The Effect of Oxygen at Elevated Atmospheric Pressure and Hypothermia on Tissue Metabolism.

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SUMMARY

The therapeutic potentialities of hyperbaric oxygen have been intensively investigated in Amsterdam and Glasgow during the past decade but scientists have been interested in the biological properties of high pressures of air or oxygen since the discovery of the phenomenon of atmospheric pressure.

The use of hyperbaric oxygen can be classified into three main categories and examples of these form the three principal sections of this thesis:

1. The use of hyperbaric oxygen in anoxic states, such as carbon monoxide poisoning, where tissue oxygenation is maintained at adequate levels until the normal method of oxygen transport is restored.
2. The use of the metabolic effects of hyperbaric oxygen on normal tissues to reduce their oxygen consumption and thus prolong the period during which the circulation may be totally arrested as an aid to heart or brain surgery.
3. The toxic effects of hyperbaric oxygen, which may be

of use as selective toxic agents against malignant tumour cells or pathogenic bacteria.

CARBON MONOXIDE POISONING

Killick and Marchant (1959) showed clearly that 5% carbogen removed carbon monoxide from the blood more rapidly than pure oxygen only but there was much controversy regarding the administration of carbon dioxide in an asphyxial state in which it was presumed carbon dioxide retention would already exist. Experiments are described which show that hyperventilation occurs during carbon monoxide intoxication causing respiratory alkalosis. When respiratory depression supervenes, the pCO_2 rises to normal levels only and carbogen mixtures are thus not contra-indicated in the treatment of this condition. Controversy next arose as to whether 5% or 7% carbogen would reduce the blood level of carboxyhaemoglobin more speedily and experiments are described which show that there is no difference between the efficiency of these agents in this respect. Experiments are also described in which it is shown that oxygen at two atmospheres pressure will reduce the blood-level of carboxyhaemoglobin about twice as fast as carbogen

mixtures and it is pointed out that the main benefit derived from this therapy is the rapid correction of tissue anoxia by dissolution of oxygen in physical solution in the plasma, thus by-passing the blocked haemoglobin mechanism. An account is also given of a group of patients treated successfully with oxygen at two atmospheres pressure.

METABOLIC EFFECTS OF HYPERBARIC OXYGEN.

In order to determine the metabolic effects on tissues of administering high pressures of oxygen for the relatively short periods of time required for heart surgery, the oxygen consumption of tissue homogenates was measured over a two hour period when the tissue was exposed to pressures of oxygen of 150 mm. Hg., 300 mm. Hg., 760 mm. Hg., or 1520 mm. Hg. at 37° C., 28° C. or 15° C. At 37° C. a linear depression in oxygen consumption was found as the pO_2 rose so that there was a 32% reduction in the oxygen consumption of tissue exposed to a pO_2 of 1520 mm. Hg. as compared to that exposed to a pO_2 of 150 mm. Hg. At 28° C. and 15° C. there was an initial rise in oxygen consumption with increasing pO_2 but beyond a certain level (about 500 mm. Hg. at 28° C. and 1000 mm. Hg. at 15° C.) further increase in oxygen pressure caused a fall in oxygen consumption. In terms of the prolongation of the safe period during which the circulation may be totally arrested

maximum benefit should be found at normothermia and though less is to be gained at hypothermia considerable advantage may accrue by ensuring adequate oxygenation at low temperatures.

Experiments, in dogs, show that the safe duration of total circulatory arrest at 37° C. can be increased from 5 minutes to 8 minutes if oxygen at two atmospheres pressure is breathed as compared to one atmosphere pressure. At 28° C. the time is increased from 20 minutes to 30 minutes while at 20° C. the safe duration of total circulatory arrest is 40 minutes whether the animal is breathing oxygen at one or two atmospheres pressure.

OXYGEN TOXICITY

Ten rats exposed to oxygen at two atmospheres pressure for 18 hours died while another ten rats exposed for six hours survived. Of ten rats exposed for 12 hours, two died. Mortality was not avoided by administering the same total quantity of oxygen in three divided doses, each separated by twenty-four hours, but mortality was reduced to 50% of that obtained from continuous exposure for 12 or 18 hours. Clinically, neurological signs occurred in association with pulmonary signs and histologically there was patchy atelectasis, pulmonary oedema, thickening of alveolar septa and perivascular oedema in those rats which died.

Exposure of cultures of pathogenic bacteria to oxygen at two atmospheres pressure for 18 hours revealed a bacteriostatic effect which was particularly well marked with Pseudomonas pyocyanea and Aspergillus fumigatus, less well marked with Staphylococcus aureus and hardly seen with Proteus vulgaris or Escherichia coli. This implies a spectrum of bacterial sensitivity to

hyperbaric oxygen, which may prove a valuable adjunct in the treatment of infections by certain organisms.

PREFACE

This thesis deals with the biological effects of oxygen at high atmospheric pressure and indicates the possible use of this in therapeutics.

Hyperbaric oxygen can be classified into three main categories according to its use in various clinical states. In conditions such as carbon monoxide poisoning or the respiratory distress syndrome of the new-born, oxygen at high pressure can be used to maintain adequate tissue oxygenation until normal, physiological methods of oxygenation are re-established. Local anoxic conditions such as traumatic vascular disturbances of limbs or coronary artery occlusion are also included in this category. Section I deals with carbon monoxide poisoning and details a series of experiments, in dogs, designed to assess the relative efficiency of hyperbaric oxygen and more conventional therapeutic techniques in resuscitation from carbon monoxide poisoning. The results obtained from the use of hyperbaric oxygen in the treatment of all

severely gassed patients admitted to the Western Infirmary, Glasgow, during a period of one year are then given.

The second category includes those situations in which benefit is derived from the metabolic effects of high pressures of oxygen on tissues whose normal supply of oxygen is not impaired. It seemed reasonable to suppose that the period of time during which the circulation might be completely arrested with safety - for the purposes of cardiac or brain surgery - could be prolonged by preliminary super-saturation of the blood and tissues with oxygen at high pressure, particularly if this were used in conjunction with hypothermia. In section II the effect of oxygen at various pressures on the oxygen consumption of tissue homogenates at 37° C., 28° C. and 15° C. is demonstrated and an attempt has been made to evaluate the part played by metabolic factors in the prolongation of the safe period during which the circulation may be totally arrested if oxygen at high atmospheric pressure is used. An account is also given of a series of experiments in dogs in which the circulation was arrested for various periods of time when the animals had been breathing oxygen

at either one or two atmospheres pressure.

The third category is oxygen poisoning. Oxygen toxicity is a well known entity and section III deals with an investigation of this phenomenon, in rats, with particular reference to their tolerance to oxygen at two atmospheres pressure and the clinical and pathological effects of prolonged exposure to it. An account of the protection which might be obtained from intermittent rather than continuous exposure is also given. Fischer and Andersen (1926) and Boerema (1963) have shown that malignant cells may be more susceptible to the damaging effects of hyperbaric oxygen than normal mature host cells and it seemed possible that another therapeutic use of oxygen poisoning might present itself if pathogenic bacteria were found to be unduly sensitive to high pressures of oxygen. An account is thus given, in this section, of a series of IN VITRO experiments on the effects of high pressures of oxygen on a variety of aerobic, pathogenic micro-organisms.

The three headings under which this study has been

conducted are thus, the use of hyperbaric oxygen in anoxic conditions; the investigation and use of the metabolic effects of hyperbaric oxygen and the investigation and possible use of the phenomenon of oxygen poisoning.

INTRODUCTION

The Use of Pressure Vessels in Therapeutics.

Robert Boyle showed that air was essential for life and combustion in the seventeenth century and the doctrine which regarded the lungs as bellows which cooled the fiery heart had thus to be discarded. Since then biologists have been interested in the effects of various concentrations of air, or its active principle oxygen, on living tissue.

The medical profession, at this time, was already aware of the efficacy of a change of climate in a variety of chronic disease processes and Henshaw (1664) considered the, "salutary effects of change of climate" to be due, in great measure, to change of barometric pressure. Exercised by the waste of time and energy spent in travelling to other climates and the serious condition of many patients, which precluded their undertaking long and hazardous journeys, he constructed a chamber by means of which patients could be subjected to air at raised or lowered barometric pressure.

