who are adapted to a raised concentration of CO_2 in air which is breathed for a period of two to three days show a diminished ventilatory response to CO_2 as shown by Schäfer (1949) and Chapin, Otis and Rahn (1955).

Even normal subjects without any preparation, can be assigned to one of two groups according to their ventilatory response to breathing CO_2 mixtures, as noted by Schaeffer (1958). The group showing a higher response had a significantly lower arterial mean CO_2 tension than the group showing a lower response to breathing CO_2 mixtures. It is of interest from a consideration of the results of Gesell (1940) and Bjurstedt (1946) noted earlier in this discussion, that the high ventilatory response group, who tended to have lower arterial CO_2 tensions, also showed a greater ventilatory sensitivity to hypoxia than those with higher arterial CO_2 tensions and less response to CO_2 breathing.

Some recent work of Cherniack and Snidal (1956) is also of great interest in its implications for an understanding of the respiratory responses in subjects with emphysema. These authors found that artificial obstruction to the respiration of normal subjects resulted in a fall in the ventilatory response to CO_2. This simulated the diminished response to CO_2 observed in patients with obstructive airway disease. They concluded that the lowered response to CO_2 of patients with emphysema

might be related in some way to the increased work of breathing required to overcome bronchial obstruction. The diminished ventilatory response to CO_2 of normal subjects with airway obstruction was confirmed by Tobakin and Hanson (1960).

(iii) High Altitude Studies.

The ventilatory adaptations of altitude acclimatised subjects have been studied in great detail.

Fitzgerald showed in 1914, that the alveolar CO_2 tension falls regularly with increase in altitude. The experiments of Barcroft (1911) in Teneriffe seemed to confirm the prevalent assumption of that period, that there was a lactic acidaemia in response to the hypoxaemia of high altitude. Barcroft explained his findings of an oxygen dissociation curve of the same shape and position as that found at sea level, as a balancing effect of a shift of the curve to the right due to lactic acidaemia and a shift to the left due to CO_2 washout.

It has since been amply confirmed that the alkali reserve of the blood is diminished regularly with increasing altitude exposure over a period of time, as noted by Haldane, Kellas and Kennaway (1919) and Henderson and Haggard (1919) (1920), and confirmed by Dill, Talbottand Consolazio (1937). The cause of this diminution in alkali reserve in response to the chronic anoxaemia of high altitude seems to be adequately explained by the known renal tubular response to lowered arterial CO_2 tensions which consists of a decreased reabsorption of base bound bicarbonate.

There has also been much investigation of the apparently related phenomenon of increased ventilatory sensitivity of altitude acclimatised individuals. Winterstein (1956) suggested that the enhanced response of such subjects to the breathing of CO_2 in oxygen mixtures

was a simple consequence of the reduction in buffer base of the blood. Recently Rahn, Bahnson, Muxworthy and Hagan (1953) agreed with this view but thought that this could not be the entire explanation since Stroud (1953) had noted that when the alkali reserve was reduced 20% at sea level by the ingestion of ammonium chloride, the breathholding time was only slightly reduced from the normal. The difference between the resting alveolar CO_2 tension and that at the breaking point of breath-holding being the same as before ammonium chloride acidosis was induced. During altitude adaptation, however, Rahn (v.s.) had found a large reduction in the breathholding time (after breathing oxygen for some time in order to eliminate any hypoxic ventilatory stimulus through the peripheral chemoreceptors) and a considerable reduction in the alveolar CO_2 tension difference between resting and breaking point. They concluded that there must be an altered sensitivity of the respiratory centres at altitude which did not exist after ammonium chloride ingestion. These findings agreed with those of Nielsen and Smith (1951) who studied the same problem in a different way.

The conclusions of these, and most other investigators into the altered ventilatory responses of altitude acclimatised subjects, e.g. Kellog, Pace, Archibald and Vaughan (1957), are the same as those of the authors whose work in the field of chronic CO_2 retention has been reviewed earlier in this Introduction; namely that while there is a certain amount of support for the idea that altering blood buffers might marginally

influence the respiratory response to chemical stimuli, the major factor was the state of sensitivity of the respiratory centres.

(iv) Metabolic acidosis.

Most of the authors already mentioned who investigated states of altered respiratory sensitivity, depended heavily on the work of Gray (1950) who postulated a multiple control of the ventilation by changes in arterial CO_2 and O_2 tensions and pH of the blood: these factors being additive in their effect. Winters, Lowden and Ordway (1958) in a study of the arterial CO_2 tension of blood during the recovery phase from metabolic acidosis, pointed out that Gray's hypothesis appeared inapplicable since in these circumstances the minute ventilation is markedly increased but all of the above three factors are altered so as to theoretically decrease the respiration. They suggested that a raised level of circulating fixed acid in the blood acted as a ventilatory stimulus. In support of this, they quoted the work of Brown, Hemingway and Visscher (1950) who found, in the recovery phase from prolonged passive hyperventilation, an increase in the ventilatory sensitivity to CO_2 in similar circumstances of hypocapnia and alkalosis with a normal arterial oxygen tension. Winters et al. (v.s.) postulated that the increase in ventilation observed in both of the above circumstances might be explained on the basis of a reduced buffering capacity of the blood leading to a similar reduction in the intracellular fluid buffers of the respiratory centres. This reduced buffering capacity

within the centres would tend to lag behind that of the blood in the recovery period, because of the difference in diffusability through the cell membrane of CO_2 and bicarbonate, the latter tending to be slower. When the blood buffers had returned to normal levels, those within the respiratory neurones would be still lowered. In support of this argument, Brown (1950) had found a reduced buffering capacity of the homogenates of guinea pig brains, when these animals had hyperventilated on exposure to hypoxia. The magnitude of the change was such that a real change in the buffer content of the intracellular fluids had probably occured.

It may be pertinant at this point to note that Leusen (1954) and Winterstein and Göklan (1953) have shown the pH of the cerebro-spinal fluid to vary directly with that of the blood in respiratory disturbances of acid-base equilibrium, but inversely in acute metabolic upsets; implying that CO_2 permeates freely into the C.S.F. but bicarbonate does not.

(v) Muscular exercise.

The increase in pulmonary ventilation associated with muscular exercise has been a subject for investigation since Geppert and Zuntz showed, in 1888, that some substance was released from exercising muscles into the bloodstream to stimulate respiration. They did this by tetanising the hind limbs of an animal after section of the spinal cord. Walter had shown in 1877 that the breathing was increased in animals poisoned with acids, and it was presumed by the above authors that the respiratory stimulating substance released from the muscles was also an acid.

More recently Laubender and Mertz (1941) found, during and after convulsions induced in dogs by cardiazole, that there was a lowering of the CO_2 dissociation curve of the blood comparable to that seen after injection into the bloodstream of large doses of hydrochloric acid.

Lambertsen, Owen, Wendel, Stroud, Lurie, Lockner, and Clark showed, in 1959, a very significant correlation between the ventilatory response to exercise and changes in arterial levels of fixed acids in normal subjects. Oxygen administration during exercise lowered the ventilation, restored arterial pH and CO_2 tension towards resting levels and decreased the concentration of fixed acid in the blood. It was considered that the data showed a closer correlation between changes in pulmonary ventilation and fixed acid levels than had previously been found. Comroe (1944) and Grodins (1950) had reviewed the literature on the ventilatory adjustment to exercise and

concluded that this had not been fully explained in spite of a great deal of work. In many of the papers reviewed by Comroe and Grodins (e.g. Ammussen & Nielsen 1947 and v. Euler and Liljestrand 1946) the existance of a humoral agent derived from the exercising muscles which acted as a respiratory stimulus, was postulated but never convincingly demonstrated. It was generally agreed that lactic acid did not begin to accumulate in the blood until exercise of at least moderate severity was performed (corresponding to an oxygen consumption of 1.5 to 2.0 l/minute).

Lambertsen et al. (v.s.) quoted the recent work of Huckabee (1958) who showed elevations of blood lactate and pyruvate during the mildest grades of exercise, and noted that adrenaline infusion (Himwich 1931), glucose injections (Bueding and Goldfarb 1943), and changes in acid-base balance were all known to increase the blood lactate level, suggesting that the interevention of such factors might result in a measurable increase in blood lactate in mild and moderate work. Huckabee had found that the increases of lactate in the blood even in mild work, occurred in less than one minute from the start of exercise. He also showed that lower values for lactate concentration were found in arm venous blood than in mixed venous or arterial blood and suggested that this might account for the failure of some previous workers to detect changes in the blood in work of mild degree, since most of these investigations were concerned with arm venous blood.

The decrease in ventilation which occurs when a subject changes from air to oxygen breathing while exercising at a steady rate, as noted by Lambertsen et al (v.s.), had been known before (Asmussen & Nielsen 1947 and Bannister et al. 1954) and there was much discussion about the possible causes, some authors considering that a hypoxaemic stimulus was being inhibited, (Bannister, Cunningham and Douglas (1954), others thought that an unknown respiratory stimulus of a chemical nature from the exercising muscles, was depressed by increased oxygenation of the arterial blood, (Asmussen and Nielsen (1947 & 1958). Lambertsen's results are therefore of great interest in view of the support which they give for the idea that changes in fixed acid levels of the blood may influence pulmonary ventilation in exercise and presumably in other conditions in which an excess of these substances can be shown.

(c) Metabolic Acidosis in Pulmonary Anoxaemia as a Possible Factor in Respiratory Control.

Boycott and Haldane, in 1908, formulated the hypothesis that the increase in ventilation observed in subjects exposed to hypoxia, was the result of a lactic acidosis due to a process of anaerobic glycolysis in the tissues. This idea of an 'asphyxial acidosis' was later rejected by many workers because of a failure to demonstrate an increase in blood lactate in acute hypoxia.

Kamei (1931), Theil (1933) and Hashimoto (1936) found increased lactate in the blood in conditions of asphyxia but this did not go far to support the argument for a metabolic acidosis in milder degrees of oxygen lack.

Gesell, Krueger, Gorham and Bernthal showed, however, (1930) that in cases where the hyperventilation of oxygen lack was artificially hampered, a considerable increase in blood lactic acid occurred. This observation is of interest because of the implication arising from it for the study of emphysematous subjects with anoxaemia.

Although it seems clear that in normal subjects at rest who are made hypoxaemic, there is only a small increase in blood lactate (See - Bock, Dill & Edwards (1932) Jervell (1928) and Friedemann, Haugen & Kmieciak (1945)), this may not be the case in patients with emphysema. In this condition there are likely to be more than one of the factors operating, which are known to be associated with raised blood lactate levels.

These are:-

A. Anoxaemia, sometimes of extreme severity. This degree of oxygen lack is known to be a factor in raising lactate levels in the blood (See - Koehler, Behneman, Bessell & Loevenhart (1925) and Macleod (1921).

B. Increased muscular effort associated with increased work of breathing. The role of muscular exercise in producing raised lactate concentrations has already been reviewed in this Introduction.

C. Circulatory failure, which occurs commonly in the cor pulmonale syndrome, has been reported in association with high blood lactate levels by many authors (e.g. Lewis, Ryffel, Wolf, Cotton and Barcroft 1913), presumably on a basis of tissue anoxia in this condition.

D. It has been suggested that this last factor might be augmented in it's effect by an element of delayed metabolism of lactate in the liver due to chronic congestive damage to that organ (Altschule 1950). Certainly liver damage is known to be associated with high blood lactate levels (See Schumacher, 1928 Adler and Lange, 1927; Beckmann 1929 Snell and Roth 1932).

In some of these conditions the effects of breathing high concentrations of oxygen have been studied; and this results in a decrease in blood lactate -

A. In hypoxaemia (Huckabee 1958).

B. In conditions of increased muscular exertion

B.(contd.) (Hewlett, Barnett and Lewis 1926-27, Lambertsen et al. 1959).

C. In patients with congestive cardiac failure (Barach 1931, Jervell 1928).

The highest values for blood lactic acid in the literature are those found in studies dealing with severe grades of exercise. Laug (1934) obtained figures of 16.1 to 19.3 mM./litre shortly after a 440 yard run by untrained subjects. In such a case, either the supply of oxygen to the tissues is inadequate or the rate of formation by the muscles exceeds the maximum possible rate of removal of lactate from the blood by the liver. It is likely that both of these possibilities are operating. A relative deficiency of oxygen supply in the arterial blood would therefore act on both the muscles and the liver to increase the blood lactic acid. This argument has implications for the emphysematous situation where hypoxaemia exists and possibly some liver damage also.

Some recent work of Brown (1960) is of interest in this connection. He found a profound lowering of blood pH in dogs with severe CO_2 retention, the arterial CO_2 tension being 100 mm.Hg. approx. This acidaemia was partly due to the CO_2 retention itself, but also due to a co-existing metabolic acidosis with a bicarbonate "deficit" in the blood of 9.0 mM/Litre. This combined respiratory and metabolic acidosis produced a blood pH of 7.09. He pointed out that this bicarbonate deficit was precisely opposite to the change required to compensate for

the respiratory acidosis. The factors operating to produce this metabolic acidosis were not found. Earlier work of Miller, Brown and Vasco (1950) had shown no increase in the blood lactate of dogs under similar conditions.

Beecher and Murphy (1950) found a similar bicarbonate deficit, or metabolic acidosis, in patients undergoing thoracic surgery, of 9.0 mM/Litre.

(d) The Problem of Respiratory Failure in Pulmonary Emphysema.

Barach made the first observations on the narcotic effect of oxygen therapy on patients with hypercapnia due to emphysema in 1937. He thought that this state of stupor was temporary and reversible by continuing oxygen breathing (1941). It has since been recognised that in many cases the condition will progress unless the administration of oxygen is stopped or other measures are undertaken to stimulate the respiration, e.g. the use of chemical stimulants or mechanically assisted ventilation of the lungs.

It is now generally agreed that the essential features of this syndrome can occur in many different conditions where there is an increase in the blood and tissue CO_2 tensions to a level at which CO_2 itself acts as a narcotic. (See Donald 1949 & 1953, Hickam et al. 1952, Bickerman and Beck 1952, Lovejoy et al. 1954, Simpson 1954, Westlake et al. 1955, Sieker and Hickam 1956, Cohn et al. 1954, Stone et al. 1953).

Sieker and Hickam (1956) reviewed the causes of CO_2 narcosis, which include respiratory infection (Westlake, 1954) congestive cardiac failure in patients with cor pulmonale (Harvey et al. 1951 & 1953), narcotic drugs (Wilson et al. 1954) mechanical impairment of ventilation e.g. in kyphoscoliosis (Bergofsky et al. 1959). In this respect, the action of oxygen rich breathing mixtures is similar to that of the narcotic drugs, i. e. it acts as a respiratory depressant. An important difference between

them is that narcotics invariably produce respiratory depression in some degree, whereas this effect of oxygen breathing is only seen clinically in conditions where the pulmonary ventilation is already reduced and there is a certain amount of pre-existing CO_2 retention.

Comroe and Dripps (1947 & 1950) showed that normal subjects at sea level, respond to breathing 100% oxygen by a slight increase in pulmonary ventilation. Lambertsen, Kough, Cooper, Emmel, Loeschcke and Schmidt (1953) found a significant rise in cerebral venous CO_2 tensions in normal subjects upon breathing oxygen at one atmosphere of pressure. They concluded that this finding supported the hypothesis, put forward by previous investigators (Heck and Loeschcke 1942) that the slight increase in pulmonary ventilation was due to elevation of tissue CO_2 tensions, including those of the respiratory centres, because of increased oxyhaemoglobin levels in the blood, i.e. as a consequence of the well known 'Haldane' effect of the reduced CO_2 carrying power of oxyhaemoglobin as compared to reduced haemoglobin (Christiansen et al.1914). The action of oxyhaemoglobin in causing this diminished carrying capacity of the blood for CO_2 is due to it being less alkaline than reduced haemoglobin. The effect of giving high concentrations of oxygen in the respired air is therefore the same, in the effect produced on the CO_2 dissociation curve, as the addition of hydrogen ions to the blood; (L. J. Henderson 1928), the CO_2 dissociation curve becoming lower and less steep in its slope (see Fig. 2).

AIMS AND METHODS

OF THE PRESENT STUDY.

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The depressant effect of oxygen breathing upon the respiration of emphysematous subjects has been generally assumed to be a result of a decrease in the peripheral chemoreceptor activity. It was suggested that this anoxaemic stimulus to the chemoreceptors of the aortic arch and carotid sinuses was of great importance in maintaining the ventilation, the respiratory centres having become, in some way insensitive to CO_2 and hydrogen ions.

Since there is good reason for doubting the importance of the hypoxaemic stimulus through the peripheral chemoreceptors in maintaining ventilation in subjects with CO_2 retention and respiratory acidosis, as indicated in the Introduction, and since there is evidence to suggest that the diminished ventilatory response to CO_2 observed in such subjects might be a result of an increase in the buffering power of the blood, it seems that an experimental approach to this problem of the hypoxic drive in emphysema is called for.