The chamber was made of wood and a huge set of organ bellows furnished with a suitable arrangement of valves

allowed the pressure within the chamber to be raised or lowered as desired. Pressure changes were monitored by means of a large mercury manometer situated outside the chamber but in communication with the interior; the normal working pressure was 4 lb./square inch above atmospheric pressure.

It was Dr. Henshaw's practice to use "condensed air for the treatment of acute diseases and rarefied air for those of a chronic character." The duration of each treatment in the chamber was, "as long as the patient continued to feel his breathing to be easy or at least not in any way rendered more difficult." It appears that the uses of the chamber extended to the healthy state also for he says that, "In time of health this domicilium is proposed as a good expedient to help digestion, to promote insensible perspiration, to facilitate breathing and expectoration, and, consequently, of excellent use for the prevention of most affections of the lungs."

This was certainly the first pressure vessel to be built for therapeutic purposes but it was not the first pressure vessel to be used for biological investigations for Boyle, himself, had built a pressure chamber to observe the effects of high atmospheric pressure on small animals.

Indeed, the glint he observed in a viper's eye following rapid decompression was probably the first nitrogen bubble to be observed in caisson disease. (Dugan, 1960).

Simpson (1857), in reviewing the history of pressure vessels in therapeutics, says that "Dr. Henshaw's experiments did not produce any special results and no-one was encouraged to follow this line of investigation even although there was a proposal of "the effects of condensed air on animal and vegetable life" as a subject for a competition by the Royal Society of Sciences at Haarlem about 1797 - a proposal which met with no response."

Interest in pressure chambers was next aroused in France in the first half of the nineteenth century and it is difficult to separate those genuinely interested in the possible therapeutic effects of air at raised atmospheric pressure from their less scrupulous contemporaries who realised that such appliances had great commercial potentialities as a form of therapy for the ills which afflict mankind. Some of these early pressure chambers were actually mobile and Duncum (1947) describes one which was proudly drawn from town to town by two magnificent black stallions!

M. Emile Tabarie was the first of the French workers, and he began a series of investigations in 1832. He was followed a few years later by Junod, Fraves and Bertin all working independently. Tabarie appears to be the most genuine of these investigators. He considered that "an element so indispensable as atmospheric air to the existence of all organised beings, ought also, by modification of its physical and chemical properties to become an inexhaustible source of beneficial influence on the system". He believed in slow compression and decompression (1 lb./min.) to about 6 lb./square inch which he held for an hour. In Junod's first experiments (Junod, 1835) no precautions were taken - "the transitions rapid, and the pressure high" - and he caused "tachycardia, cerebral excitement, and a state resembling intoxication". His results were thus "calculated to deter from further trial", and the great Majendie (Bertin, 1856) declared the system "to be not susceptible of application in medicine". It is possible that Junod either caused a convulsion from oxygen poisoning or more likely a transitory attack of caisson disease and, if so, he was the only early investigator to have reached a sufficiently high pressure to be of

physiological significance.

Bertin's paper in the British Journal of Homoeopathy (1856) opens with a denunciation of contemporary medicine and his exotic and journalistic style casts suspicion upon his motives and his honesty. He observed a fall in pulse rate and temperature brought about by compression which was subsequently noted frequently by other workers (Quinquand., 1884; Bert, 1878; Benedict and Higgins, 1911) but in spite of this his general conclusion clearly indicates his worth as an experimenter, "Under the influence of a pressure carried to 2/5th of an atmosphere, which a long experience has shown to be the most advantageous for general use, permanent congestions of the skin and mucous membranes in contact with the air are found to yield".

Pravas (Bertin, 1856) tended to use even lower pressures than Bertin and Taberio and he reports his successful treatment of asthma, congestion of the liver, haemorrhoids, purpura, anaemia from uterine haemorrhage, menorrhagia in young girls and deafness.

The British school, stimulated by this continental work, once again became interested in condensed air and Macleod (1857) introduced a pressure chamber into his hospital at

Ben Rhydding in Yorkshire. He stated that he believed condensed air in combination with existing measures to be "the only real and efficacious means which we possess for coping with phthisis." The Ben Rhydding chamber was carefully described by Simpson (1857). It was constructed of iron plates rivetted together and had several small windows, each glazed with a single piece of strong plate glass, while the interior was lined with wood. The attention of the attendant could be attracted by an air whistle and there was a food locker, by means of which small articles could be passed in and out of the chamber without disturbing the pressure of the air inside. "A steam engine of power proportional to the size of the chamber, works a pair of force pumps, which communicate indirectly with the chamber by a pipe opening under its floor, which is pierced by numerous small apertures, so that the air may enter with as little noise as possible. From the roof of the chamber, a pipe similarly arranged passes out; and this is furnished with a screw-valve, by means of which the amount of air passing off may be regulated, while the amount of that which enters is regulated by the rapidity of motion of the engine and pumps. While the air is being condensed, and after it

has been brought to the maximum pressure desired, a sufficient quantity of air is constantly allowed to enter and escape, to keep that in the chamber of sufficient purity for respiration." He also describes a barometric tube to give a continuous reading of pressure within the chamber and he describes a device for regulating the temperature of the condensed air. This pressure chamber thus appeared to have all the refinements of those being planned today! Simpson and Macleod were chiefly interested in phthisis and they felt that increased air pressure had a marked beneficial effect on this condition and other chronic inflammatory diseases of the lungs.

From this time investigation of the effects of high atmospheric pressures fortunately fell into the hands of true scientists. The first of these was Paul Bert and he became interested in the lot of labourers who worked in caissons under bridges and in tunnels. He pointed out the importance of the oxygen component of compressed air and directed attention from its physical to its chemical effects: "Pressure acts on living beings not as a direct physical agent, but as a chemical agent changing the proportions of oxygen contained in the blood, and causing asphyxia where there is

not enough of it, or toxic symptoms where there is too much". Probably Bert's most important discovery was the effect of nitrogen breathed under pressure and his explanation of the aetiology of caisson disease. (Bert, 1878). He suggested slow decompression to prevent caisson disease and practiced recompression when it occurred. The safety of divers and caisson workers has provided the main stimulus to research in pressure physiology until the present decade and those pressure chambers which were built were used for the treatment of patients suffering from caisson disease. More recently the Admiralty recompression chambers at Portsmouth have also been used for treating pulmonary barotrauma (Liebow, Stark, Vogel and Schaefer 1959; Miles and Wright (1963).

Pressure vessels have, however, been used occasionally in the past as a means of administering oxygen at increased pressures to patients suffering from conditions other than caisson disease. The first reported use of hyperbaric oxygenation was from a Spanish Physician, Valenzuela (1887), who used it in a case of pneumonia with apparently good results. Using a pressure of 1520 mm. Hg. of oxygen he had observed a reduction in temperature of rabbits over 24 hours and a greater reduction in temperature of rabbits suffering from

septicaemia than similarly infected rabbits maintained at normal pressures. With this experimental background he proceeded to treat cases of pneumonia and other severe infections using high pressures of oxygen on account of its antipyretic properties.

From the time of Valenzuela until the present day clinical applications of hyperbaric oxygen have been rare. Auler (1929) - following the work of Fischer and Anderson (1926) who showed that high tensions of oxygen preferentially interfered with the vitality of malignant cells - treated some patients suffering from malignant tumours with high pressures of oxygen, but without success. The first successful, clinical use of hyperbaric oxygen was not till 1954, when it was again applied for the treatment of malignant tumours, but in combination with irradiation (Churchill-Davidson, Sanger and Thomlinson, 1955; 1957). These workers used a small, perspex pressure chamber capable of housing only the patient. It was compressed with pure oxygen and the tumour area irradiated through the perspex. This form of treatment has given good results and Van Den Brenk (1961), working in Melbourne, has undertaken several hundred compressions in patients with tumours.

The next major development was the introduction of large experimental pressure chambers into the departments of surgery of the Universities of Amsterdam and Glasgow by Boerema of Amsterdam and Illingworth and Smith of Glasgow. These chambers were introduced for the investigation of the potentialities of high pressures of oxygen in cardiac surgery, but since their installation they have been used to treat a wide range of clinical conditions (Illingworth, Smith, Lawson, Ledingham, Sharp, Griffiths and Henderson, 1961; Illingworth, 1963; Boerema, 1956; 1961). Both chambers work on similar lines but the Glasgow chamber operates at a pressure of 2 atmospheres absolute, while the Amsterdam chamber normally operates at a pressure of 3 atmospheres absolute.

The Glasgow chamber (Plates 1 and 2) consists of a steel cylinder some 10 feet in diameter by 16 feet in length and it consists of a main chamber and an air-lock. The pressure is raised with air to two atmospheres and when that pressure is reached a discharge valve opens while compression continues. The air in the chamber is thus continuously renewed. The patient breathes oxygen from a cylinder and thus only the patient is exposed to the

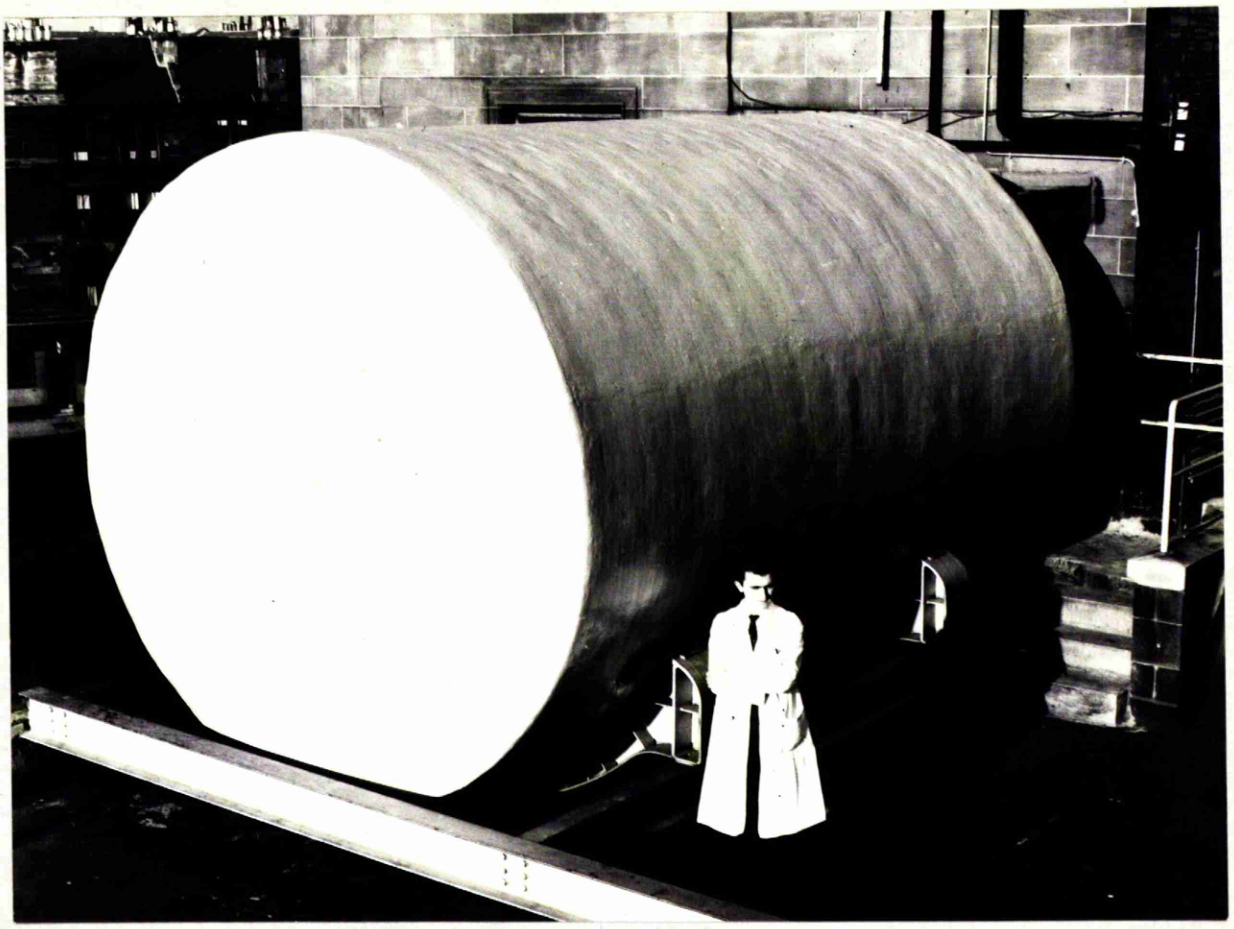

Plate 1.

The pressure chamber at the Western Infirmary, Glasgow.

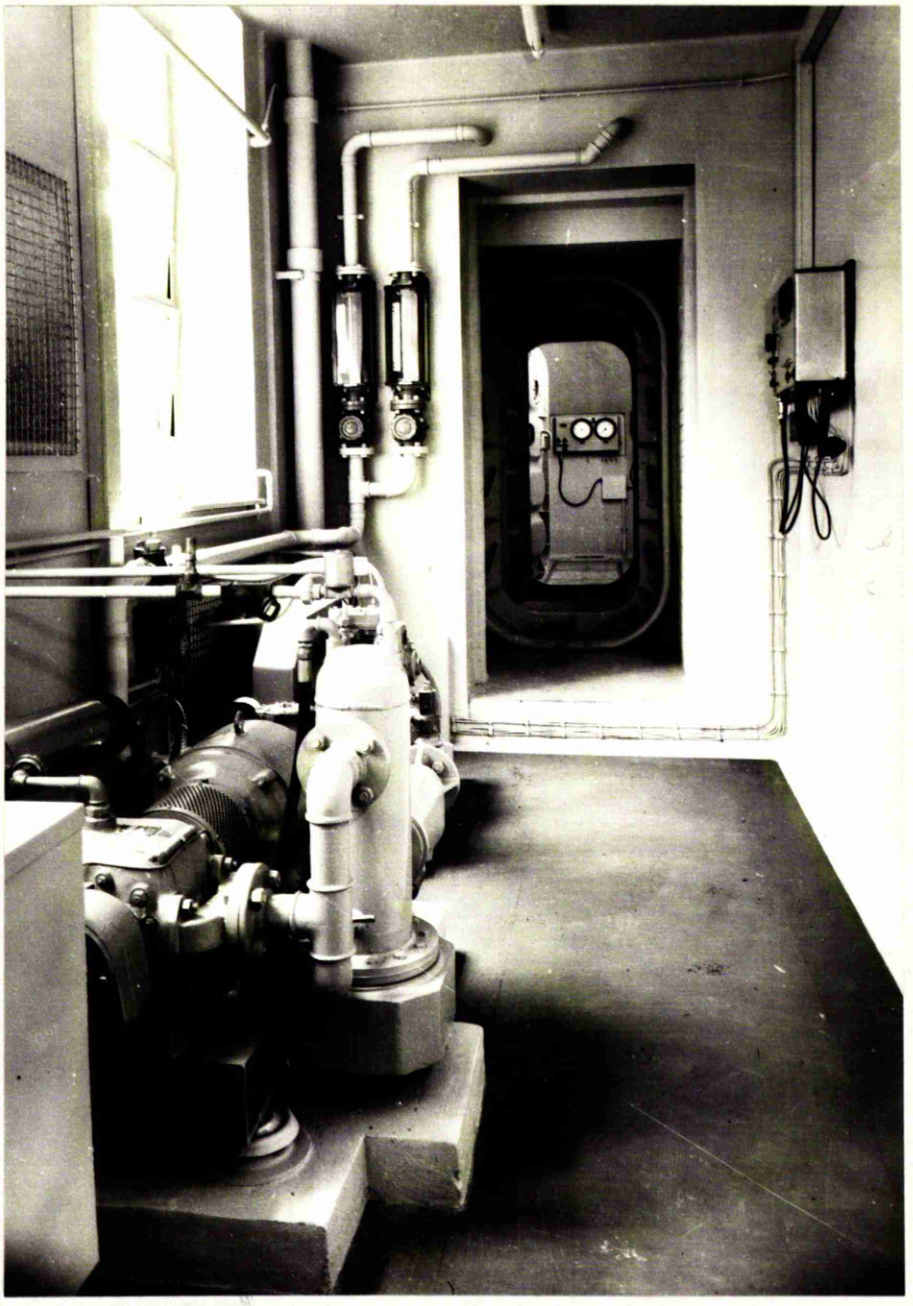

Plate 2.

The pressure chamber at the Western Infirmary, Glasgow, showing the compression room and entrance to the chamber.

effects of hyperbaric oxygen, the attendants breathing air at two atmospheres pressure.