The effects of 100% oxygen breathing were studied in a group of patients who were routinely under treatment in the general medical wards for chronic bronchitis and emphysema; many of them were suffering from exacerbations of respiratory infection but some were chosen for study as representing milder degrees of severity of respiratory failure.

Respiratory failure or insufficiency, has been defined by Woolmer (1956) as that condition which exists

"when gas exchange between the lungs and the blood falls below that between the tissues and the blood: when external respiration cannot keep pace with internal respiration." This concept of a continuum of respiratory failure from the most severe, to conditions which merge into the normal gas exchange state was felt to be suitable for an enquiry such as the present one. The variation in blood gas measurements and acid-base values observed in such a group of subjects under the influence of differing degrees of oxygenation might throw some light on the underlying causes of respiratory failure arising spontaneously and under oxygen therapy in pulmonary emphysema.

The problems arising from a review of previous work seemed to fall into three main groups. These therefore, provide the headings under which the results are presented:-

A. The hypoxic drive in emphysema.

B. The metabolic acidosis of anoxaemia.

C. Variations in the carbon dioxide dissociation curves of blood in emphysema.

This outline of the methods used in investigating these three major problems is also subdivided according to these headings.

(a) The Hypoxic Drive in Emphysema.

The current hypothesis to explain the ventilatory depression produced by oxygen breathing in subjects with CO_2 retention and anoxaemia, as outlined in the introduction, supposes a 'hypoxic drive', or stimulus to the respiration through the peripheral chemoreceptors, as a major factor in control of the respiration in these conditions. There

appear to have been no attempts to verify this suggestion by actually determining the ventilatory depression induced by producing full oxygenation of the blood in a series of such subjects. This was the first line of enquiry adopted in the present study.

A group of subjects with CO_2 retention and anoxaemia of widely varying severity were investigated. The conditions were standardised as far as possible, in that all measurements and specimens were taken while the subjects were at rest lying down in bed or on a couch and after intervals of 10 to 20 minutes to ensure steady state conditions of breathing and metabolism.

It was found that measurement of the pulmonary ventilation was often not possible in those subjects who were severely disabled, as they were usually intolerant of the mouthpieces and valves required, possibly because of the extra resistance to breathing these caused. In as many studies as possible, however, the minute ventilation was recorded while breathing air at rest over a period of 15 to 20 minutes, with a Tissot spirometer until the readings were steady within limits of 0.5 litres/minute. The expired air was then collected for a further three minutes; the volume being recorded on a moving constant speed drum.

During the collection of the expired air over this three minute period blood was withdrawn under anaerobic conditions from an indwelling needle in the brachial artery, into a lubricated syringe, the dead space of which was filled with heparin solution. Ten or twelve mls. of blood were usually sufficient for this experiment.

This was stored in ice until blood gas determinations could be made. The delay in making these estimations was never greater than two hours from the time of obtaining the sample.

Before undertaking the blood gas measurements and immediately the collection of expired air was finished, a sample of gas was withdrawn from the Tissot into a rubber bag for estimation of the CO_2 content at the earliest opportunity.

Unknown to the subject, 100% oxygen was substituted for the room air by changing over the inlet tube of the breathing valve from one Douglas bag to another. Again, a steady level of breathing was the signal for the collection of expired air and arterial blood. In this case however the period of oxygen breathing was restricted to 10 minutes; the specimens being collected during the last three minutes.

The above procedure was modified for those subjects who could not tolerate the mouthpiece and breathing equipment. In this case, arterial blood samples were withdrawn, taking care to ensure steady state conditions, immediately before and after 10 minutes of 100% oxygen breathing as before. Care was taken to adjust the disposable plastic oxygen masks which were used in this group of studies so that gross leaks were avoided. In two of the subjects studied, full arterial oxygen saturation was not achieved by this means, but since the observer only required a knowledge

of the increment in arterial blood oxygen tension to compare with other values, this did not invalidate the results.

Changes in arterial blood CO_2 tension were used in this second group of subjects in place of the actual ventilation measurements obtained in the less disabled subjects. Since there was no reason to suppose that the increment of CO_2 tension produced by the change from breathing air to oxygen was due to any other factor than a decrease in ventilation, this procedure seemed justified. The change in CO_2 tension was in fact used in all the statistical work as an index of altered alveolar ventilation.

Calculations, using the data provided by the specimens of blood and expired air after appropriate manipulation, were made to examine the role of the hypoxaemic factor in the control of the respiration of these subjects.

(b) The Metabolic Acidosis of Anoxaemia.

As indicated in the Introduction, there is reason to suspect that emphysematous subjects with severe anoxaemia might show an increase above the normal blood level of fixed acids. In order to test this hypothesis in a qualitative fashion, the CO_2 dissociation curves obtained from such subjects's arterial blood were examined before, and at varying intervals during, the breathing of oxygen rich mixtures.

This procedure was intended primarily as a pilot study before arrangements were made to measure blood lactate levels. It was assumed that an increase in height of the CO_2 dissociation curve under the influence of full oxygenation, would indicate roughly a corresponding decrease in the blood level of fixed acid.

The subjects were resting in bed or on a couch and breathing room air. No oxygen therapy had been given to these patients within the previous two hours before the study. An exact repetition of the conditions of the previous experiment followed, blood being withdrawn through an indwelling needle in the brachial artery while the subject was breathing air and then at varying intervals of time when breathing oxygen through a plastic disposable face mask.

In this case, however, two syringefulls of blood were taken at each sampling. One syringe of blood (10 mls.) was used to determine the CO_2 and oxygen tensions of that subject's arterial blood while breathing air. Plasma CO_2

content and oxygen saturation were also estimated from that sample. The other of the pair of samples was used to construct a CO_2 dissociation curve of the blood by the following method.

Into each of two glass tonometers, with stop-cocks at each end, 5 mls. of blood were placed. The tonometers were then filled with a mixture of air and a known tension of CO_2. The CO_2 contents in the tonometers were chosen to give two reasonably separate points when the resulting blood CO_2 tensions were plotted as a CO_2 dissociation curve i.e. about 40 and 80 mm. Hg. tension.

The tonometers were then mechanically revolved in a water bath at a temperature of 37.5°C. for 40 minutes, and the CO_2 tension of the blood, together with the Plasma CO_2 content, was then measured. In this way a dissociation curve for the CO_2 of that blood could be drawn with reasonable accuracy between the two points obtained on a plot of tension against content.

The most serious error in such an equilibration technique is the displacement of the dissociation curve so obtained, due to the in vitro formation of lactate in the blood during equilibration. In an attempt to minimise this factor as an interference in the results, the time of equilibration was kept strictly the same for all samples treated in this way.

This procedure was simplified when dealing with the blood samples taken during oxygen breathing. It was felt in this case that one specimen treated in the above

fashion would give one point on the plot of tension against content of CO_2 and this would reveal, by comparison with a point of the same tension on the dissociation curve previously obtained from the air breathing specimens, whether there had been any displacement of the curve under the influence of oxygen breathing. This later sample, taken during oxygen breathing, was immersed in a water bath before measuring, as the earlier samples were. As will be seen in the results to be presented later, this preliminary experiment indicated that there might be a considerable increase above normal in the amounts of circulating fixed acid in subjects with severe anoxaemia.

A quantitative estimation of the total fixed acid in the blood is technically difficult but an index of this can be obtained from lactic acid measurements. A series of measurements of blood lactate were made in anoxaemic emphysematous patients at rest. None of these had breathed oxygen rich mixtures for at least two hours at the time of sampling. The great majority were investigated before any oxygen therapy had been started.

In a smaller number of subjects the blood lactate levels were again estimated from blood obtained by an indwelling needle in the brachial artery, 10 mimutes after starting to breath 100% oxygen from a face mask, taking the same precautions as previously described to ensure absolute resting conditions. From the same samples of blood the CO_2 tensions and contents, together with the

oxygen saturations were measured. These estimations, including the blood lactate concentrations, were repeated on further samples of arterial blood withdrawn after more prolonged oxygen breathing. A comparison could then be made between the decreased blood lactate levels while breathing oxygen and the change in CO_2 tensions observed, using the latter as indications of the changes in pulmonary ventilation.

In order to be sure that the changes in arterial CO_2 tensions used in this comparison were not due to changes in the oxygenation of the blood affecting a peripheral chemoreceptor stimulus to the ventilation, it was necessary to exclude all studies from this comparison in which such changes in arterial oxygenation had occurred. This requirement made it difficult to obtain a larger number of suitable studies, since in many cases the arterial oxygen saturation continued to rise for some time after beginning oxygen breathing. Any change in arterial CO_2 tension demonstrated in these conditions might be attributed to this improving oxygenation of the blood acting upon the peripheral chemoreceptors to depress the respiration. A sufficient number of studies were obtained, in which the arterial oxygen saturation remained unchanged throughout, to enable certain conclusions to be drawn.

(c) Variations in the Carbon Dioxide Dissociation Curves of the Blood in Emphysema.

Fig. 2 from Haldane and Priestley's work (1935) shows CO_2 dissociation curves of fully oxygenated and reduced blood. A point corresponding to a tension of 40 mm.Hg. and a content of 52 vols.% on the lower curve (Oxygenated blood) is taken to represent the normal resting arterial blood CO_2 measurements. The figure shows lines connecting this point with points on the upper curve (reduced blood) which represent the venous blood CO_2 measurements predicted at varying respiratory quotient (R.Q.) levels, assuming the venous blood to be completely reduced of oxygen. Since venous blood is normally only 20% desaturated (16 vol.% oxygen content, approx.), the true venous point will fall 1/5 of the way up the appropriate R.Q. line from the arterial point. At an R.Q. of 0.8, this would indicate a venous CO_2 tension of 46 mm. Hg. and content of 56 vols.%. There would then be a venous arterial CO_2 tension difference of 6 mm.Hg.

It was noted in the Introduction to this thesis that the blood CO_2 dissociation curves vary in height in different conditions affecting the blood acid base balance. In chronic CO_2 retention, the curves are elevated according to the increase in total CO_2 content of the blood. The slope of the curves is mainly a function of the haemoglobin content of the blood; showing less slope in anemia and greater slope in polycythaemia, as explained by Peters and Van Slyke (1931). L. J. Henderson in a review of previous

studies of CO_2 dissociation curves (1928) noted that increase in CO_2 content of the blood is also associated with increase in slope.

Both of these factors, i.e. increase in haemoglobin content and increase in CO_2 content are a feature of chronic CO_2 retention and anoxaemia such as occurs in emphysema.

From Fig. 2, it can be seen that any increase in slope of the curves will result in a counter-clockwise rotation of the R.Q. lines about the arterial CO_2 point. The venous arterial CO_2 tension difference might therefore be expected to decrease directly with increase in CO_2 content of the blood and this decrease in CO_2 tension difference should be greater, for any given amount of CO_2 retention, in subjects with polycythaemia than in those with normal haemoglobin levels. (See also Fig. 12).

Lambertsen et al., in the study of respiratory control at rest and exercise in normal subjects breathing air and then oxygen, already mentioned (1959), suggest that blood gas measurements obtained from the internal jugular venous blood are a more reliable index of the acid base balance within the tissues of the respiratory centres than measurements obtained from arterial blood, since this is dependant for it's blood gas contents on the level of pulmonary ventilation. They also point out that figures of blood gas content of the internal jugular blood represent conditions in a large mass of nervous tissue of which the respiratory centres are a very small part. In general however, trends in these figures obtained from the internal

jugulars should indicate similar trends within the centres. Assuming this to be true, it is interesting to note that Lambertsen, Kough, Cooper, Emmel, Loeschcke and Schmidt in an earlier paper (1953 (a)) reported a significant increase in the CO_2 tension of internal jugular venous blood of normal subjects changing over from breathing air to oxygen at sea level. This was attributed by these authors to the decreased CO_2 carrying power of the relatively better oxygenated venous blood when breathing oxygen, and it was suggested that the slight rise in tissue CO_2 tension which was thus indicated, was responsible for the increase in pulmonary ventilation observed in their subjects when breathing oxygen. A later paper by the same authors showed that this small increase in central CO_2 tension was sufficient to account for the actual increase in ventilation (1953(b)).

The increase in ventilation noted by these investigators resulted in a fall in the arterial CO_2 tension. The net effect of this together with the rise in cerebral venous CO_2 tension observed was therefore to increase the venous arterial CO_2 tension difference.

These findings of Lambertsen and colleagues prompted the present investigator to consider the possibility of a shift in the opposite direction of the venous arterial CO_2 tension difference occuring in subjects whose respiration was depressed by breathing oxygen rich mixtures. It has been shown above that on theoretical grounds such a decrease in tension difference of CO_2 between

venous and arterial blood might be expected in subjects with chronic CO_2 retention, and that this decrease might be greater in those who also had a secondary polycythaemia.

Thus it now seemed possible that the tendency to decreasing venous-arterial CO_2 tension differences which is postulated in these subjects while breathing air might be reinforced by a further decrease in the V-A tension differences by breathing oxygen rich mixtures. On examining figures 2 & 12 again, it can be seen that these combined effects might result in an actual reversal of the normal venous-arterial tension gradient.

Such a reversal of the CO_2 tension gradient could have a bearing on the problem of irreversible CO_2 narcosis; since a situation where the CO_2 in the respiratory centres being built up by an additional source besides the supply of CO_2 from the tissue metabolism itself, i.e. from the arterial blood, could give rise to a self perpetuating system resulting in very high tissue CO_2 tensions.

To test this hypothesis, a series of experiments were planned in which blood from the jugular bulb was withdrawn simultaneously with blood from the brachial artery in a group of patients with chronic CO_2 retention while they were breathing air and then oxygen. Ideally, CO_2 dissociation curves should have been constructed from these samples of blood, but the limitations imposed by time and what was physically possible for a single worker, made it necessary to limit the object of the experiment to a

demonstration of the venous-arterial blood gas differences between the internal jugular and arterial blood of this group. It was felt that these figures would suffice to test the validity of the above hypothesis.

Eight subjects with chronic CO_2 retention and anoxaemia of varying severity were investigated. None of them had received oxygen therapy for at least two hours before the study began. All measurements were made while the subjects were lying in bed, and 30 minutes were allowed before sampling, to ensure basal conditions.

A needle fitted with a stilette was inserted into the internal jugular vein at a point above the angle of the jaw and as nearly as possible in the jugular bulb, according to the technique described by Myerson, Halloran and Hirsch (1927). A similar needle and stilette were introduced into a brachial artery. Both of these operations were preceded by the use of 1.0% procaine as a local anaesthetic for the skin and deeper tissues. The subjects were allowed to rest after the completion of these procedures until they were judged to have returned to basal conditions with respect to breathing and relaxation of stress.

Samples were withdrawn, in quick succession, from both indwelling needles with the subject still breathing air. Oxygen was then administered by means of a plastic disposable mask and further samples withdrawn 10 minutes later while oxygen breathing continued.

Much difficulty was experienced in obtaining

samples during the period of oxygen breathing from the internal jugulars by this method. This was probably due to unavoidable neck movements leading to displacement of the needles from the lumen of the veins. The initial air breathing samples were obtained in all seven of the subjects studied in this way, but in four of them no further sample could be withdrawn during the later oxygen breathing.

Four other subjects who were in hospital with other complaints, and who had no CO_2 retention or anoxaemia were also studied. In two of these, the above method proved successful in providing internal jugular samples during air and oxygen breathing. In the other two subjects, and one more subject with chronic CO_2 retention, a radio-opaque catheter was passed from the median cubital vein into the internal jugular under X-ray control. The sampling procedure was identical to that described above in those subjects studied by direct jugular vein puncture.

DESCRIPTION OF THE TECHNICAL PROCEDURES.

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(I) Measurement of Minute and Alveolar Ventilation.

Figure 3 shows the arrangement of the apparatus used in investigating the effects of 100% oxygen breathing upon the minute and alveolar ventilation, and blood gases.

The subject, fitted with a nose clip, was breathing through a mouthpiece connected to a combined inspiratory and expiratory demand valve (Siebe Gorman Ltd.). The total dead space of mouthpiece and valve was 60 mls. and the resistance to opening of the valve was 0.75 inches of water.

The valve was fitted to lengths of flexible gas tight tubing on the inspiratory and expiratory sides. The expiratory tubing being attached to a 70 litre capacity Tissot spirometer with a constant speed, pen and ink, recording drum. The minute ventilation measured in this way was corrected to B.T.P.S. The inspiratory tubing was left open, at the far end, while the subject was being investigated during air breathing, and it was connected during the oxygen breathing experiments to a Douglas bag of 40 litres capacity which was kept full from an oxygen cylinder.

The Tissot spirometer was washed out several times with the expired gas while the minute ventilation was settling to a steady volume, i.e. within 0.5 litres/ minute, when air breathing, for three successive minutes. It was then emptied of gas and a three minute collection period begun. The minute ventilation was taken to be the mean of volumes recorded over this three minute period.

During this collection period, blood samples were withdrawn from the indwelling arterial needle, which had been inserted before the start of the experiment. A sample of 10 ml. was withdrawn into a lubricated glass syringe, the dead space of which was filled with heparin solution, avoiding any contact of the blood with air. Blood samples were stored in a refrigerator until the estimations could be performed.

A sample of expired gas was withdrawn into a rubber bag from the tap on the Tissot spirometer, and was analysed immediately at the end of the experiment.

The whole procedure was repeated after the subject had been breathing oxygen for 10 minutes.

Alveolar ventilation was calculated from the formula of Rahn and Fenn (1955):

$$\dot{V}A(L/min.B.T.P.S.)=\frac{\dot{V}Co2(ml/min.\ S.T.P.D.)\ x\ .863}{PACo2}$$

where $\dot{V}A$ = alveolar ventilation/unit time

$\dot{V}Co2$ = Co2 production/unit time.

PACo2 = alveolar Co2 pressure in mm.Hg. This was assumed to be identical with arterial CO_2 pressure.

$\dot{V}Co2$ was calculated from the formula of Comroe et al. (1950)

$$\text{i.e. } \dot{V}Co2=\frac{(FECo2\ (I-FICo2) - FICo2\ (I-FECo2)}{(I-FICo2-FI02)}\ .VE$$

where F indicates a gas concentration either expired (E) or inspired (I) of Co2 or 02, and $\dot{V}E$ = expired gas volume/unit time.

(2) Measurement of expired gas concentrations.

Oxygen and CO_2 in the expired gas was estimated by the Scholander micro-method (1947). Duplicate samples were required to check within 0.03%.

(3) Estimation of plasma CO_2 content.

Whole blood CO_2 content was measured from a 1ml. sample by the manometric method of Van Slyke and Neill (1924). Duplicate estimations were required to agree within 0.2 vol.%. The plasma CO_2 content was derived from the mean of these readings by use of the line chart of Van Slyke and Sendroy (1928).

(4) Estimation of blood oxygen content and capacity.

Again, the manometric apparatus of Van Slyke and Neill (v.s.) was used. Duplicate estimates were to agree within 0.2 vol.%.

(5) Estimation of blood CO_2 and oxygen tension.

The blood gas tensions were estimated by the bubble equilibration method of Riley, Proemmel and Franke (1945) as modified by Riley, Campbell and Shepherd(1957). This technique gave accurate results when checked against tonometer estimations for CO_2 tensions, as described by Riley, Proemmel and Franke (v.s.). The regression line of bubble equilibration against tonometer equilibration CO_2 tensions was $y = 5.80 + 0.86\ (\pm\ 1.76)$ which compares favourably with the figures of Riley, Campbell and Shepherd (v.s.). Standard correction factors for CO_2 tension estimates were derived from these figures and applied in subsequent estimations. Duplicate measurements were required to agree within 6.0 mm.Hg.

Oxygen tension measurements by the bubble equilibration method were not as accurate as those for CO_2, when compared with tonometer equilibration oxygen tensions of the same blood samples. It was decided not to place too great a reliance on these alone but to compare the bubble equilibration derived figures for oxygen tension with those estimated from a knowledge of the oxygen saturation and pH of the blood when applied to the standard oxygen dissociation curves of Dill (1944). The accuracy of this procedure was probably at least as great as that of the bubble method when dealing with oxygen tensions below 80 mm. Hg., in the hands of the present investigator. Duplicate estimations of bubble equilibration oxygen tensions were required to agree within 6 mm. Hg. In dealing with oxygen tensions above 80 mm. Hg., the estimations were rounded off to the nearest 10 mm. Hg., as it is generally agreed that the bubble method is less accurate above this level. When the subjects were breathing oxygen through plastic disposable masks, the blood oxygen tensions were usually about 120 mm. Hg.

(6) Measurement of blood pH values.

The pH of the blood was estimated from the Henderson Hasselbalch equation, using a pK value of 6.11 and the estimates of Plasma CO_2 content and tension as derived above. The maximum error introduced into the estimate of blood pH by the errors allowable in the estimations of content and tension were not likely to

affect the second decimal place and it was felt to be justifiable to calculate to three places.

(7) Measurement of blood lactic acid concentrations.

The estimation of blood lactic acid was by the method of Avery and Hastings (1931). This is based on the manometric estimation in the apparatus of Van Slyke and Neill (v.s.), of the CO_2 liberated from lactic acid by oxidation with potassium permanganate in strongly acid solution.

The method has the advantages, for the single investigator, of speed and simplicity in operation and the stability of the samples after preparation, for up to 48 hours. When a number of other technical procedures were to be undertaken this was a most useful feature of the technique. It does suffer from the disadvantage of over-estimating blood lactate slightly because of a small amount of CO_2 liberated from substances other than lactic acid. Avery and Hastings (v.s.) found that an empirical correction of -0.5 mM/L., when applied to the results, gave close agreement with older distillation methods.

The repeatability of the method was good. The mean difference between duplicate estimations in 30 consecutive samples was 0.16 mM/L., with a standard deviation of 0.09 mM/L. Only one pair of determinations out of the total was more than two standard deviations but less than three S.D. of the mean difference. (See Table 9).

RESULTS

RESULTS.

(a) The Hypoxic Drive.

If it is assumed that the peripheral chemoreceptors in a group of subjects with anoxaemia and CO_2 retention, are in a state of continuous excitation in response to the lowered blood oxygen tensions, then the depression of the pulmonary ventilation produced by oxygen breathing in such a group should be directly proportional to the amount by which the hypoxaemic stimulus is reduced.

This hypothesis was tested by the procedure explained in the section dealing with methods. The results are given in Table I. Thirteen subjects who showed a wide range of resting blood gas figures at rest while breathing air, all showed changes in arterial oxygen and CO_2 tensions while still breathing high oxygen mixtures after 10 minutes. In spite of an increase in arterial oxygen tension of all subjects studied, eleven of them to a figure of 120 mm. Hg., approximately, there was a varying change in arterial CO_2 tension. The greatest increase in CO_2 tension was 16 mm.Hg., and the smallest were in the region of two or three mm. Hg., One subject showed no change in arterial CO_2 tension, and one showed a decrease of 2 mm.Hg., Although the error involved in CO_2 tension measurements by the technique used in this study (+ or - 2mm. Hg. approx.), must be taken into account, it is clear that the majority of these subjects did not show a large increase in arterial CO_2 tension during the first 10 minutes of oxygen breathing. The mean increase

was 6.7 mm. Hg. The increase in arterial oxygen tension was considerable in most of these subjects (mean increase = 56 mm. Hg. approx.). These figures would suggest that the average ventilatory response of such a group of subjects to breathing high oxygen mixtures for a brief period is a slight decrease in alveolar ventilation.

The seven subjects in whom it was found possible to measure the actual change in alveolar ventilation were mainly those with less severe degrees of respiratory insufficiency, as shown by their arterial oxygen tensions while breathing air (See Table I). The mean decrease in alveolar ventilation of this group was quite large (1.77 L/minute), and the increment of arterial CO_2 tension was larger than in the group of thirteen subjects as a whole (mean increase = 9.1mm. Hg.). The correlation between increase in CO_2 tension and decrease in alveolar ventilation was high ($r = +0.76$, $P < 5\%$), even in such a small group of seven subjects, thus tending to justify the use of changes in arterial CO_2 tension to indicate changes in alveolar ventilation where these could not be directly measured.

When the increases in arterial CO_2 tension of the total thirteen subjects were compared to the observed air breathing arterial oxygen tensions (See Figure 4), no significant correlation was found ($r = +0.37$, $P > 5\%$).

Similarly in comparing the decreases in alveolar ventilation observed in the group of seven subjects with the initial arterial oxygen tensions, there was no

significant correlation ($r=+0.13$, $P > 5\%$).

There is no support from the above findings for the concept that a hypoxaemic ventilatory stimulus through the peripheral chemoreceptors plays a significant part in regulating the respiration of a group of subjects with CO_2 retention even when the degree of hypoxaemia is often severe.

It is relevant at this point to present comparable results obtained by Brodovsky et al. (1960), taken from a different experimental context but using an exactly similar procedure to that adopted in this study, except that this group of ten anoxaemic and hypercapnoeic patients had been breathing oxygen for twenty minutes when the arterial blood samples were repeated, as compared to ten minutes of oxygen breathing in the present experiment. These results are set out in Table 2. Unfortunately the actual arterial oxygen tensions while breathing oxygen are not available, but the assumption was made by the present author that full saturation was achieved in all cases. This is likely to be the case since these subjects all had chronic CO_2 retention as a result of respiratory insufficiency, without superadded acute disturbances which might make full arterial oxygen saturation difficult to achieve.

When the increment in arterial CO_2 tension is compared to arterial oxygen tension when breathing air in this group of subjects, again no significant correlation emerges, ($r = -0.25$, $P > 5\%$)

The mean rise in CO_2 tension of this series however is larger than that found in the present study (Brodovsky's mean rise equals 9.0 mm. Hg., this present series equals 6.7 mm. Hg.). The difference between these means may be accounted for by the difference in the period of oxygen breathing between the two studies.

It was noted in the Introduction to this thesis that the animal experiments of Bjurstedt (1946) and Gesell (1940) had shown activity of the peripheral chemoreceptors in response to hypoxaemia under conditions of low arterial CO_2 tensions and high pH, but that an increase in arterial CO_2 tension or decrease in pH of the arterial blood resulted in a corresponding decrease in the hypoxaemic ventilatory stimulus. If this relationship were to hold true for a group of human subjects with varying degrees of oxygen lack and CO_2 retention, one would expect to find an inverse relationship between the levels of arterial CO_2 tension while breathing air and the change in CO_2 tension while breathing oxygen over a short period of time. This relationship should be more marked in the case of a comparison of arterial pH while breathing air and increment of CO_2 tension breathing oxygen, according to the observations of these experimenters.

From the data of Table I a comparison of the initial arterial CO_2 tensions while breathing air with the increments in CO_2 tension observed while breathing oxygen (See Figure 5) shows a correlation which is almost, but not quite, significant at the 5% level. ($r = -0.51$, $P > 5\%$).

The correlation between alveolar ventilatory decrease in the group of seven subjects, and the original arterial CO_2 tension is also not significant, ($r = -0.46$, $P > 5\%$). Since the actual increase in arterial oxygen tensions in this group of subjects varied widely (see Table 1) a more precise indication of the effect of CO_2 retention in modifying the hypoxaemic ventilatory stimulus could presumably be obtained if it were possible to study a group of subjects in whom this increase in oxygenation was the same. The data of Table I were adjusted so that a predicted value for the increment in CO_2 tension could be obtained on the basis of an assumed arbitrary increase in arterial oxygen tension in each case of 75 mm. Hg. The observed increase in oxygen tension was divided into this figure and the factor so obtained was used to multiply the observed rise in CO_2 tension. The results of this manoeuvre are set out in Table 3. The correlation between CO_2 tension of the arterial blood while breathing air and the increment in this tension predicted as above on oxygen breathing, was significant at the 5% level ($r = -0.61$, $P < 5\%$).

Table 1 also shows the arterial pH values found in this present series, and a comparison of these values with the observed increments of CO_2 tension breathing oxygen (See Figure 6), gives a correlation ($r = +0.66$, $P < 5\%$) which is statistically significant, thus tending to support the animal experimental results previously noted.

Using the figures for predicted increment of arterial CO_2 tension on the basis of an assumed standard

rise in arterial oxygen tension, as calculated above, the correlation between pH and predicted rise in CO_2 tension is now highly significant. ($r = +0.86$, $P < 0.1\%$).

Similarly, the correlation obtained from Brodovsky's figures when an arbitrary standardisation of the oxygen tension rise is applied in the same way as in the above data, (See Table 2), is closer than the correlation previously noted for the actual figures (See Table 4 below), although this in itself was probably significant ($r = -0.70$, $P < 5\%$). (Predicted rise in CO_2 tension correlation with air breathing CO_2 tension, $r = -0.72$, $P < 5\%$) (See Table 2).

When the pH figures obtained in the present study were compared with the figures for decrease in alveolar ventilation as shown in Table I, a significant correlation was also obtained. ($r = +0.85$, $P < 5\%$). A summary of the above correlations is given in Table 4.

These results are consistent with the hypothesis that the magnitude of the increment in CO_2 tension of the arterial blood, and also the decrease in alveolar ventilation which is observed when subjects with anoxaemia and CO_2 retention change from breathing air to high oxygen mixtures, is a function of the arterial blood pH. These results agree with the conclusions of Bjurnstedt (1946) and Gesell (1940), which were based on animal experiments, that the 'hypoxic drive' of the peripheral chemoreceptors becomes quantitatively less important in maintaining the ventilation of hypoxaemic subjects as the pH of the arterial blood decreases.

(b) The Metabolic Acidosis of Anoxaemia.

For the reasons stated in the section on methods, it was thought possible that the blood of subjects with chronic anoxaemia and CO_2 retention might contain an excess of fixed acid and that this might be demonstrated in a qualitative fashion by a small pilot study designed to show displacements of CO_2 dissociation curves on breathing high oxygen mixtures.

The left hand diagram of Figure 7 shows a CO_2 dissociation curve drawn from data obtained by analysing the arterial blood of a subject who had not previously had oxygen therapy and who had an arterial oxygen tension of 54 mm. Hg. After 15 minutes of oxygen administered through a face mask, the arterial blood which was subjected to the same procedure as that used for the dissociation curve measurements, showed an increase in total CO_2 content of approximately 15 vols. %. This was equivalant to a decrease in circulating fixed acid of 19 m.Eq./L. approximately. After three days of continuous oxygen therapy and antibiotics, the patient was allowed to breathe air for two hours and the CO_2 dissociation curve of his arterial blood was again estimated as shown in the right hand diagram of Figure 7. There had been a considerable improvement in the patients condition and this was reflected in the improved arterial oxygenation; the oxygen tension now being 7 Imm. Hg. After 15 minutes of breathing oxygen, an arterial blood sample now showed no increase in total CO_2 content, but a slight decrease, from

a point of the same CO_2 tension on the dissociation curve.

The curve drawn after three days of oxygen is elevated by an amount equivelant to 25 vols. %. of CO_2 content, when compared to that drawn before oxygen therapy.

Figure 8 shows results obtained when the same procedure was applied in studying the CO_2 dissociation curves of a patient whose arterial oxygen tension, before oxygen therapy was begun, was 53 mm. Hg. After 15 minutes of oxygen breathing, the plasma CO_2 content had increased by approximately 7 vols.%. Three days later, during which time he had continuous oxygen therapy, the arterial CO_2 curve had shifted upwards by an amount equivelant to 15 vols.%. of CO_2 content, but his general condition had not greatly improved. The arterial oxygen tension after two hours breathing air was now 50 mm. Hg., i.e. about the same as the value obtained three days earlier. In contrast to the results noted in studying the previous patient, there was still a slight upward deviation of the curve, after 15 minutes of oxygen breathing by the patient, as indicated by the new arterial CO_2 point on the plot.

Although it is true that any interpretation of these results must take into account the possible errors due to in vitro formation of lactic acid in the equilibrated blood as previously discussed, there seemed to be evidence of two distinct processes involving the blood acid-base balance under the influence of variations in arterial blood oxygenation.

The long term effect of oxygen therapy on the blood acid-base pattern of anoxaemic patients appears to result in an increase in CO_2 content of the plasma. It is probable that this is due to the well known increase in renal tubular reabsorption of bicarbonate in response to increase in blood CO_2 tension. The blood CO_2 tension increase would be expected in such patients as the result of a decrease in alveolar ventilation induced by oxygen breathing.

This renal mechanism is a slow one, and could not account for the rapid increments in bicarbonate content of the blood indicated by the dissociation curve shifts after only 15 minutes of oxygen breathing. These rapid increases in blood bicarbonate levels seemed to be related to the degree of oxygen deficit in the arterial blood, since the first study showed no further rise in blood CO_2 content when the patient had improved after three days of oxygen therapy to the extent that his arterial oxygen tension when breathing air had risen from 54 to 71 mm. Hg.

The most likely cause of this rapid increment of blood bicarbonate seemed to be a decrease in circulating fixed acid due to improved blood oxygenation. This possibility was investigated by measuring the blood lactate concentrations in the way described in the section concerned with methods.

Table 5 shows the concentrations of lactate measured in the arterial blood of sixteen subjects with

varying degrees of anoxaemia and chronic CO_2 retention, and in some cases, a superimposed acute respiratory failure. These samples were withdrawn before treatment was given.