The principle of the Amsterdam chamber (Plate 3) is the same but it is larger and more speedily compressed than the Glasgow chamber. Since three atmospheres of oxygen are used in Amsterdam care must be taken lest oxygen poisoning occurs. In Glasgow oxygen poisoning has not been experienced clinically even after breathing oxygen at two atmospheres pressure, through a B.L.B. mask, for 48 hours. Following compression to three atmospheres it is also necessary to adhere to a strict decompression routine but this is not strictly necessary in decompressing from two atmospheres.

Following the tumour therapy of Churchill-Davidson et al. (1955), the next clinical use of hyperbaric oxygen was in the treatment of severe carbon monoxide poisoning (Smith and Sharp, 1960). In the same year Boerema (1960) - following the experimental work of Ozorio de Almeida (1941) - indicated the value of hyperbaric oxygen in gas gangrene. Numerous reports have followed on the use of this type of therapy for arterial occlusion (Illingworth, 1963), trauma (Donald and Tankel, 1963; Smith, Stevens, Griffiths,

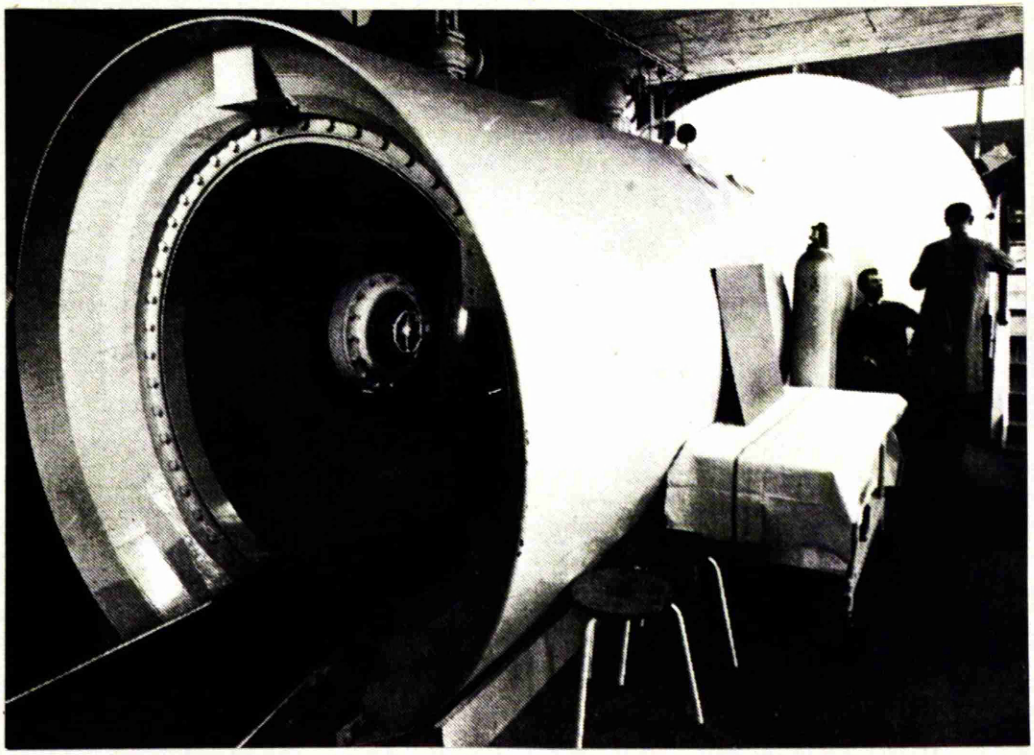

Plate 3.

The pressure chamber in the Wilhelmina Gasthuis, Amsterdam.

Ledingham, 1961; Attar, Esmond and Cowley, 1962) and a wide range of anoxic conditions, (Smith and Lawson, 1958; 1962; Sharp, Ledingham and Norman, 1962; Jacobson, Bloor, MacDowell and Norman, 1963; Hutchison, Kerr, McPhail, Douglas, Smith, Norman and Bates, 1962; Hutchison, Kerr, Williams and Hopkinson, 1963; Emery, Lucas and Williams, 1960; Ivanov, 1959).

Henshaw's "adaptation of one of Mr. Boyle's speculations" has thus advanced far in the past decade by the application of scientific thought and experimentation. The effect has been to stimulate thought and investigation in many of the leading centres in the world so that the ultimate value of hyperbaric oxygenation may at last be evaluated and its place may be found "among the recognised recources of our art". (Lee, 1867).

CARBON MONOXIDE POISONING

INTRODUCTION

Carbon monoxide is a gas which has been known since ancient times and references to carbon monoxide poisoning are contained in the earliest medical writings. It was used by the Greeks and Romans for the execution of criminals and as a means of committing suicide (Best and Taylor, 1955). The natural distribution of the gas is wide and it has been isolated in such unlikely places as the swim-bladder of the Portuguese Man-of-War and the blood of the Weddel seal (Pugh, 1959a). Carbon monoxide poisoning is commonly associated with life in urban areas and the blood of town dwellers normally contains 0.1 - 0.2 vols. per cent of the gas but it has even been encountered in such a desolate and isolated situation as the continent of Antarctica, where it was nearly responsible for the untimely demise of the famous Admiral Richard Byrd during his epic Antarctic winter. Elevated levels of carboxyhaemoglobin have also been found in the blood of tractor drivers in Antarctica (Pugh, 1959b) and Irving, Scholander and Edwards (1942) have drawn attention to

the danger of carbon monoxide intoxication from the use of primus stoves in tents and snow-houses during polar travel.

The mode of action of carbon monoxide eluded the earlier workers for many years. Chenot (1854) suggested that the gas acted as a reducing substance which removed oxygen from the blood to oxidise itself to carbon dioxide with the liberation of considerable heat. The answer was eventually provided by Bernard (1870) who discovered the affinity of carbon monoxide for haemoglobin and indicated the disturbance in oxygen transport which occurs when these two substances combine, while Haldane (1895a) showed that the formation of carboxyhaemoglobin is an equilibrium reaction, which depends upon the relative partial pressures of carbon monoxide and oxygen in inspired air.

The dissociation of carboxyhaemoglobin follows the same laws as the dissociation of oxyhaemoglobin and the carboxy-haemoglobin dissociation curve is governed by the same factors of temperature, pH and salt content as the oxyhaemoglobin dissociation curve (Douglas, Haldane and Haldane, 1912; Joels and Pugh, 1958). The main difference between the two curves lies in the range of partial pressures; whereas the

haemoglobin of human blood becomes half saturated with oxygen at a partial pressure of about 30 mmHg. it is half saturated with carbon monoxide, under the same conditions, at a partial pressure of about 0.12 mmHg. (Killick, 1940). The inspiration of air containing 0.1% carbon monoxide will thus cause symptoms of intoxication within 30- 60 min. (Lovatt Evans, 1952). The oxyhaemoglobin dissociation curve is also displaced to the left in the presence of carbon monoxide and this causes a marked lowering of the partial pressure at which oxygen is available for tissue metabolism. Thus, despite the possible presence of two or three times the amount of oxygen necessary for normal tissue function profound anoxaemia develops early in carbon monoxide poisoning. A patient suffering from anaemia may appear reasonably well when the concentration of haemoglobin has fallen to 50% of the normal value while a patient whose haemoglobin is 50% saturated with carbon monoxide would be practically dead. (Stadie and Martin, 1925).

When blood is exposed to a mixture of carbon monoxide and oxygen the haemoglobin is divided between the two gases, the reaction obeying the law of Mass Action. Thus the proportion of haemoglobin combined with either gas depends

upon the relative partial pressures of oxygen and carbon monoxide present and upon a constant which expresses the relative affinity of the blood for the two gases (Haldane and Smith, 1897). Under the same conditions of pH, temperature and concentrations of reagents oxygen combines with haemoglobin about 10 times as fast as carbon monoxide and the great affinity of carbon monoxide for haemoglobin is explained on the grounds that carboxyhaemoglobin dissociates 245 times more slowly than oxyhaemoglobin. The stability of carboxyhaemoglobin is thus not related to the speed of its formation but to the slowness of its dissociation. (Hartridge and Roughton, 1923).

Mode of Action of Carbon Monoxide.

Haldane (1895 a) stated that carbon monoxide was a physiologically inert gas exerting its effects entirely by blocking the haemoglobin. "Carbon monoxide passes in by the lungs and passes out - far more rapidly than is generally supposed - by the lungs, without there being the smallest loss". This conclusion was partly based upon the observation that the same concentration of carbon monoxide apparently became progressively less toxic as the concentration of

oxygen, with which it was administered, increased. Haldane then placed a mouse in a jar containing sufficient carbon monoxide to saturate completely the haemoglobin, which could thus no longer serve to transport oxygen to the tissues. The jar also contained 2 atmospheres of oxygen, however, so that 3 to 4 volumes per cent of oxygen was carried by the blood in physical solution. This was sufficient for the needs of the animal and it remained perfectly well.

Haldane (1895b) also exposed a cockroach - which has no haemoglobin - to an atmosphere containing 80% carbon monoxide and 20% oxygen. The animal remained perfectly well despite an exposure which lasted for 1 week.

Despite Haldane's work, the effect of carbon monoxide upon respiratory metabolism has been the subject of a long controversy and many workers have enquired whether carbon monoxide does, in fact, react in some additional manner in the body, whether there is any possible conversion of carbon monoxide into carbon dioxide, or other compound, or whether there is any other way in which the body can take up and store the gas.

Warburg (1927) showed that carbon monoxide diminished the respiration of yeast and cocci but this only occurred

when the concentration of the gas was in excess of 79%. He also demonstrated that this effect was neutralised by strong light and concluded that carbon monoxide combined with a catalyst in the cells with which oxygen must combine before it can oxidise other substances. This substance, he states, was an iron containing compound analogous to haemoglobin. Subsequent workers all refer to Warburg's experiments when endeavouring to demonstrate histotoxic properties for carbon monoxide but it should be noted that Warburg was only able to reveal these effects at concentrations of carbon monoxide many times greater than could ever occur in the body.

J.B.S. Haldane (1927) subjected moths to progressively lower tensions of oxygen until they became immobile, an event which occurred when the concentration of oxygen fell to 1%. The moths remained normal when the concentration of oxygen was maintained at 2%. In the presence of 80% carbon monoxide, however, the moths became immobile when the concentration of oxygen fell below 8.4% and they only behaved normally when the concentration of oxygen was kept above 14%. A similar effect was observed in cress, the germination of which was delayed by the presence of carbon

monoxide in a tension of oxygen at which germination will normally occur. From these observations Haldane concluded that cells contain a respiratory enzyme which is poisoned by carbon monoxide.

More recently Halperin, McFarland, Niven and Roughton (1959) have used visual sensitivity to differences in light intensity as a sensitive index of the effects of carbon monoxide and have observed the persistence of the detrimental effects on visual function, caused by carbon monoxide, for some time after elimination of the gas from the blood. Administration of 100% oxygen caused immediate improvement in visual function which regressed when ordinary air was again breathed. These workers postulated the existence in the central nervous system or the peripheral visual system of an enzyme or other visually important constituent, which combines competitively with carbon monoxide and oxygen.

The oxidation of carbon monoxide to dioxide is probably not important and Haldane (1895a) states that it does not occur since he was able to recover all the carbon monoxide administered to his subjects, from their expired air. Fenn and Cobb (1932 a, b,) and Schmitt and Scott (1933) have, however, observed the production of carbon dioxide from

monoxide in IN VITRO studies of various tissues. The effect was most pronounced in skeletal and heart muscle, but, like Warburg's experiments, it could only be demonstrated when the concentration of carbon monoxide exceeded 80%

These conditions cannot be compared with mammalian carbon monoxide poisoning, where the tension of gas is very much less. Tobias, Lawrence, Roughton, Root and Gregensen (1945) have repeated Haldane's balance experiments using tagged carbon monoxide and more sensitive analytical techniques and they concluded that the carbon monoxide oxidised to carbon dioxide by the body amounted to less than 0.1%, if any.

Treatment of Carbon Monoxide Poisoning.

Treatment of carbon monoxide poisoning is directed towards shortening the period of anoxia by hastening the elimination of the gas. In man the rate of uptake of carbon monoxide depends upon the partial pressure of the gas in the air breathed and the volume and rate of pulmonary blood flow. The reaction,

$$HbO_2 + CO \rightleftharpoons HbCO + O_2$$

is reversible and the carbon monoxide gradually disappears

when the poisoned animal breathes fresh air. The rate of elimination of the gas is hastened by any factor which increases the volume of pulmonary ventilation, the circulation rate of the blood or that raises the partial pressure of oxygen in the alveoli. (Stadie and Martin, 1925).

Hill and Flack (1908) noted the considerable increase in pulmonary ventilation caused by carbon dioxide and Henderson and Haggard (1920, 1922) and Sayers and Yant (1923) applied this to resuscitation of man and dogs poisoned with carbon monoxide. Henderson and Haggard (1920) first used 10% carbon dioxide with 90% oxygen but later recommended the use of a mixture of 5% carbon dioxide with 95% oxygen (Haggard and Henderson, 1922). Nicloux, Morson, Stahl and Weill (1925 a,b.) and Walton, Eldridge, Allen and Witherspoon (1926) were unable to confirm the great increase in the speed of carbon monoxide elimination which Henderson and Haggard claimed to be due to the presence of carbon dioxide. They therefore advocated the use of pure oxygen only as the treatment of choice. Carbogen mixtures, however, were almost universally adopted throughout the world and although some controversy persisted 5% carbogen was eventually shown to be undoubtedly superior to oxygen

alone by Killick and Marchant (1959).

Henderson and Haggard and Sayers and Yant believed that the hyperventilation caused by carbon dioxide was responsible for the increased speed of elimination of carbon monoxide but Stadie and Martin (1925) advanced the view that it may be due more to the increase in hydrogen ion concentration, brought about by the carbon dioxide, than to the increase in pulmonary ventilation. In animals gassed until the blood level of carboxyhaemoglobin reached a constant level, these workers compared the speed of elimination of the gas brought about by each of the following methods:

1. Breathing air with constant ventilatory rate.
2. Decreasing blood pH by breathing 10% carbon dioxide with constant ventilatory rate.
3. Administering dilute hydrochloric acid intravenously with constant ventilatory rate.
4. Hyperventilation with air.

The results obtained are shown in Figure 1 and Stadie and Martin conclude that hyperventilation itself is of minor importance in the elimination of carbon monoxide. Decreasing pH by any acid, carbon dioxide or hydrochloric acid, causes a

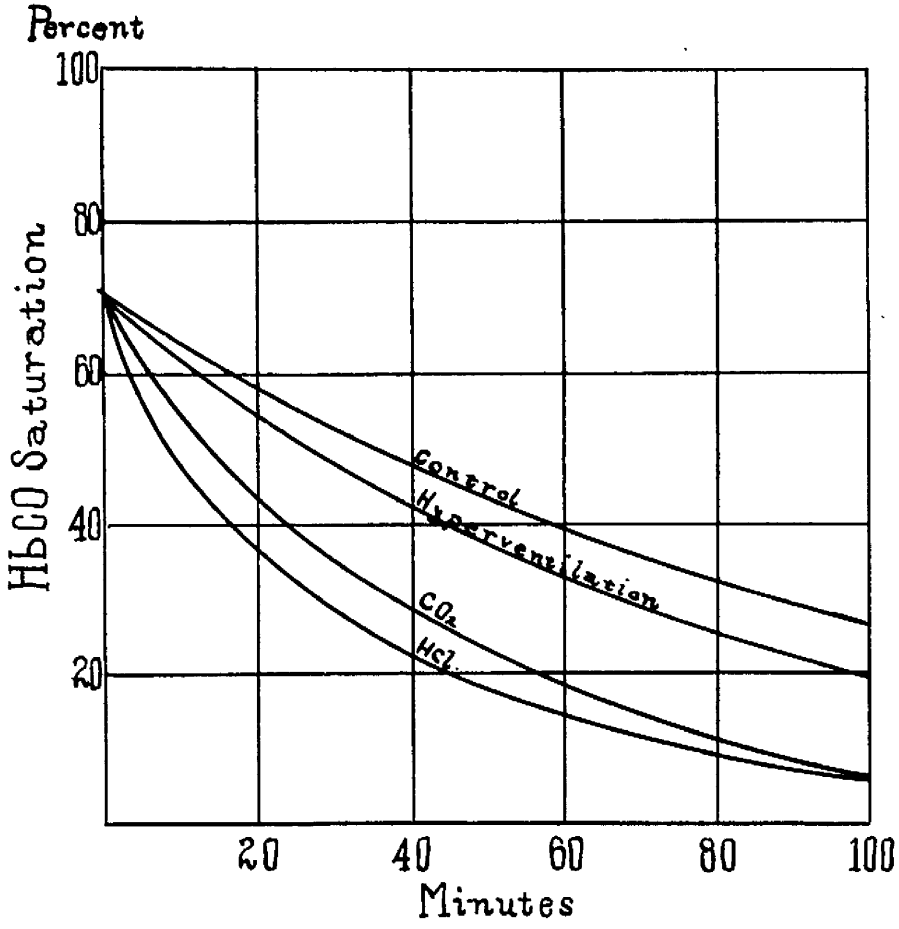

Fig. 1.