The association between arterial oxygen tension and blood lactate concentration is shown in Figure 9. Because at least four factors were thought to be possibly of importance in producing any excess of circulating lactate, it seemed unlikely that a correlation could be shown between lactate concentration and any one of them. It was surprising therefore to note a highly significant correlation between arterial oxygen tensions and lactate concentrations. ($r = -0.67$, $P < 0.01\%$).

Eleven of the sixteen subjects showed arterial blood lactate figures above the normal range for resting subjects given by Laug (1934), who used the same technique.

The time course of the decrease in blood lactate was followed in six patients for periods of 30 to 45 minutes and the change in arterial CO_2 tension was also noted. The results are shown in Table 6, and Figures 10 and 11 illustrate the association between decreasing blood lactate and increasing arterial CO_2 tension. The initial CO_2 tensions and blood lactates shown in the table and figures are those found after each subject had been breathing oxygen for 10 minutes. In each case the arterial oxygen saturation did not show an appreciable change during the study.

The mean 15 minute decrease in lactate was 0.5mM/L.

and the mean 15 minute increase in CO_2 tension was 3 mm.Hg. Allowing for the errors involved in making these measurements, the changes in lactate and CO_2 tension were small in four subjects but relatively large in the two subjects (17 & 18) who developed early symptoms of CO_2 narcosis. It seems reasonable to suppose that a constant rate of change would be maintained, if oxygen breathing were continued, until blood lactate levels approached zero. Assuming this constant rate of change, subject 17 (see table)6) who had the highest blood concentration of lactate in the group, would have shown an increase in arterial CO_2 tension of 36 mm. Hg. after three hours of oxygen breathing. He was already developing the neurological manifestations of CO_2 narcosis after 45 minutes when his arterial CO_2 tension was 104 mm. Hg.

This subject (no. 17) and one other (no.18) showed greater increments of CO_2 tension in the test period together with more rapid fall in blood lactate concentrations associated with the symptoms of CO_2 narcosis, than the remaining subjects; none of whom reacted unfavourably to breathing oxygen.

(c) Some Effects of Variations in CO_2 Dissociation Curves

Table 7 shows blood gas values observed in the arterial and internal jugular venous blood of eight subjects with anoxaemia and CO_2 retention while breathing air at rest. The difference between the arterial and venous oxygen contents, is small in all subjects except subject 8 where it is within the normal range as found by Gibbs et al. (1942). This subject also shows only slight CO_2 retention and anoxaemia while the figures for the others show considerable degrees of abnormality in blood gas status.

The differences between arterial and venous plasma CO_2 contents are all larger than the range of values found by Gibbs et al., except those of subjects No. 1 and 2, which are rather smaller than normal. In the six subjects No. 3, 4, 5, 6, 7 & 8, the differences in CO_2 content are much larger than would be expected on the basis of the small oxygen content differences between arterial and venous blood. Since the oxygen content difference between arterial and venous blood is responsible for approximately 70% of the difference in CO_2 carrying power between relatively oxygenated blood coming to the tissues and reduced blood leaving them, it follows that the CO_2 content difference, between arterial and venous blood which has a small oxygen content difference, should also be small (see Peters and Van Slyke 1931).

There is apparently an anomaly here in that the CO_2 content differences between arterial and internal

jugular venous blood are normal or greater than normal in these six subjects with small oxygen content differences. From Figure 12 it can be seen that such large CO_2 content differences between arterial and venous blood must be associated with large CO_2 tension differences, if it is assumed that the slope of the dissociation curves is normal. Table 7 shows that the CO_2 tension differences of all eight subjects studied are smaller than normal. It follows, therefore, that some other factor has not been considered in interpreting these results.

Figure 12 shows that it is possible to explain this anomaly if it is assumed that the slope of the CO_2 dissociation curves is greater than normal. In a pair of such steeply sloping curves, the CO_2 content difference associated with a given CO_2 tension difference is larger than the content difference produced by the same tension difference in a pair of relatively flat curves.

It is well known that the slope of the blood CO_2 dissociation curves is increased in polycythaemia since increase in haemoglobin content is one of the major factors producing an increase in slope (see Peters and Van Slyke 1931). Two of the subjects here showing evidence of an increase in slope of their blood dissociation curves i.e. subjects No. 3 and 5, with blood oxygen capacities of 23.3 and 25.7 vols. respectively, can be excluded from further consideration because of this obvious explanation for the anomalous blood gas differences of content and tension.

In four studies (4,6,7, & 8) there appears to be no other reasonable cause for the presumed increase in slope of the CO_2 dissociation curves than the increase in slope which is known to occur with increase in height of the curves due to increase in CO_2 content (See L. J. Henderson 1928).

In summary, of the eight subjects with CO_2 retention whose blood gas measurements were studied while breathing air, two (1 & 2) show figures consistent with CO_2 dissociation curves of normal slope. Six subjects show figures which are most readily interpreted on the assumption that the slope of the curves is greater than normal (subjects 3,4,5,6,7, & 8). Two of these (3 and 5) show greater than normal blood oxygen capacities, thus at least in part, accounting for the evidence of increased slope of the dissociation curves. Four subjects, however, must be presumed to have blood CO_2 dissociation curves of increased slope due to increased CO_2 content of the blood alone (Subjects 4, 6, 7 & 8).

Since it has been shown at an earlier stage of this enquiry that displacements of the CO_2 dissociation curves of arterial and venous blood occur when high concentrations of oxygen are substituted for air in the respired gas of anoxaemic subjects, a series of studies were carried out to determine the effects of such alterations in acid-base balance on the blood gas parameters of arterial and internal jugular venous blood in subjects with chronic CO_2 retention and anoxaemia and to compare these effects with those shown in subjects with other

disabilities.

Table 8 shows the blood gas measurements obtained from the arterial and internal jugular venous blood of seven subjects while breathing air, and then oxygen for ten minutes. Three of these (Nos. 2, 3 & 7) had CO_2 retention and anoxaemia. The remainder (Nos. 9, 10, 11 & 12) had normal blood gas measurements while breathing air. Two of these (Nos. 9 & 12) suffered from bronchial asthma. Subject No. 10 had angina pectoris, and subject No. 11 had chronic nephritis and uraemia.

There were some notable differences in the pattern of change in the blood gas measurements between these two groups of subjects. Three out of the four subjects with no blood gas abnormality when breathing air, (Nos. 10, 11 & 12) showed the normal response to breathing oxygen i.e. there was a decrease in the arterial CO_2 tension, implying an increase in pulmonary ventilation. The internal jugular blood of two of these subjects showed, at the same time, a slight rise in CO_2 tension on breathing oxygen. These findings agree with those of Lambertsen et al. (1953) in normal subjects, and might similarly be interpreted as indicating a slight rise in cerebral tissue CO_2 tension as a result of a decrease in cerebral venous blood CO_2 capacity due to the small increase in hydrogen ion concentration in the venous blood with a greater proportion of oxyhaemoglobin in that blood. This rise in the tissue CO_2 tension might be expected to result in an increase in pulmonary ventilation, with a

consequent decrease in arterial CO_2 tension. The arterio-venous oxygen content difference did decrease in these two subjects on changing over from breathing air to oxygen.

Subject No. 12, however, while also showing a decrease in arterial CO_2 tension on breathing oxygen, shows a much larger decrease than the other two subjects, and this is accompanied by a small decrease in cerebral venous CO_2 tension instead of the small increase noted in the others. It seems likely that this subject was voluntarily over-breathing to some extent, perhaps in response to the discomfort of the mask. Kety and Schmidt (1946) showed a similar decrease in cerebral venous CO_2 tension accompanying a decrease in arterial CO_2 tension in response to voluntary hyperventilation.

Apart from the three subjects discussed above, one other showed no evidence of blood gas abnormality while breathing air (No. 9). The results in this case are of particular interest in showing an increase in arterial CO_2 tension while the subject breathed oxygen. His arterial CO_2 content when breathing air (50.4 vol. %) is just at the upper limit of normal as found by Gibbs et al. (1942) in 50 normal subjects. (Range equals 44.6 to 50.2 vols.%). The figures obtained from this subject also differ from those discussed above in showing a slight decrease in cerebral venous CO_2 tension when breathing oxygen. It seems likely that the decrease in jugular venous CO_2 tension was due to a moderately large increase in venous CO_2 capacity as reflected in the increase in CO_2 content from 57.5 to 60.0 vols.%. This could be explained by

assuming an increase in blood pH due to decrease in circulating fixed acid levels as previously demonstrated in subjects with CO_2 retention breathing oxygen.

When the blood gas figures of the three subjects who had CO_2 retention and anoxaemia while breathing air (Nos. 2, 3 & 7) are examined, it can be seen that subjects 3 and 7 show a similar response to that of subject 9 on breathing oxygen. There was a decrease in cerebral venous CO_2 tension accompanied by a rise in arterial CO_2 tension in each case. Subject 7 is of particular interest as this decrease in the venous-arterial CO_2 tension difference has gone so far as to result in a higher arterial CO_2 tension than the venous CO_2 tension. This subject was the only one in those studied to develop the signs of CO_2 intoxication while on prolonged oxygen therapy.

The blood gas results of subject 2 show no pattern which falls into any of the above types of response to oxygen breathing. There appears to have been a decrease in pulmonary ventilation, shown by a rise in arterial CO_2 tension on oxygen. At the same time, however there was a rise in cerebral venous CO_2 tension, which according to the above line of reasoning should have resulted in a decrease in arterial CO_2 tension. It is possible that there was an error in the CO_2 tension measurements in this case, but it should be noted that this subject along with one other (No. 1) showed no evidence of an increase in slope of the CO_2 dissociation curves in the blood gas figures derived from his arterial and venous blood when

breathing air. (See Table 7).

In conclusion, a consideration of these results provides evidence to support the hypothesis of Lambertsen et al. (1953) that a slight rise in cerebral venous CO_2 tension, and presumably of tissue CO_2 tension, in normal subjects (i. e. without evidence of CO_2 retention in the arterial blood) might account for the normal slight increase in pulmonary ventilation on breathing oxygen. The likeliest explanation for this increase in tissue CO_2 tension is a decrease in CO_2 carrying power of the venous blood, relative to that of the arterial blood, caused by a greater oxyhaemoglobin content of the venous blood when breathing oxygen than when breathing air, as proposed by Lambertsen (v. s.).

These results also show that the opposite effect of a decrease in pulmonary ventilation produced by oxygen breathing in subjects with CO_2 retention and anoxaemia may be due to a decrease in cerebral venous and tissue hydrogen ion concentration caused by a decrease in circulating fixed acid levels as previously demonstrated in this thesis. The resulting increase in CO_2 carrying power of the venous blood produces a fall in the tissue CO_2 tension and thus a decrease in pulmonary ventilation and an increase in arterial CO_2 tension.

It is also tentatively suggested that an exaggeration of this effect may result in such an increase in arterial CO_2 tension, a decrease in cerebral venous CO2 accompanying this, that the arterial CO2

tension becomes, at least for a short period of time, higher than the venous. Such a reversal of the normal arterial and venous CO_2 tension relationship may play a part in producing the conditions which result in the syndrome of CO_2 intoxication.

D I S C U S S I O N

D I S C U S S I O N

The Hypoxic Drive

Respiratory failure or insufficiency is most commonly seen in clinical practice as a feature of the progression of various pulmonary disease states which lead to alveolar hypoventilation.

The large volume of published work in this field makes it difficult to accurately summarise the present day knowledge of the factors which are responsible for the condition. Much of the relevant literature appears contradictory, and certain observations of importance appear to have been overlooked by many authors. The introduction to this thesis was an attempt to place some of the previous work in perspective in order to assess the results of this present investigation. It was pointed out that while the animal experiments of Frédéricq (1901) and Heymans (1927) had established the importance of the peripheral chemoreceptors in the carotid sinuses and aortic arch in regulating pulmonary ventilation in response to anoxaemia, other animal work of Bjurstedt (1946), Gessell (1940) and Germandt (1946) indicated that the activity of the peripheral chemoreceptors in response to a given degree of oxygen lack varied with the pH of the blood. Most modern writing on the problems of respiratory failure has assumed that the peripheral 'hypoxic drive' plays a major part in regulating the respiration even in conditions of extreme respiratory acidosis and anoxaemia.

Depression of this peripheral chemoreceptor activity by increasing the arterial blood oxygenation as in the breathing of oxygen rich air mixtures is often stated to be the reason for the further ventilatory depression noted in subjects with anoxaemia and CO_2 retention. The medullary respiratory centres are presumed to be relatively insensitive to the normal stimuli of CO_2 and hydrogen ion excess. This last hypothesis has so far appeared unverifiable.

Some of the earliest investigators, on the other hand, have suggested that the diminished ventilatory response of subjects with chronic respiratory failure to blood CO_2 and hydrogen ion might be a simple physico-chemical result of the altered blood acid base equilibrium itself. This hypothesis has met with partial acceptance by some authorities (e.g. Bahn et. al. 1953, Prime and Westlake 1954) but they have produced evidence to suggest that alterations in buffering capacity of the blood can not account for the entire change in ventilatory response to the CO_2 and hydrogen ion stimuli observed under various conditions of altered blood acid-base equilibrium.

Some objections to the complete acceptance of the hypothesis that variations in blood and tissue buffering capacity might determine ventilatory response to chemical stimuli, have been based on the observed discrepancies between response of the respiration to the breathing of CO_2 mixtures in subjects with chronic CO_2 retention and the response predicted by taking into

account the altered blood buffers. (Prime and Westlake 1954). Other grounds for rejection of the hypothesis include observed differences in ventilatory response to the blood levels of CO_2 and hydrogen ion at high altitude and at sea level (Rahn et al. 1953), and the ventilatory response to exercise when breathing air and then oxygen (Asmussen & Nielsen 1947 and Bannister et al. 1958).

In many such studies care was taken to exclude the possibility of interference in the results by the intrusion of a hypoxic drive through the peripheral chemoreceptors. This was done by having the subjects breathe oxygen while the ventilatory responses to CO_2 and pH changes in the blood were being measured. Recent evidence of the effects of altered blood oxygenation on the blood acid base equilibrium (Lambertsen et al. 1959) indicate that insufficient account has been taken of this factor in these previous studies.

The present results under the heading of "The hypoxic drive" support the conclusions of Bjurnstedt (1946) Gesell (1940) and Gernandt (1946) that the ventilatory depression induced by breathing oxygen rich mixtures in subjects with hypoxaemia and respiratory acidosis is negligable within the short period of time (10 minutes) when depression of peripheral chemoreceptor activity would be expected to show its maximum effect on respiration. In a group of subjects with varying degrees of anoxaemia and CO_2 retention there was no significant correlation between the arterial oxygen tension while breathing air

and the decrease in alveolar ventilation (7 subjects) or the rise in arterial CO_2 tension (13 subjects) while breathing oxygen for ten minutes.

In spite of a wide variation in arterial oxygen tensions of this group of thirteen subjects while breathing air, a significant correlation was obtained between the arterial blood pH while breathing air and the increase in arterial CO_2 tensions on breathing oxygen for ten minutes, ($r=+0.66$, $P < 5\%$). Similarly, the correlation between air breathing arterial pH and oxygen breathing decrease in alveolar ventilation (7 subjects) was significant, ($r=+0.85$, $P < 5\%$). When air breathing arterial CO_2 tensions were substituted for pH values in the above correlations the results were only slightly less significant.

Figures taken from the literature, pertaining to a different experimental context, but from a similar set of experimental conditions, when examined in the same way, supported the above findings (Brodovsky et al. 1960).

These results are consistent with the hypothesis that the 'hypoxic drive,' or activity of the peripheral chemoreceptors in response to any degree of anoxaemia, is not a major factor in regulating the ventilation of subjects with respiratory acidosis when the arterial blood pH values are lower than normal.

The Metabolic Acidosis of Anoxaemia.

Since it has been shown in the preceding discussion that the peripheral chemoreceptor response to any degree of anoxaemia is probably insignificant in uncompensated respiratory acidosis (i.e. blood pH values below normal), the chemical control of respiration is presumably entirely under medullary or central chemoreceptor control in such conditions of anoxaemia and CO_2 retention with acidaemia; but since the pulmonary ventilation is depressed in respiratory acidosis while the CO_2 and hydrogen ion stimuli are increased, it must be assumed that some part of the physiological mechanism normally responsible for the chemical control of pulmonary ventilation has become relatively insensitive to these stimuli.