The rate of elimination of carbon monoxide from the blood caused by 4 different methods. From Stadie and Martin (1925).

great increase in the rate of elimination of carbon monoxide and is the most important factor. They admit, however, that although hyperventilation plays a minor part yet it is a distinct one since any means of increasing ventilatory rate is beneficial. Carbon dioxide has therefore a dual function in the treatment of carbon monoxide poisoning. Lowering the pH will, of course, displace the oxygen dissociation curve to the right and Stadie and Martin point out that lowering the pH from 7.4 to 7.0 requires a 20% increase in pCO to maintain the haemoglobin 50% saturated with carbon monoxide.

Warburg (1927) showed that carbon monoxide was a specific respiratory poison but that red blood corpuscles were practically unaffected in the presence of sufficient methylene blue. Brooks (1932) investigated the use of methylene blue in carbon monoxide poisoning in rats. It was claimed that the animals treated with methylene blue recovered significantly faster than the controls but Nadler, Green and Rosenbaum (1934) pointed out that methylene blue converts haemoglobin to metheamoglobin and it must therefore increase the degree of anoxia in carbon monoxide poisoning.

The administration of cytochrome in carbon monoxide

poisoning has been reported from time to time and Gros and Leandri (1956) used infusions of 15 - 60 mg. intravenously in twenty cases of carbon monoxide poisoning. Conventional therapy was also applied and a variety of different types of case is presented but the particular manner in which cytochrome was of benefit is not apparent from the information given. Since the affinity of cytochrome for oxygen is 7 - 14 times greater than for carbon monoxide it is unlikely that the concentration of carbon monoxide in the body would be sufficiently high in practice for the cytochrome system to be markedly affected.

Since Haldane's observation that a mouse placed in 2 atmospheres of oxygen was completely protected from the addition of 1 atmosphere of carbon monoxide the use of oxygen at elevated pressures as a form of therapy for carbon monoxide poisoning has been suggested by many workers including Mosso (1900), End and Long (1942), Bean (1945), Pace, Strajman and Walker, (1950) and Lawson, McAllister and Smith (1959; 1961). It was not until 1960, however, that Smith and Sharp first reported the use of oxygen at a pressure of 2 atmospheres absolute in the treatment of acute carbon monoxide poisoning in man. Hyperbaric oxygen has a dual function in carbon

monoxide poisoning. The considerable increase in the alveolar tension of oxygen greatly accelerates the dissociation of carboxyhaemoglobin and, secondly, the increased volume of oxygen dissolved physically in the plasma by-passes the blocked haemoglobin mechanism and oxygenates the tissues immediately thus terminating the hypoxic state.

Interest in hyperbaric oxygen arose at a time when various methods of resuscitation from carbon monoxide poisoning were under active investigation in Glasgow. Experiments were carried out in which the efficiency of oxygen at elevated pressures was compared with existing methods which included 5% and 7% carbon dioxide in oxygen. The following section gives an account of some of the experiments.

EXPERIMENTAL METHODS

A series of experiments designed to elucidate various aspects of carbon monoxide poisoning and its treatment has been carried out in dogs. In order to maintain some continuity and to facilitate the comparison of one group of experiments with another a standard technique was used to produce carbon monoxide poisoning and to administer the various resuscitative gases. An account of this technique is given below.

The dog was anaesthetised by the intravenous route with minimal doses of sodium pentobarbitone and a cuffed Magill endotracheal tube inserted. A Portex cannula was passed down the external jugular vein into the right atrium to permit sampling of mixed venous blood and the femoral artery was cannulated so that mean arterial blood pressure could be measured, and samples of central aortic blood obtained.

The circuit shown in Fig. 2 was attached to the endotracheal tube. Coal gas and air were withdrawn from cylinders of these gases and passed through a system of flowmeters into a 20 litre rubber bag and then to the dog through a

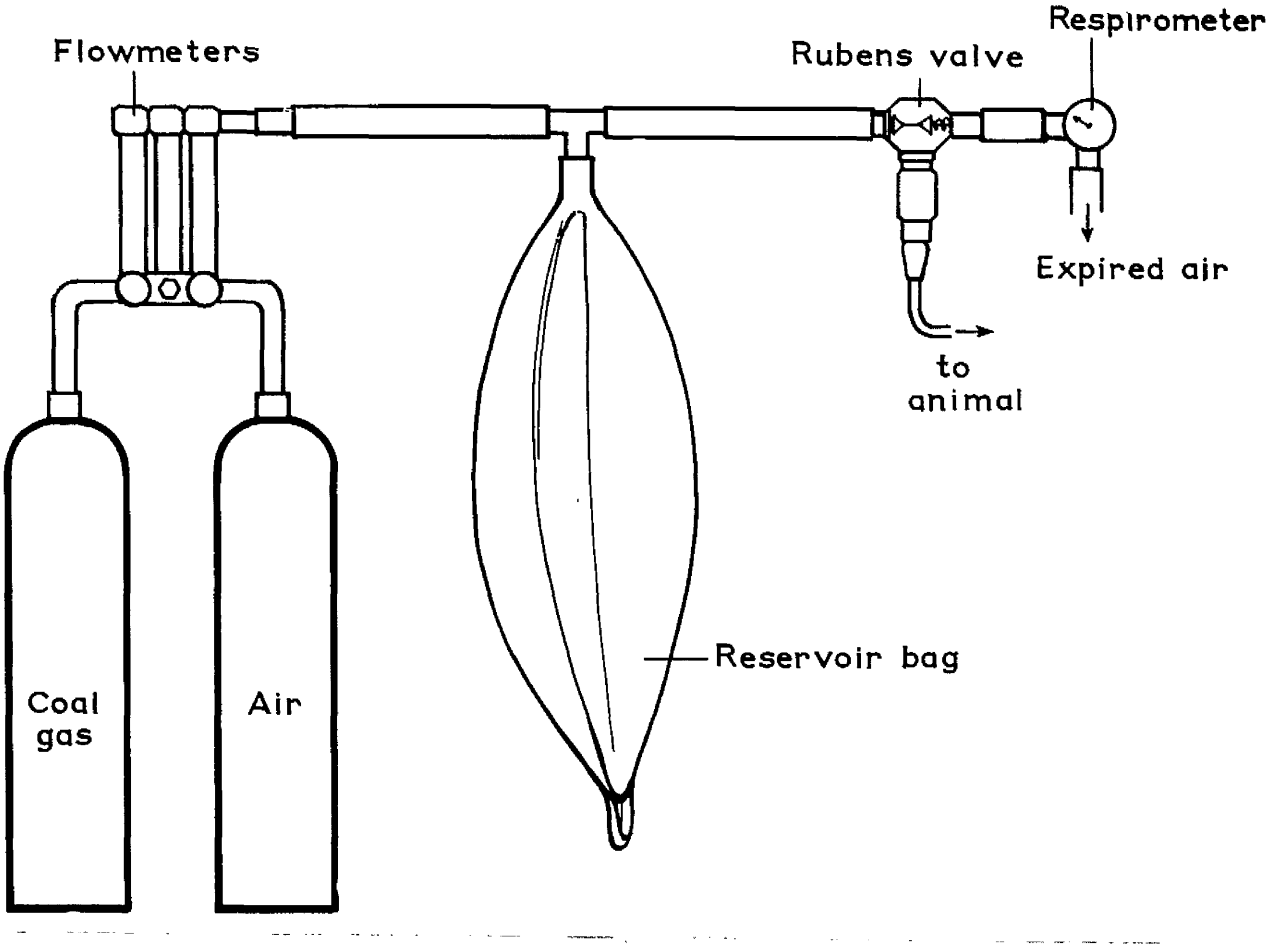

Fig. 2.

Circuit used to gas dogs.

Ruben non-return valve. A Wright respirometer was attached to the expiratory side of the Ruben valve and this provided measurements of respiratory rate and minute volume. Coal-gas from the cylinder was analysed by the Orsat technique (Campbell, 1951) and found to contain 18.8% carbon monoxide. The flowmeters delivered 100 ml. coal-gas/minute and 5 litres air/minute. The gas which the dog breathed thus contained 0.37% Carbon monoxide. The Ruben valve ensured that the gas mixture delivered to the animal was of known composition by preventing rebreathing. The rising levels of carboxy-haemoglobin were recorded and when the haemoglobin was 70% saturated with carbon monoxide (after an average of two hours) the resuscitative gas under test was fed into a 2 litre rubber bag which was connected directly to the inspiratory side of the Ruben valve.

From the beginning of resuscitation blood samples were removed at 1, 3, 5, 7, 9, 12, and 15 minutes and thereafter at five minute intervals until carboxyhaemoglobin could no longer be detected. From this time the animal breathed air. The values obtained during resuscitation allowed clearance curves of rate of elimination of carbon monoxide from haemoglobin to be drawn and the criterion of

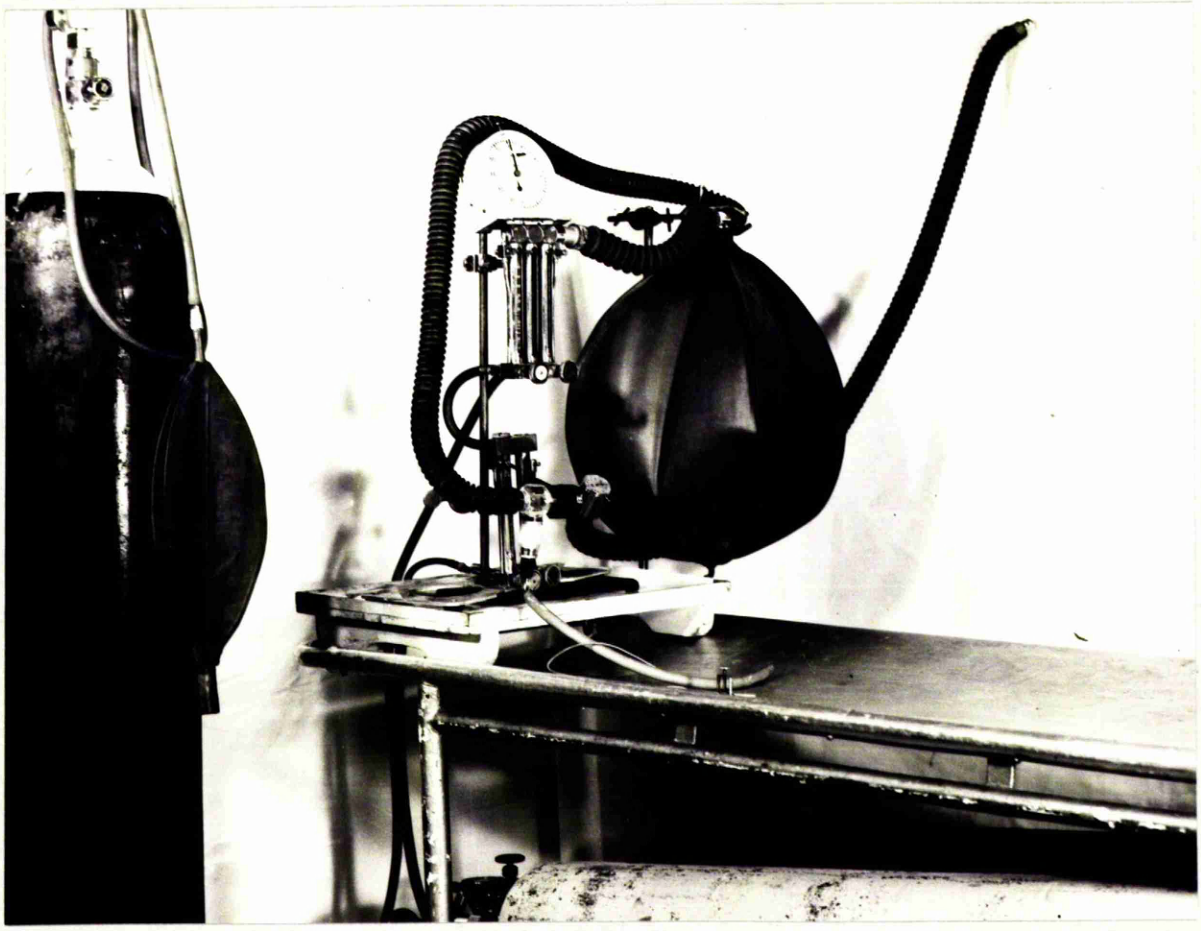

Fig. 3

Gassing apparatus mounted on trolley to enable whole preparation to be moved into pressure chamber without interrupting experiment.

efficiency of a method of resuscitation was taken as the time required to reduce the concentration of carboxy-haemoglobin by half or the half clearance time.

In the experiments in which oxygen at two atmospheres pressure was used for resuscitation, the gassing circuit was mounted on a trolley, Fig. 3, below which the cylinders of coal-gas and air were mounted. The animal was gassed in the laboratory until the haemoglobin was 50% saturated with carbon monoxide and the trolley was then wheeled into the pressure chamber. By the time the pressure had been raised to two atmospheres absolute the haemoglobin was usually approaching 70% saturation with carbon monoxide and there was no delay in the institution of resuscitation. It was thus possible to gas and resuscitate this group of dogs in the same way as those resuscitated with gas mixtures at normal atmospheric pressure.

ALVEOLAR GAS SAMPLING.

In some experiments alveolar gas was collected using the apparatus shown in Fig. 4. The samples were aspirated into a 20 ml. greased syringe attached to a 1 mm. bore polythene catheter, which was inserted through the wall of the endotracheal tube and passed down the bronchial tree until resistance was encountered. The tube was then withdrawn for a distance of ½ cm. Gas was aspirated at the end of expiration, during compression of the chest, and was passed from the syringe into a gas sampling tube by means of a two-way tap. The carbon dioxide content of the gas was measured by the Haldane gas analysis apparatus.

X ? monoxide ?