The present results show that the effects of oxygen breathing on the blood acid base equilibrium of subjects with anoxaemia and CO_2 retention are considerable, and it may be that previous objections to the hypothesis, which suggests that alterations in acid-base equilibrium of the blood and tissues might explain the diminished ventilatory response of emphysematous subjects to chemical stimuli, could be overcome by a further consideration of these effects of increased blood oxygenation. In this study sixteen subjects with varying degrees of anoxaemia and CO_2 retention were investigated when breathing air and levels of blood lactate as high as 6.0 mM/L. were obtained. There was a significant correlation between

the arterial oxygen tensions found in these subjects while breathing air and the arterial concentrations of lactate ($r=-0.67$, $P < 0.01\%$). Eleven of the sixteen subjects had blood lactate levels above the normal range as defined by Laug (1934) using the same technique of measurement (i.e. 0.58 to 2.40 mM/L.). These were mostly subjects with arterial oxygen tensions below 60 mm. Hg. (9 out of 10 subjects). Those with arterial oxygen tensions higher than this had usually normal blood levels of lactate (4 out of 6 subjects).

A small pilot study had previously shown that the blood CO_2 dissociation curves became elevated when subjects with extreme anoxaemia breathed oxygen for both short (15 minutes) and long (3 days) periods of time. Although much of the upward deviation of the curves during prolonged oxygen breathing could be explained on the basis of a renal tubular reabsorption of increased amounts of bicarbonate, the upward shift of the curves in 15 minutes of oxygen breathing was too great to be a result of this slowly acting renal effect, and was most likely to be due to a lowering of circulating fixed acid levels.

This was confirmed by measuring the decrease in arterial blood lactate concentration in six subjects over a thirty to forty five minute period of oxygen breathing. The decrease in blood lactate was a gradual process and there was an accompanying gradual increase in arterial CO_2 tension in all subjects. Correlation between decrease in lactate and increase in CO_2 tension was close ($r+0.84$,

$P < 5\%$ almost 1.0%).

A further point of interest in these results was the appearance of early neurological signs of CO_2 intoxication in two subjects, who had the highest initial arterial CO_2 tensions. In both of these subjects the mean 15 minute decrease in lactate and increase in CO_2 tensions was greater than in the remaining four subjects.

It has been shown (Lambertsen et al. 1953) that the small increase in pulmonary ventilation and consequent reduction in arterial CO_2 tension which occurs in normal subjects breathing oxygen at sea level is probably due to a decrease in CO_2 carrying power of the blood produced by a slight increase in hydrogen ion content, resulting from an increased oxyhaemoglobin concentration. The maximum increase in oxyhaemoglobin content of the blood when breathing oxygen would occur within the first ten minutes. The present observations were made after the subjects had already been breathing oxygen for ten minutes and any further alteration in the blood acid base balance would presumably be independant of the oxyhaemoglobin effect. It seems reasonable to conclude that the decrease in pulmonary ventilation, as reflected by the increase in arterial CO_2 tensions shown by these six subjects, was a result of the decrease in circulating fixed acid and consequent decrease in blood and tissue hydrogen ion concentration induced by the improved blood and tissue oxygenation.

This progressive decrease in blood fixed acid concentrations and accompanying increase in blood CO_2

tensions when severely anoxaemic subjects breath oxygen rich air mixtures appears to explain the gradual onset of CO_2 intoxication in some of these subjects who have already high blood and tissue CO_2 tensions.

The oxygen induced CO_2 narcosis most commonly observed is a gradual process extending over a period of an hour or two or even more (Westlake, Simpson and Kaye 1955), but occasional cases have been reported in the literature of a rapid beginning and progression of the syndrome on starting oxygen therapy (e.g. Donald 1949, Sieker and Hickam 1956, Godfrey, Pond and Wood 1948, Motley 1950). It may be that a depressed hypoxic drive mechanism does play a part in producing these occasional rapidly developing oxygen induced CO_2 intoxications, but it would have to be shown that the arterial blood pH levels were high enough to allow a significant hypoxaemic peripheral chemoreceptor activity while air breathing in these subjects. If the pH levels were of this order it would appear to be unlikely that the CO_2 narcosis syndrome would develop since this is generally agreed to occur usually in subjects with an uncompensated respiratory acidosis. However, Comroe, Bahnson and Coates (1950) have reported three patients with normal arterial blood pH levels and CO_2 retention, who developed the mental changes of CO_2 intoxication while receiving oxygen therapy.

The Effects of Variations in the Carbon Dioxide Dissociation Curves of Blood.

It was suggested in an earlier section of this thesis (Aims and Methods) that, on theoretical grounds, the CO_2 tension differences between the arterial and venous blood of subjects with chronic CO_2 retention might be smaller than normal. This seemed a likely result of the increase in slope of the CO_2 dissociation curves of arterial and venous blood. (See figure 12).

In eight subjects with CO_2 retention and anoxaemia, the differences in CO_2 tension between internal jugular and arterial blood were considerably smaller than those found in normal subjects by previous authors. (Gibbs et al. 1942). They were also smaller than the tension differences found in four subjects, in the present study, with no evidence of CO_2 retention or anoxaemia. (See Table 8). It was realised that these small CO_2 tension differences could occur with CO_2 dissociation curves of normal slope if the CO_2 content differences were also smaller than normal. This appeared to be the case in two of the eight subjects. The remaining six had large CO_2 content differences between the cerebral venous and arterial blood while breathing air. Assuming that the R.Q. of these subjects was not grossly lowered at the time of sampling, these findings confirm the predicted arterial venous blood gas relationships.

It also seemed possible that a rise in the already high CO_2 carrying power of the venous blood due

to a decrease in the hydrogen ion content of the blood accompanying a decrease in fixed acid concentration, as previously demonstrated in anoxaemic subjects breathing oxygen, might cause a decrease in the tissue CO_2 tension. This decrease in tissue CO_2 tension would be expected to result in a decrease in pulmonary ventilation. The opposite effect of an increase in tissue CO_2 tension of the brain has already been shown (Lambertsen et al. 1953) to be probably responsible for the increase in ventilation noted in normal subjects on breathing oxygen. The result should be a decrease in the already low CO_2 tension difference between venous and arterial blood.

This hypothesis was tested by measuring the arterial and cerebral venous gas parameters of seven subjects while breathing air and then oxygen for ten minutes. The results showed that three of the four subjects who had no evidence of CO_2 retention while breathing air had a normal blood gas response to oxygen breathing. The arterial CO_2 tension decreased in all three, but the cerebral venous CO_2 tension only showed the expected rise in two of them. In one subject the arterial CO_2 tension decrease was large and there was a slight decrease in venous CO_2 tension. This last finding may have been due in part to voluntary over-breathing since Kety and Schmidt (1946) showed a similar arterial and cerebral venous blood gas changes on voluntary hyperventilation in normal subjects. The remaining subject who was considered to have no evidence

of CO_2 retention while breathing air showed a rise in arterial CO_2 tension on breathing oxygen. This is the typical response of subjects with CO_2 retention to oxygen breathing, and the arterial CO_2 content of this subject was just at the upper limit of normality.

Including this subject, there were four with some degree of CO_2 retention. Three of these showed an increase in arterial CO_2 tension associated with a decrease in cerebral venous CO_2 tension on changing over from air to oxygen breathing. One subject also showed the expected rise in arterial CO_2 tension but there was an associated rise in cerebral venous CO_2 tension. This last finding is difficult to explain by the present line of argument, but it is suggested that the findings in the other three subjects support the hypothesis that the decrease in alveolar ventilation noted in subjects with CO_2 retention on breathing oxygen, may be due to a decrease in tissue CO_2 tension associated with a decrease in blood hydrogen ion content leading to an increase in the CO_2 capacity of the blood.

In an earlier discussion of the possible effects of shifts in the blood CO_2 dissociation curves, it was suggested that the reduction in CO_2 tension difference between the tissues and arterial blood might be large enough to result in an actual reversal of the normal situation where the venous and tissue tensions are higher than the arterial. The figures for one subject show this effect, and while it is realised that this is insufficient

evidence to support a claim for the importance of such a reversal of the normal CO_2 tension relationship between the tissues and arterial blood, it seems reasonable to postulate that the appearance of the neurological signs of CO_2 intoxication in this subject might have an explanation in this finding. If the gradient for CO_2 were to continue in this way to be from the arterial blood to the tissues, instead of, as normally, from tissues to venous blood, it is conceivable that high tissue levels of CO_2 could build up very quickly.

The problems which arise from these observations will require more detailed work on a larger number of subjects, but this will be carried out by a number of collaborators and might not therefore be suitable for inclusion in this thesis, which merely presents the results of the present investigator's work in this field.

SUMMARY

SUMMARY.

A short period of oxygen breathing, in a group of subjects with pulmonary anoxaemia and CO_2 retention of varying severity, produced degrees of ventilatory depression and elevations of arterial blood CO_2 tension which bore no relation to the severity of the initial anoxaemia. Significant correlations were obtained, however, between the initial arterial pH levels and the changes in alveolar ventilation and arterial CO_2 tension.

Where the blood pH was greater than 7.35, approximately, these changes were large but below this level of pH they were small. Animal experiments reported in the literature, supported these findings and it was concluded that a 'hypoxic drive', mediated by the peripheral chemoreceptors, was not a factor in the control of respiration in subjects with pulmonary anoxaemia and CO_2 retention in the presence of an acidaemia.

It was suggested that the blood concentrations of fixed acids in subjects with severe hypoxaemia and CO_2 retention might be high, and that in such subjects who are also acidaemic the ventilatory depression commonly observed upon breathing oxygen over prolonged periods, might be due to decrease of the blood fixed acid levels under the influence of improved tissue oxygenation.

A preliminary pilot study of the effects of oxygen breathing, over a brief period, on the CO_2 dissociation curves of arterial blood from subjects with anoxaemia and CO_2 retention supported this hypothesis,

and actual measurements of blood lactate gave values as high as 6.00 mM/L. The majority of subjects with arterial oxygen tensions below a level of 60 mm. Hg. had raised blood lactate concentrations.

A group of subjects with anoxaemia and CO_2 retention were investigated while breathing oxygen for periods up to forty-five minutes. A significant correlation was demonstrated between decrease in blood lactate values and increase in arterial CO_2 tensions.

Previous investigators have noted that the slight increase in pulmonary ventilation observed in normal subjects breathing oxygen at sea level is probably due to a slight rise in cerebral venous CO_2 tension which occurs in these conditions. This was confirmed in a small group of subjects who had no evidence of CO_2 retention.

In a larger group of subjects who had varying degrees of CO_2 retention, the CO_2 tension differences between arterial and internal jugular blood were smaller than in the above mentioned group, and also smaller than those previously reported in normal subjects. The cerebral venous CO_2 tensions of these subjects with CO_2 retention, decreased upon breathing oxygen over a brief period and there was an increase in the arterial CO_2 tensions reflecting a depression of respiration.

It was concluded that an increase in slope of the blood CO_2 dissociation curves, for which there was evidence, might be responsible for the diminished CO_2

tension differences between arterial and cerebral venous blood, and that the effect of oxygen administration to such subjects with anoxaemia and CO_2 retention is to cause a rise in blood pH as a result of a decrease in circulating fixed acids, with a consequent lowering of cerebral venous and tissue CO_2 tensions and further ventilatory depression.

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* These papers could not be obtained through the library services, but are referred to in the text because other authors quote them as being relevant to the subject matter.

A C K N O W L E D G E M E N T S

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TABLE I.

Alveolar ventilation ($\dot{V}A$), arterial blood gas tensions (PO_2 & PCO_2) and pH values obtained in thirteen subjects with pulmonary anoxaemia and carbon dioxide retention before, and at the end of, a ten minute period of oxygen breathing.

Subject No.	Breathing air				Breathing oxygen			Change in		
	$\dot{V}A$ L/min.	PO_2 mm.Hg.	PCO_2 mm.Hg.	pH	$\dot{V}A$ L/min.	PO_2 mm.Hg.	PCO_2 mm.Hg.	$\dot{V}A$ L/min.	PO_2 mm.Hg.	PCO_2 mm.Hg.
I	--	30	79	7.360	--	I20	77	--	+90	- 2
2	--	32	66	7.343	--	40	66	--	+ 8	+ 0
3	--	36	55	7.486	--	8I	65	--	+45	+I0
4	--	45	90	7.306	--	I20	93	--	+75	+ 3
5	3.38	47	50	7.452	I.59	I20	66	-I.79	+73	+I6
6	3.64	53	45	7.338	3.29	I20	49	-0.35	+67	+ 4
7	3.50	58	60	7.3I7	2.48	I30	69	-I.02	+72	+ 9
8	--	6I	4I	7.464	--	I00	46	--	+39	+ 5
9	3.57	65	45	7.474	I.89	I30	60	-I.68	+65	+I5
I0	4.53	66	48	7.353	4.II	I20	50	-0.42	+54	+ 2
II	4.88	69	45	7.374	3.64	I20	5I	-I.24	+5I	+ 6
I2	5.86	73	38	7.483	3.03	I20	50	-2.83	+47	+I2
I3	--	8I	38	7.460	--	II0	45	--	+29	+ 7

TABLE 2.

Arterial blood gas values obtained from ten subjects with pulmonary anoxaemia and CO_2 retention immediately before and during the last three minutes of a twenty minute period of oxygen breathing.

(Data of Brodovsky et al. 1960).

Breathing Air		Breathing Oxygen	Change in	Predicted Change in
Arterial		Arterial	Arterial	Arterial
PO_2 mm. Hg.	PCO_2 mm. Hg.	PCO_2 mm. Hg.	PCO_2 mm. Hg.	PCO_2 mm. Hg.
36	60	63	3	3
47	38	50	12	12
48	51	61	10	10
49	43	57	14	15
52	40	70	30	33
57	41	47	6	7
58	55	59	4	5
62	56	57	1	1
68	41	51	10	14
69	61	61	0	0

TABLE 3.

To show the predicted change in arterial carbon dioxide tension (ΔPCO2) when the observed change in arterial oxygen tension on breathing oxygen (ΔPO2) is arbitrarily standardised to +75 mm. Hg. for all subjects represented in TABLE I. (See p.49)

Subject No.	Observed ΔPO2 mm.Hg.	Observed ΔPCO2 mm.Hg.	Predicted ΔPCO2 mm.Hg.
I	+90	-2	-2
2	+ 8	+0	+0
3	+45	+I0	+I7
4	+75	+ 3	+ 3
5	+73	+I6	+I6
6	+67	+ 4	+ 4
7	+82	+ 9	+ 9
8	+39	+ 5	+I0
9	+65	+I5	+I7
I0	+54	+ 2	+ 3
II	+5I	+ 6	+ 9
I2	+47	+I2	+20
I3	+29	+ 7	+I8

TABLE 4.

Summary of relationships between alveolar ventilation ($\dot{V}A$), arterial blood gas (P_{O_2} & P_{CO_2}) and pH values, before and during a short period of oxygen breathing. (From the data of the present investigation and that of Brodovsky et al. (1960))

Relationship examined	Correlation coefficient	Probability on t test
From the present data (13 subjects)		
P_{O_2} (air) & $\Delta\dot{V}A$ (oxygen)	+ 0.13	> 5.0%
P_{O_2} (air) & ΔP_{CO_2} (oxygen)	+ 0.37	> 5.0%
P_{CO_2} (air) & $\Delta\dot{V}A$ (oxygen)	- 0.46	> 5.0%
P_{CO_2} (air) & ΔP_{CO_2} (oxygen)	- 0.51	> 5.0%
P_{CO_2} (air) & Predicted ΔP_{CO_2} (oxygen)	- 0.61	< 5.0%
pH (air) & $\Delta\dot{V}A$ (oxygen)	+ 0.85	< 5.0%
pH (air) & ΔP_{CO_2} (oxygen)	+ 0.66	< 5.0%
pH (air) & Predicted ΔP_{CO_2} (oxygen)	+ 0.86	< 0.1%
From the data of Brodovsky et al.(10 subjects)		
P_{O_2} (air) & ΔP_{CO_2} (oxygen)	- 0.25	> 5.0%
P_{CO_2} (air) & ΔP_{CO_2} (oxygen)	- 0.70	< 5.0%
P_{CO_2} (air) & Predicted ΔP_{CO_2} (oxygen)	- 0.72	< 5.0%

TABLE 5.

Arterial blood lactic acid contents compared with arterial oxygen tensions in sixteen subjects with respiratory insufficiency.

Subject No.	Arterial oxygen tension mm.Hg.	Lactic acid mM./L.
I8	30	3.5 *
I5	35	5.5 *
I6	36	4.3 *
I9	40	4.4 *
20	45	6.2 *
I7	45	5.6 *
5	47	2.6 *
8	53	I.7
I3	55	3.2 *
I2	56	3.I *
7	60	0.8
I0	6I	3.4 *
4	65	I.0
6	66	0.8
I4	70	3.I *
9	73	2.I

Lactic acid measured by the method of Avery and Hastings (I93I). * indicates values greater than those found by Laug (I934) in normal subjects at rest, using the same method. (range = 0.58 to 2.40 mM./L.)

TABLE 6.

Effect of prolonging oxygen breathing beyond first ten minutes on arterial carbon dioxide tension (PCO2 mm.Hg.) and arterial blood concentration of lactic acid. (mM./L.)

Time =	0 mins.		I5 mins.		30 mins.		45 mins.		Total change in	
Subject No.	PCO2	Lactate	PCO2	Lactate	PCO2	Lactate	PCO2	Lactate	PCO2	Lactate
I0	46	3.4	49	3.0	5I	2.4	--	--	+ 5	-I.0
I4	45	2.0	--	--	49	I.2	--	--	+ 4	-0.8
I6	65	3.I	67	--	66	--	70	2.5	+ 5	-0.6
* I7	93	5.I	--	--	--	--	I04	3.I	+II	-2.0
* I8	78	2.8	--	--	--	--	97	I.I	+I9	-I.7
I9	68	4.I	--	--	74	3.3	--	--	+ 6	-0.8

* developed signs of carbon dioxide intoxication during the period of oxygen breathing.

TABLE 7.

Relationships between blood gas values of arterial and internal jugular venous blood in eight subjects with anoxaemia and carbon dioxide retention, while at rest and breathing air.

Subject No.	Oxygen content vols.%			Plasma carbon dioxide content vols.%			Carbon dioxide tension mm.Hg.			Oxygen capacity vols.%
	A	V	A-V	A	V	V-A	A	V	V-A	
I	I6.0	I3.4	2.6	II3.6	II6.5	2.9	6I.7	63.2	I.5	20.5
2	9.3	6.8	2.5	I08.0	II0.4	2.4	8I.0	82.I	I.I	2I.0
3	I7.4	I4.6	2.8	97.8	I08.6	I0.8	62.6	67.2	4.6	23.3
4	I9.4	I7.2	2.2	95.7	I07.7	I2.0	55.6	57.8	2.2	20.4
5	I8.6	I6.I	2.5	92.I	I00.3	8.2	66.9	69.3	2.4	25.7
6	I8.7	I6.2	2.5	82.5	95.0	I2.5	48.I	53.I	5.0	20.I
7	II.5	8.I	3.4	79.5	88.0	8.5	65.3	68.2	2.9	I8.3
8	20.4	I6.3	4.I	66.6	74.2	7.6	45.0	48.0	3.0	20.9

TABLE 8.

Change in relationships between blood gas values of arterial and internal jugular venous blood when breathing air and then oxygen for ten minutes. Figures are shown for four subjects with chronic carbon dioxide retention (2, 3, 7, 9) and three subjects with no carbon dioxide retention (I0, II, I2).

Subject No. & diagnosis	Breathing	Oxygen content vols.%			Plasma CO2 content vols.%			CO2 tension mm.Hg.			Change in V-A diff.		
		A	V	A-V	A	V	V-A	A	V	V-A	oxygen content A-V	CO2 content V-A	CO2 tension V-A
2 Emphysema	air	9.3	6.8	2.5	I08.0	II0.4	2.4	8I.0	82.I	I.I	-0.3	-0.5	+4.9
	oxygen	I9.3	I7.I	2.2	II2.8	II4.7	I.9	8I.5	87.5	6.0			
3 Emphysema	air	I7.4	I4.6	2.8	97.8	I08.6	I0.8	62.6	67.2	4.6	+0.8	+I.9	-3.5
	oxygen	23.0	I9.4	3.6	98.0	II0.7	I2.7	64.5	66.6	I.I			
7 Emphysema	air	II.5	8.I	3.4	79.5	88.0	8.5	65.3	68.2	2.9	+0.2	+3.2	-5.2
	oxygen	I7.9	I4.3	3.6	86.9	95.2	II.7	69.I	66.8	-2.3			
9 Asthma	air	20.4	I6.I	4.3	50.4	57.5	7.I	39.8	46.5	6.7	-I.5	+I.4	-4.7
	oxygen	20.6	I6.8	3.8	5I.5	60.0	8.5	43.2	46.2	3.0			
I0 Ischaemic H.D.	air	I9.0	II.2	7.8	48.4	60.I	II.7	34.2	39.0	4.8	-4.5	-2.2	+4.6
	oxygen	I9.3	I6.0	3.3	49.0	58.5	9.5	30.9	40.3	9.4			
II Uraemia	air	I7.4	I2.8	4.6	46.5	55.3	8.8	28.4	32.4	4.0	-I.0	-I.4	+6.8
	oxygen	I7.5	I3.9	3.6	46.I	53.5	7.4	24.5	35.3	I0.8			
I2 Asthma	air	I9.3	I2.0	6.3	49.I	54.4	5.3	36.7	50.0	I2.3	-2.5	-2.2	+7.9
	oxygen	I9.4	I5.6	3.8	48.5	5I.6	3.I	28.6	48.8	20.2			

TABLE 9

REPEATABILITY OF BLOOD LACTATE ESTIMATIONS

Method of Avery and Hastings (1931), 30 consecutive duplicate estimations.

Sample No.	Duplicate Measurements 1 (mM./L.)	2 (mM./L.)	Difference
1	6.24	6.10	0.14
2	2.94	3.01	0.07
3	4.36	4.47	0.11
4	4.00	4.25	0.25
5	3.26	3.48	0.22
6	3.52	3.37	0.15
7	2.72	2.88	0.16
8	1.15	1.05	0.10
9	5.67	5.46	0.21
10	5.05	5.05	0.00
11	2.94	3.16	0.22
12	4.38	4.16	0.22
13	3.09	3.16	0.07
14	2.72	2.44	0.28
15	5.49	5.57	0.08
16	4.70	4.63	0.07
17	4.38	4.38	0.00
18	2.99	3.13	0.14
19	2.02	2.02	0.00
20	1.30	1.08	0.22
21	3.27	3.20	0.07
22	2.42	2.58	0.16
23	3.37	2.89	0.48
24	2.68	2.39	0.29
25	1.15	0.09	0.06
26	1.54	1.80	0.26
27	1.65	1.58	0.07
28	2.11	2.32	0.21
29	3.20	3.49	0.29
30	2.49	2.78	0.29

mean 0.16, S.D. 0.09 mM/L.

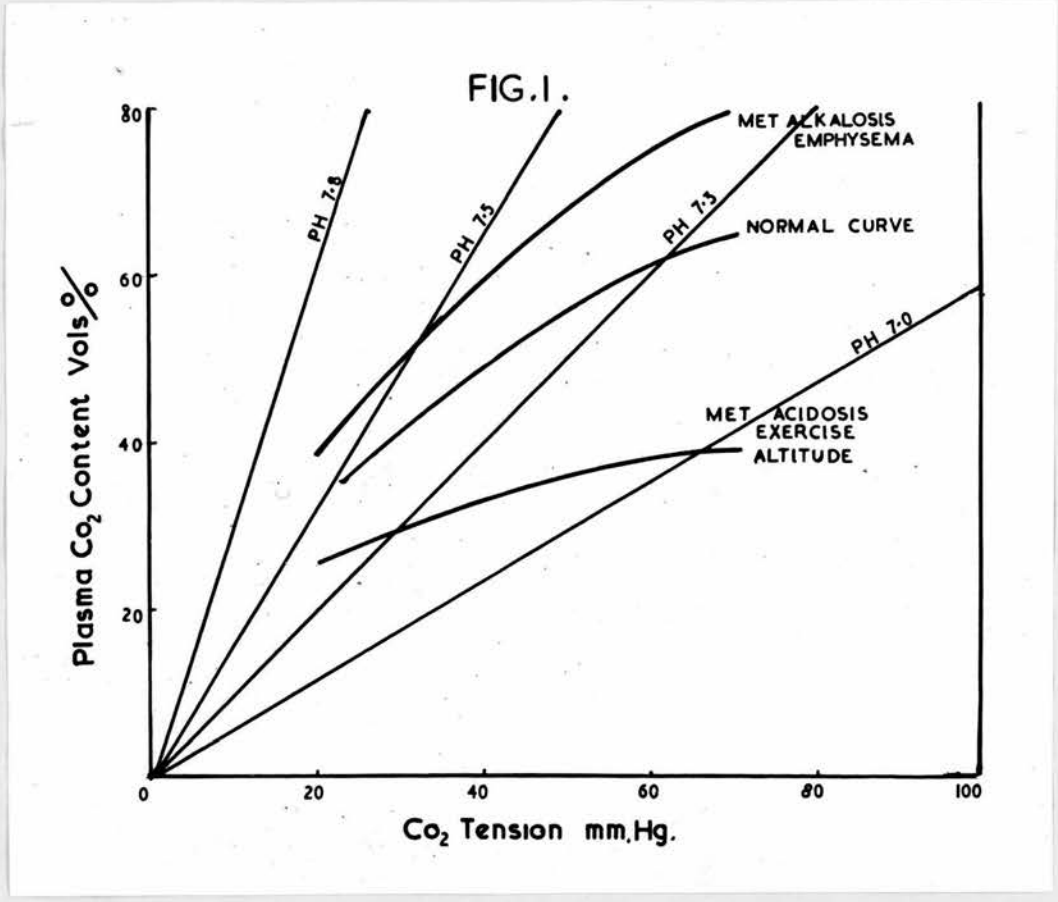

Fig.I. A diagrammatic representation of a normal carbon dioxide dissociation curve of blood, and two curves which are typical of the principal types of abnormality in disturbances of the blood acid-base equilibrium.
In conditions of chronic carbon dioxide retention and metabolic alkalosis, the curves are higher and more steeply sloping than normal.

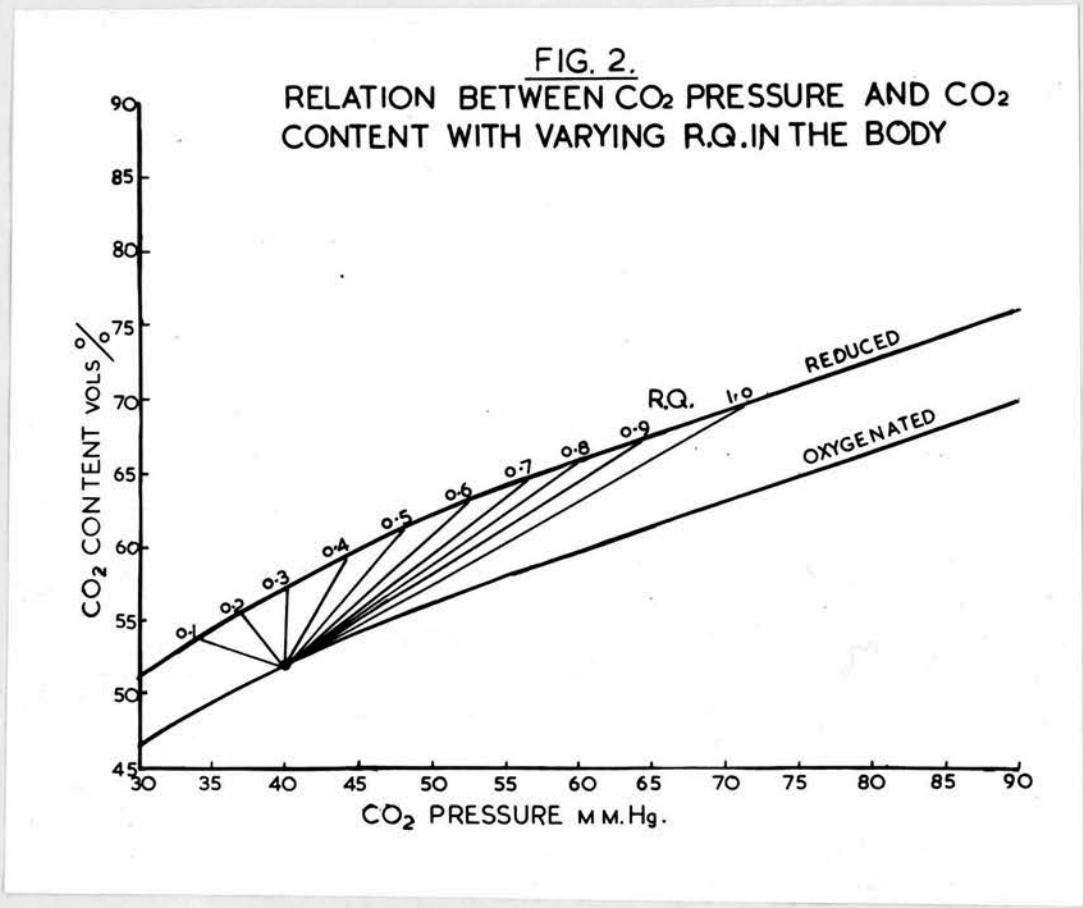

Fig.2. A diagrammatic representation of carbon dioxide dissociation curves of oxygenated and reduced blood. From the arterial blood point (lower curve) lines radiate to the reduced curve to give the CO2 values expected in such blood at various levels of R.Q.

It can be seen that an increase in slope of the curves will result in a counter-clockwise rotation of the R.Q. lines about the arterial point, leading to larger CO2 content differences and smaller CO2 tension differences between venous and arterial blood.

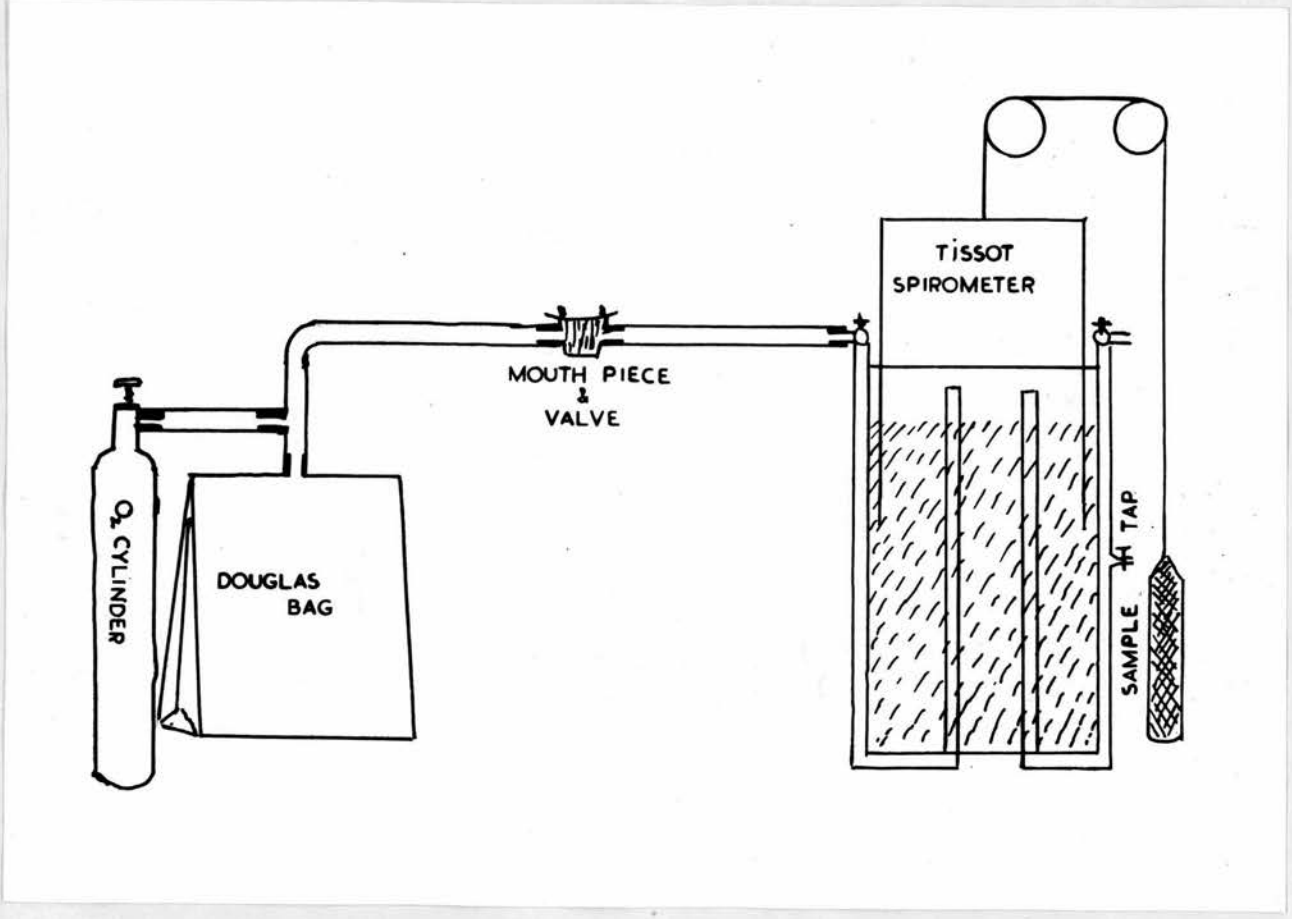

Fig. 3. Arrangement of apparatus for measuring the ventilatory response to air and oxygen breathing.

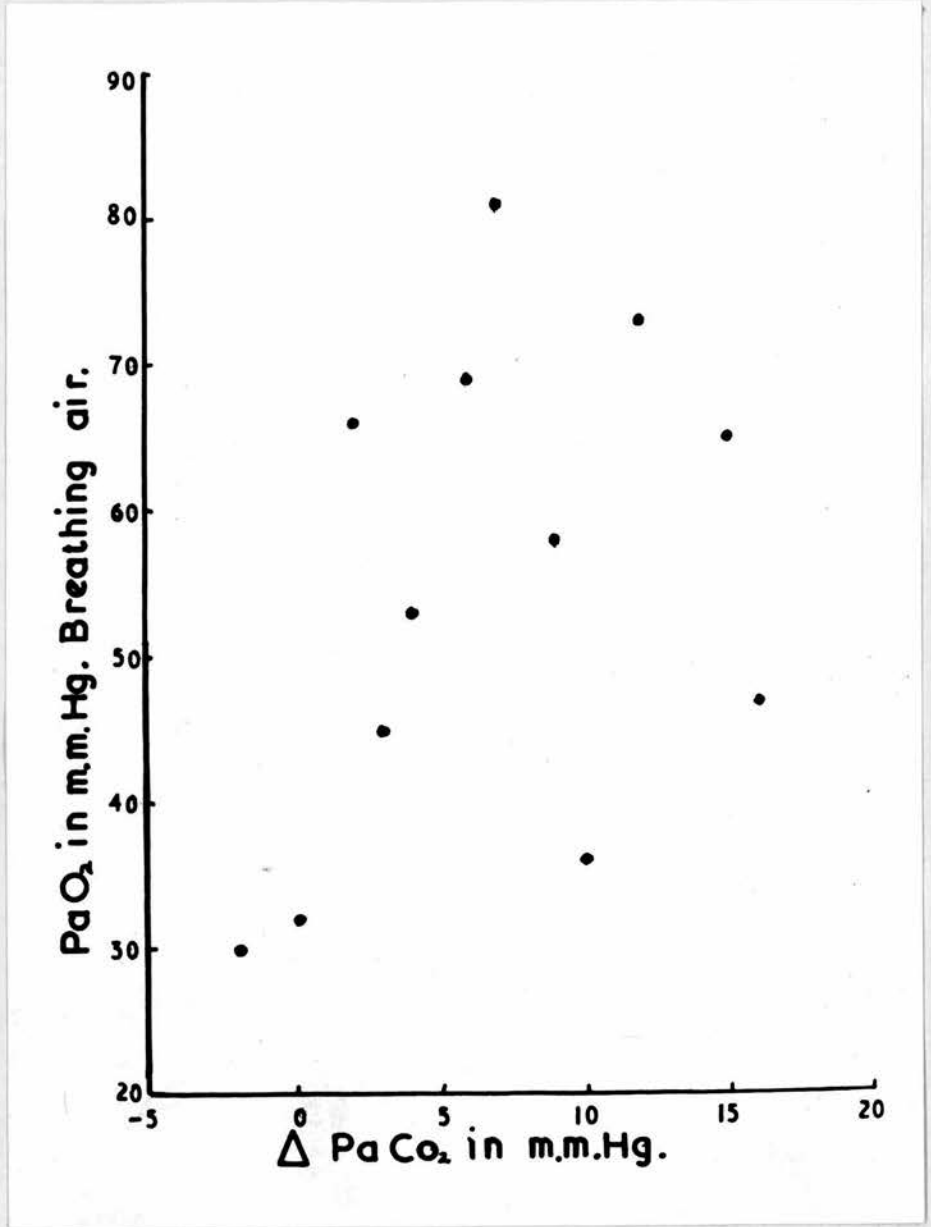

Fig. 4. Arterial blood oxygen tensions while breathing air (PaO2) compared with changes in arterial carbon dioxide tensions (ΔPaCO2) while breathing oxygen for ten minutes.
(Thirteen subjects with CO2 retention and anoxaemia)

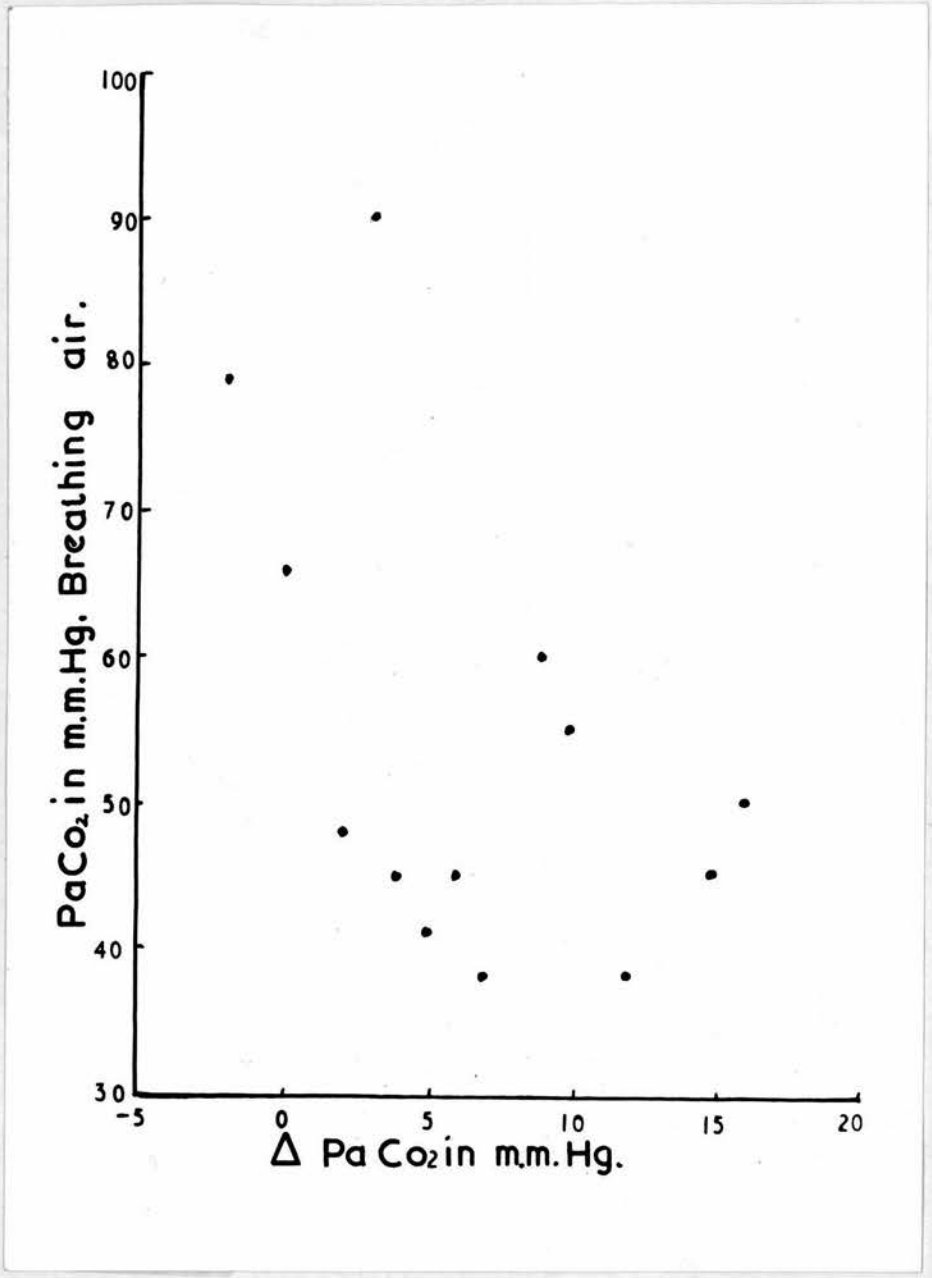

Fig. 5. Arterial blood carbon dioxide tensions while breathing air (PaC02) compared with changes in arterial carbon dioxide tensions (ΔPaC02) while breathing oxygen for ten minutes.
(Thirteen subjects with C02 retention and anoxaemia)

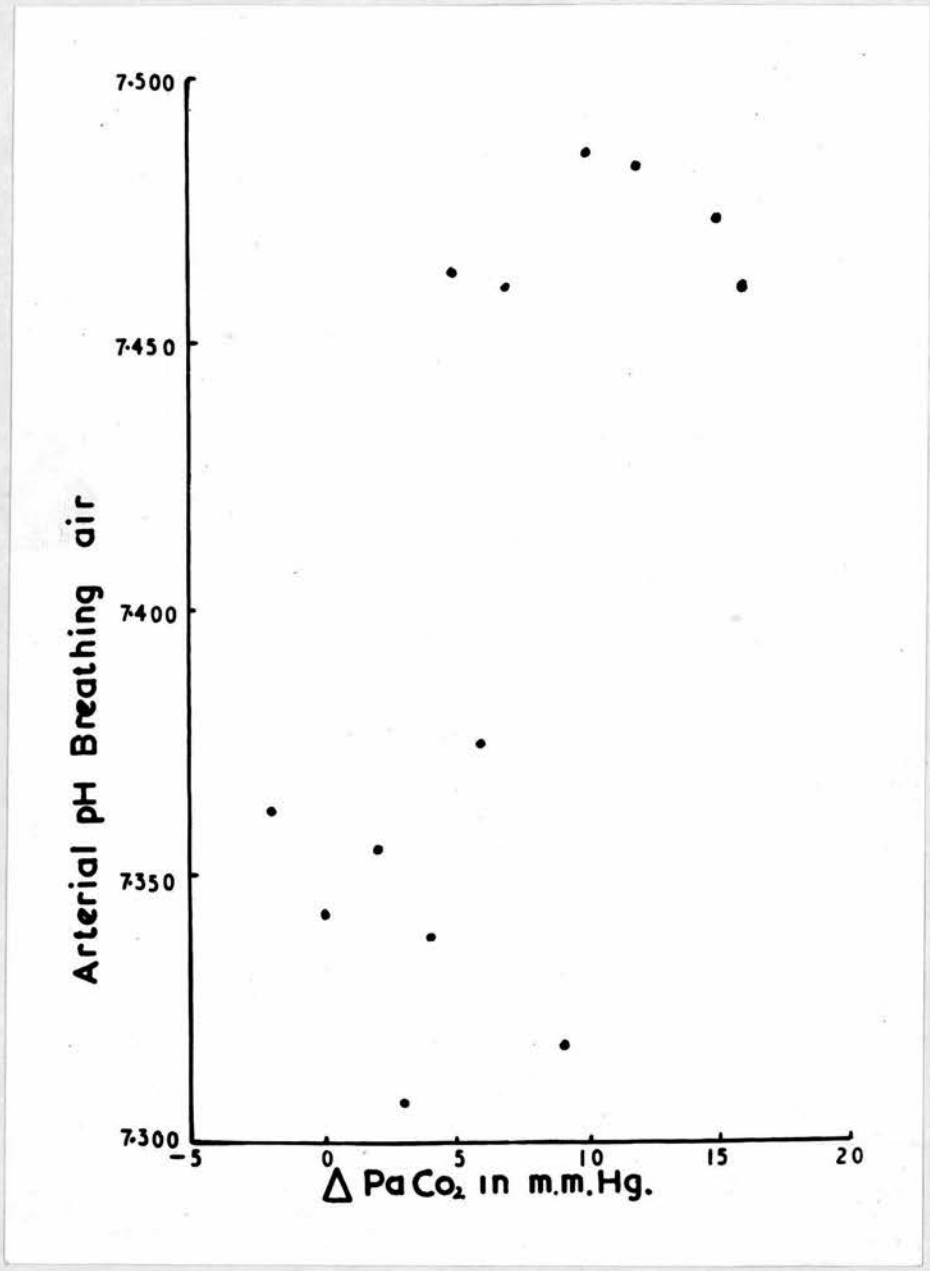

Fig. 6. Arterial blood pH values while breathing air compared with change in arterial carbon dioxide tensions (ΔPaCO2) while breathing oxygen for ten minutes.

(Thirteen subjects with CO2 retention and anoxaemia)

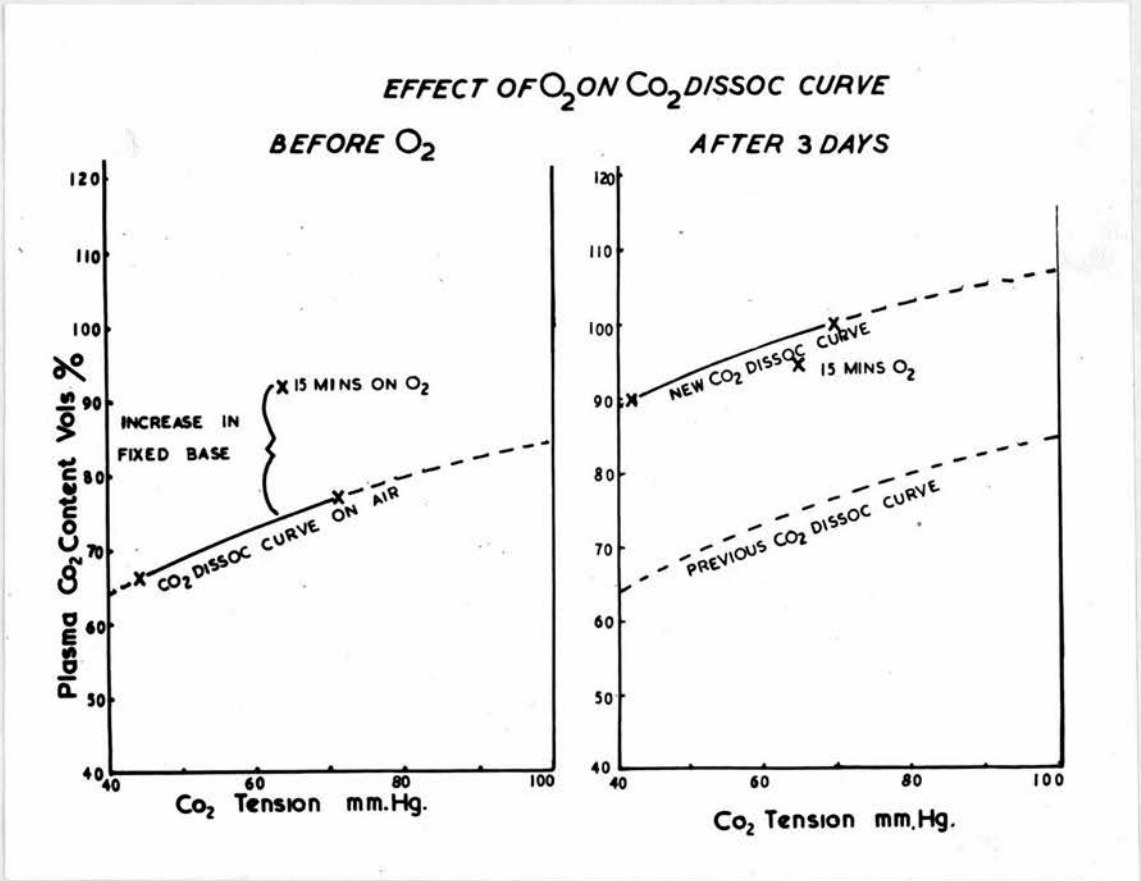

Fig.7.C02 dissociation curves constructed by tonometer equilibration from the arterial blood of a subject with severe anoxaemia (Pa02=54mm.Hg.) and C02 retention before and after three days of oxygen therapy.

Before oxygen therapy, a fifteen minute period of oxygen breathing results in a large upward shift of the curve.

After oxygen for three days, fifteen minutes of oxygen breathing results in no further upward shift. The arterial oxygen tension is now 71mm.Hg.(after breathing air for two hours).

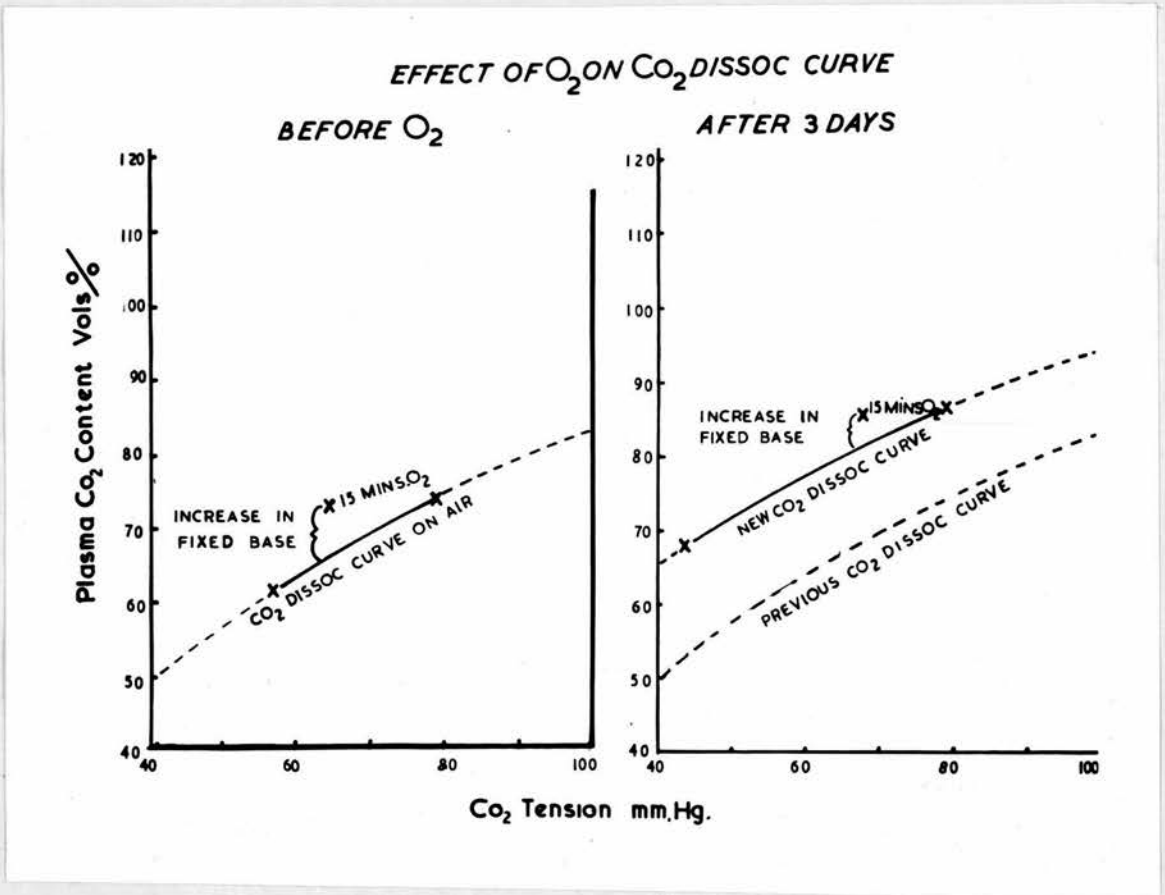

Fig.8. C02 dissociation curves constructed by tonometer equilibration from the arterial blood of a subject with severe anoxaemia (Pa02=53mm.Hg.) and C02 retention before and after three days of oxygen therapy. Before oxygen therapy, a fifteen minute period of oxygen breathing results in a large upward shift of the curve.

After oxygen for three days, fifteen minutes of oxygen breathing still results in some upward shift. The arterial oxygen tension is now only 50mm.Hg. (after breathing air for two hours).

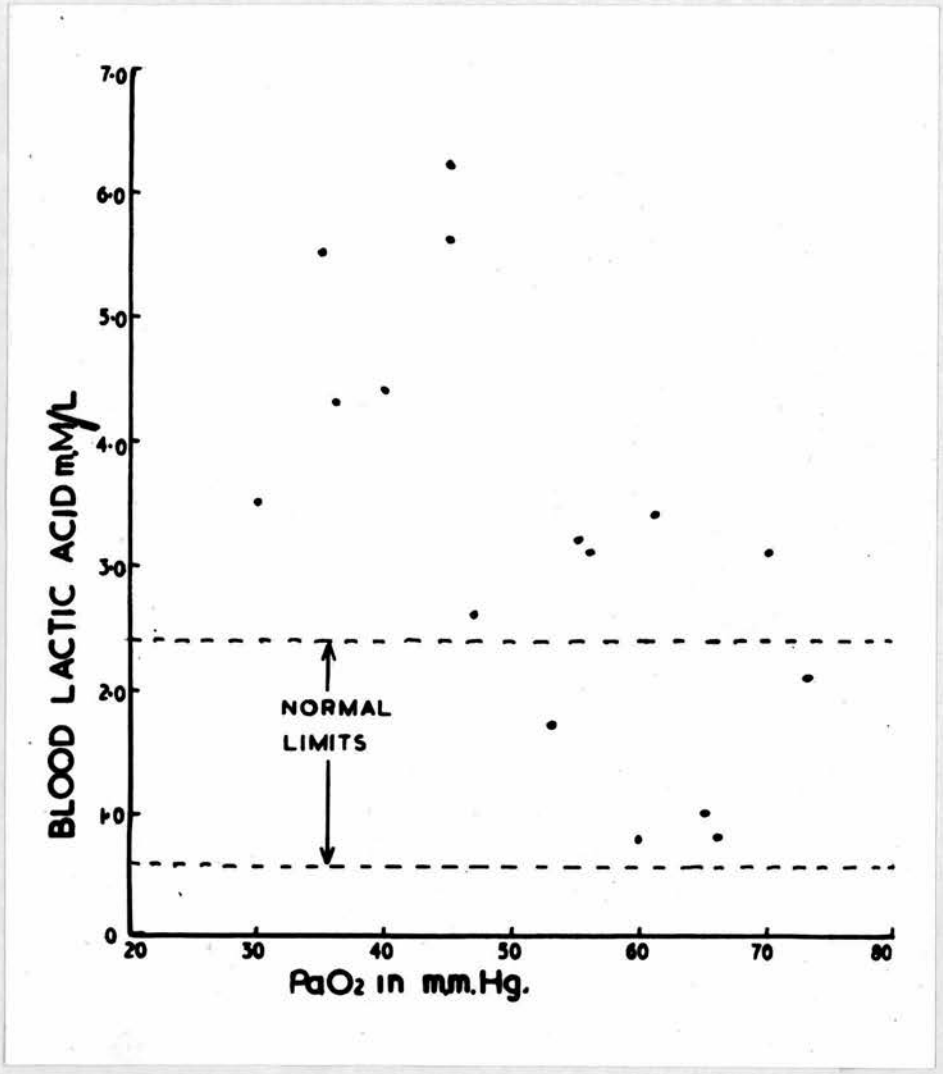

Fig. 9. Lactic acid contents of arterial blood compared with arterial oxygen tensions (Pa_{O_2}) in sixteen subjects with CO_2 retention and anoxaemia, while breathing air.

(Fig. includes normal range found by Laug (1934))

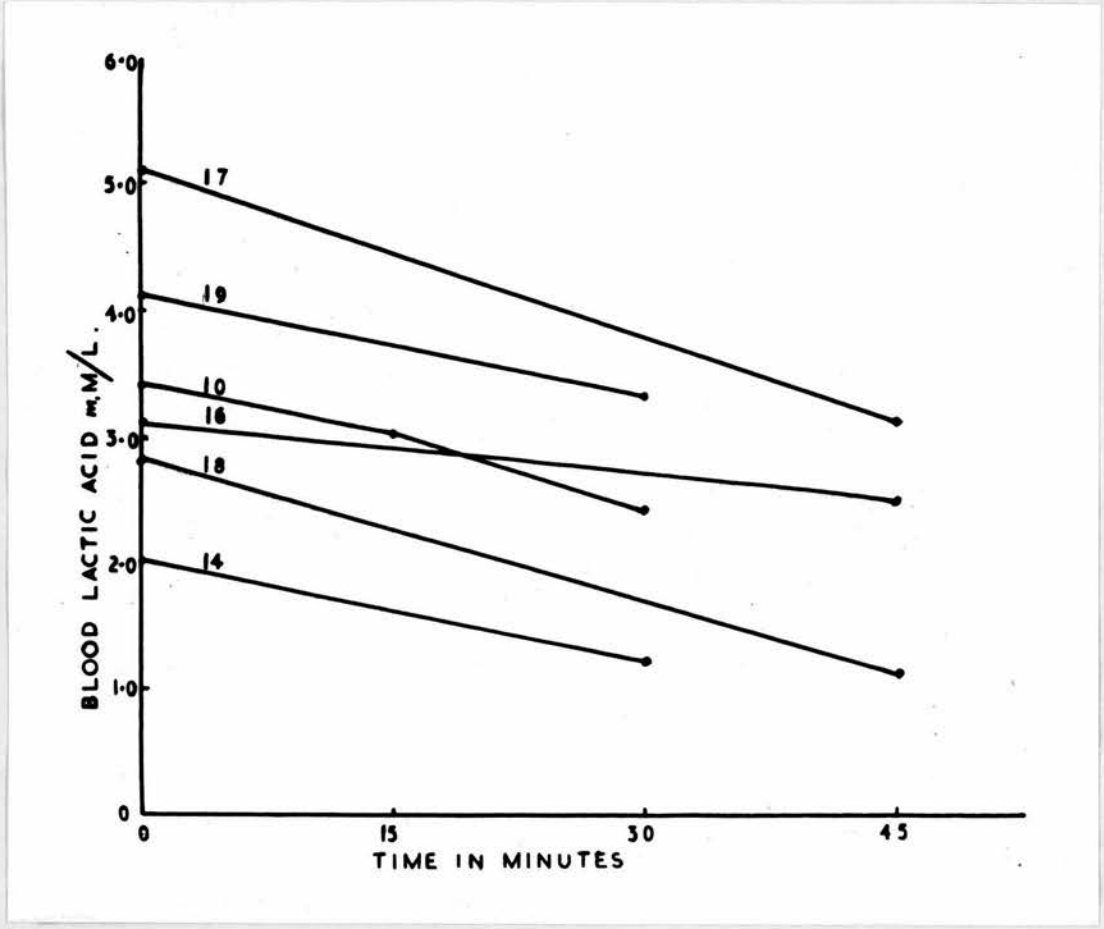

Fig.IO. Changes in arterial blood lactate concentration in six subjects with anoxaemia and CO2 retention While breathing oxygen for thirty or forty-five minutes. Zero time is after ten minutes of oxygen breathing.

(subject's number above each trend line (TABLE 6))

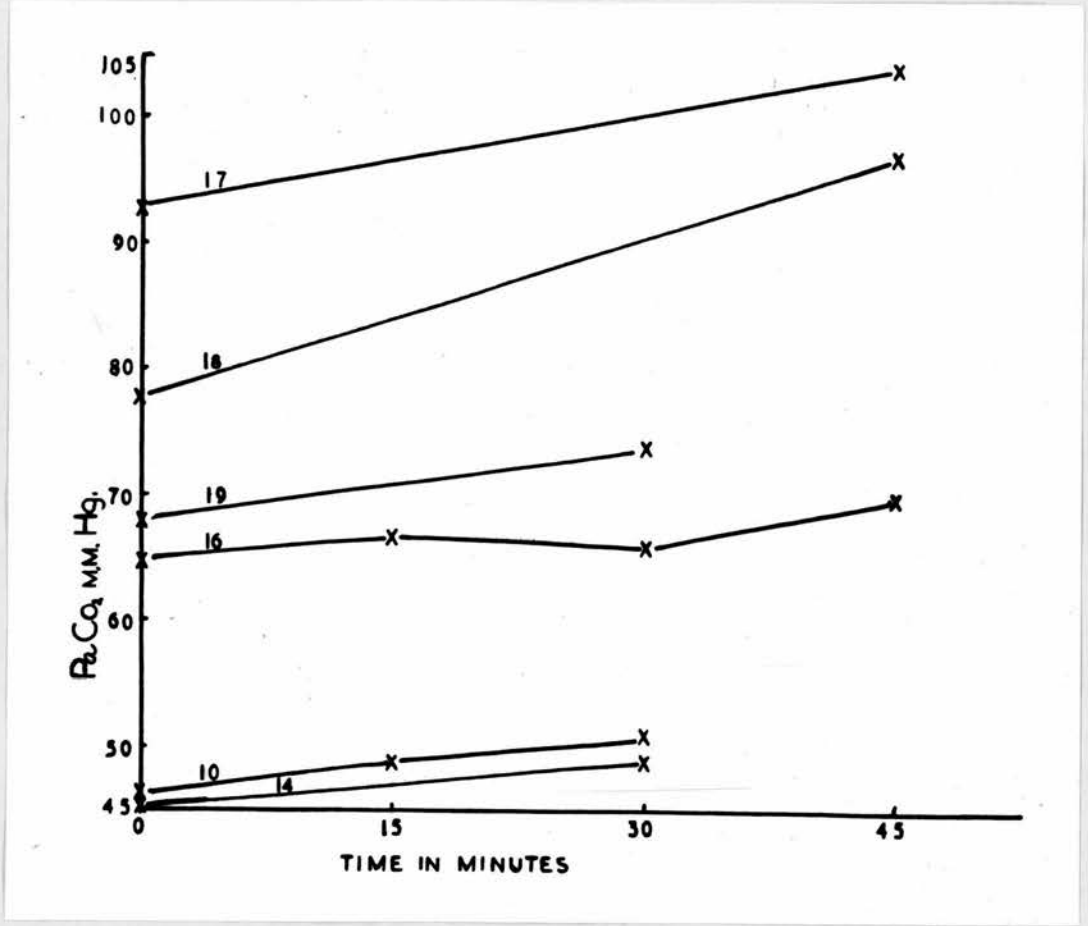

Fig.II. Changes in arterial blood carbon dioxide tension (PaCO2) in the same six subjects whose blood lactate contents are shown in Fig.IO,i.e. while breathing oxygen for thirty or forty-five minutes.

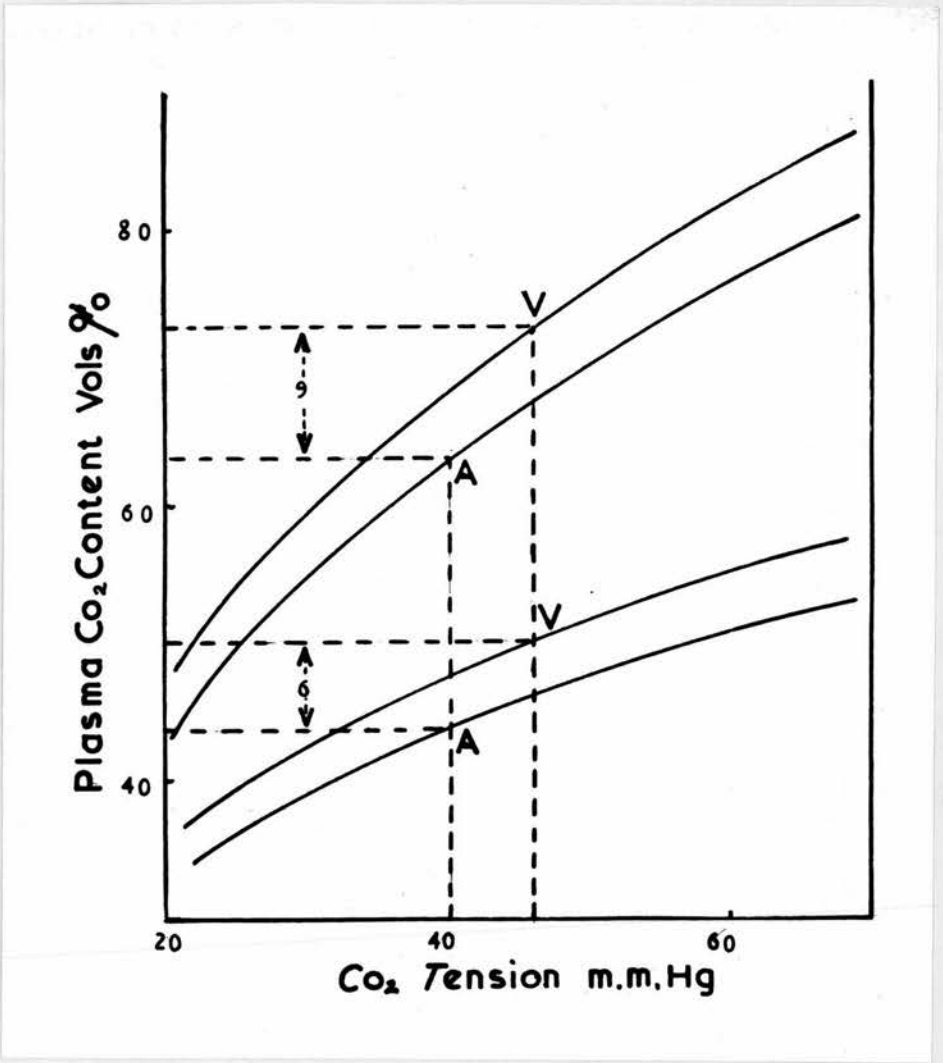

Fig.I2. A diagrammatic comparison of the change in carbon dioxide content difference between venous and arterial blood produced by a given venous-arterial carbon dioxide tension difference in two pairs of carbon dioxide dissociation curves differing only in height and slope. The upper and lower curves of each pair represent venous and arterial blood dissociation curves respectively.