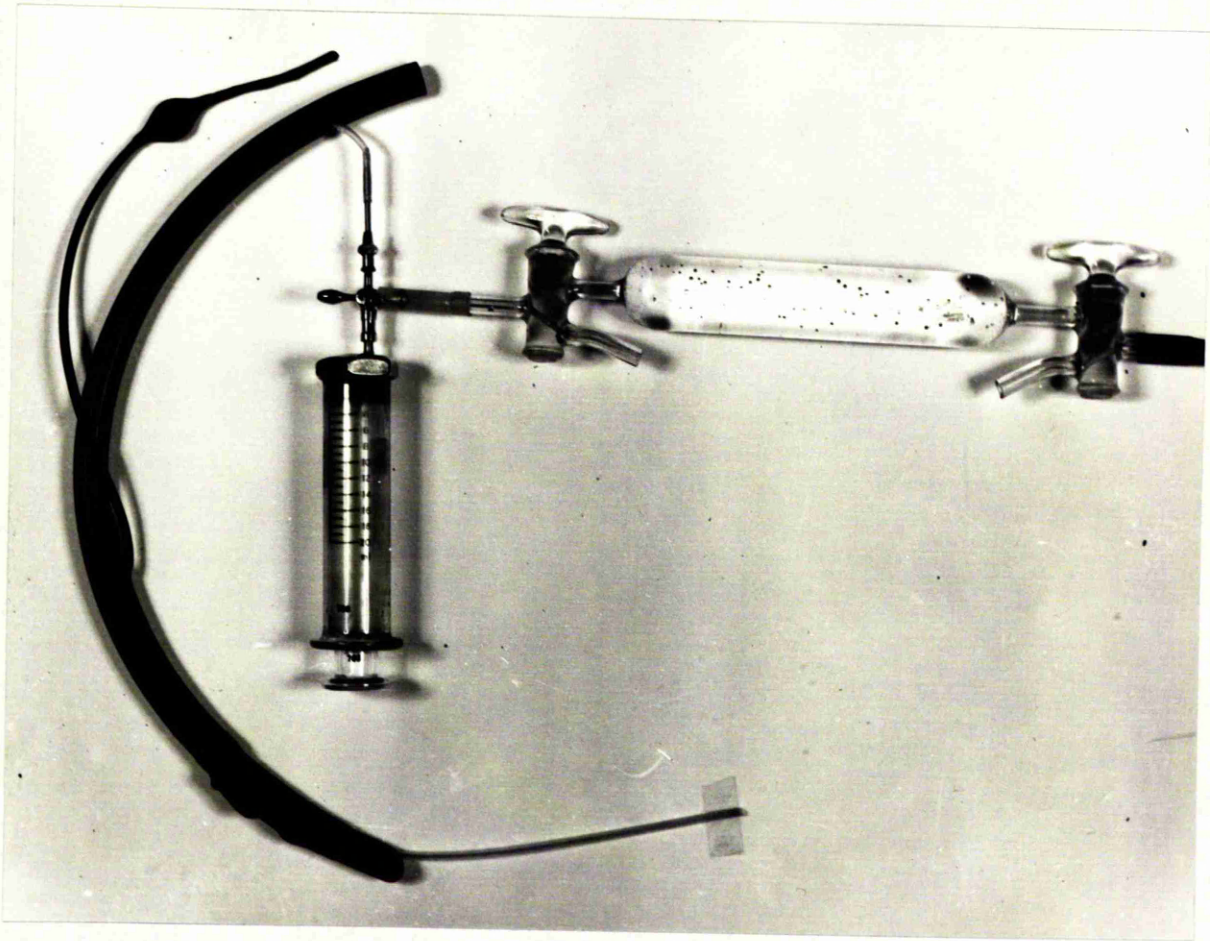

Fig. 4.

Apparatus used to obtain samples of alveolar gas.

THE ESTIMATION OF CARBON MONOXIDE IN BLOOD.

In general it is not difficult to estimate carboxy-haemoglobin in high concentrations in blood but considerable difficulty may be found in lower concentrations (Douglas, 1962). The method of Harrison (1947), using the Hartridge Reversion Spectroscope; the spectrophotometric method of Heilmeyer (1930) and the manometric method of Van Slyke and Neil (1924) as modified by Horvath and Roughton (1942) were studied. The latter method requires considerable manipulative skill with the Van Slyke manometric apparatus and is time consuming but it appears to give the most reliable results. Accordingly the manometric method was used as the standard and the other two methods compared with it.

Details of the manometric method of estimating carboxy-haemoglobin have undergone some modifications since they were first described by Van Slyke and Neil (1924). Sendroy and Lui (1930) and Horvath and Roughton (1942) amended the method and claimed to have increased the accuracy, particularly in the range 0 - 30% carboxyhaemoglobin.

Harrison (1947) described the use of the Hartridge

Reversion Spectroscope to estimate the concentration of carboxyhaemoglobin. In this instrument there are two spectra produced in the field of vision, one above the other and reversed from left to right. On examining a solution containing carboxyhaemoglobin it is found that the difference apart of the alpha bands is proportional to the concentration of the carboxyhaemoglobin. By calibrating the instrument with known concentrations of carboxyhaemoglobin, a calibration curve can be constructed, and if the curve is made and used by the same worker good results can be obtained. In the lower range of carboxy-haemoglobin, however, the difficulty of aligning the bands leads to serious errors.

The spectrophotometric method depends upon the principle that in mixtures of two pigments, if the quotient D1/D2 (in which D1 equals the optical density at the wavelength 1 and D2 equals the optical density at wavelength 2) of one pigment is A and quotient D1/D2 for the other pigment is B then any mixture of the two pigments will have a D1/D2 value somewhere between A and B depending on the concentrations of pigments.

Different calibration curves were constructed for human blood and canine blood for the Harrison and Spectrophotometric

methods. The dilution of the whole blood used was 1/150 with 0.4% ammonium hydroxide which was found to be suitable for both methods. Numerous points on the calibration curve for the spectrophotometric method were obtained by utilising cells of different light path lengths.

Six calibration curves from different samples of dog blood and six curves from different samples of human blood were obtained for the reversion spectroscope and for the spectrophotometer (Unicam SP.600). The mean of each group of curves was used.

The comparison of the methods was carried out as follows: 5 ml. of mixed venous blood was removed from a dog at various times during gassing by the standard technique described above and 1 ml. was immediately diluted to 150 ml. with 0.4% ammonium hydroxide. This was shaken gently, to ensure thorough mixing, and the solution was used for both the Harrison and Heilmeyer methods. The manometric determination was carried out immediately on the remaining whole blood. The results obtained are shown in Table 1.

It can be seen that when values of between 80 and 60% carboxyhaemoglobin are estimated the Heilmeyer method agrees well with the Van Slyke method but the Harrison method tends

Manometric (% COHb)	Spectrophotometric (% COHb)	Harrison (% COHb)
82	84	74
80	81	72
78	80	69
74	70	63
74	70	64
65	58	55
64	74	62
61	63	55
58	58	61
53	59	53
49	57	45
43	50	44
41	44	37
38	39	22
29	33	20
28	23	16
27	30	19
23	25	3
20	15	0
8	3	0
7	5	2

Table 1.

Measurements of carboxyhaemoglobin content made on the same blood sample by the three different methods.

to be a little low. When values between 60 and 30% carboxyhaemoglobin are selected, however, the Harrison method shows better agreement with the manometric method whereas the Heilmeyer method tends to be low. At levels below 30% carboxyhaemoglobin the Harrison method is unreliable and the Heilmeyer method compares favourably with the Van Slyke method.

It was found, however, that the spectrophotometer did not function accurately at increased pressures and this was probably due to the increased density of air which altered the refractive index of the air/glass barrier. It is not possible to use a Van Slyke manometric apparatus at two atmospheres pressure. The accuracy of the reversion spectroscope was not altered and since this method has the advantage of speed and facility and was the method in current use for treating patients it was decided to use this method to give some measure of continuity to the research programme. The unreliability of the method at concentrations of carboxyhaemoglobin below 30% was overcome by taking the time for the carboxyhaemoglobin level to fall from 70% to 35% - that is, the half-clearance time (T/2) - as a parameter with which to compare the efficiency of treatment of one experimental group with another.

MEASUREMENT OF BLOOD PCO_2

Blood PCO_2 was measured by the semi-micro Astrup technique. (Astrup, 1956; Astrup and Schröder, 1956). If carbon monoxide altered the reaction of haemoglobin when carboxy-haemoglobin was formed it was possible that pCO_2 measurements made by this interpolation technique, based on the measurement of pH on whole blood samples, would be inaccurate. Parsons, (1917) and Hastings, Sendroy, Murray and Heidelberger (1924) have, however, shown that carbon monoxide has the same effect on the reaction of haemoglobin as has combination with oxygen. A rising level of carboxyhaemoglobin should therefore have no effect on the pH of blood provided that the respiratory and metabolic components of acid-base metabolism remain constant.

In order to test directly the validity of pCO_2 measurements made by the Astrup technique when the blood contained carboxyhaemoglobin the following experiment was carried out:

A dog was anaesthetised with intravenous sodium pentobarbitone, intubated with a cuffed Magill endotracheal tube and ventilated with air using a positive pressure

Time	Gas Respired	COHb %	pH	pCO_2 mm.Hg.	St. Bic m.Eq./l.	Base Excess m.Eq./l.
11.00	Air	0	7.41	28.0	20.7	- 4.3
11.30	Air	0	7.43	28.0	18.9	- 5.0
12.00	Air	0	7.39	20.0	20.5	- 4.7
12.05	Air/Coal Gas	-	-	-	-	-
12.30	Air/Coal Gas	10	7.42	27.0	20.5	- 4.7
1.00	Air/Coal Gas	30	7.42	27.0	20.5	- 4.7
1.30	Air/Coal Gas	55	7.40	28.0	19.6	- 4.8
1.40	Air	-	-	-	-	-
2.00	Air	38	7.42	26.0	19.4	- 5.0
2.30	Air	10	7.40	29.0	19.9	- 4.5
3.30	Air	0	7.40	29.0	20.0	- 4.2

Table 2

pCO_2 measurements made before, during and after exposure of dog to carbon monoxide. Minute volume maintained constant by respirator.

respirator. The minute volume was kept constant throughout.

Samples of central aortic blood were obtained from a catheter introduced through a femoral artery and acid-base measurements were made on these at half-hourly intervals throughout the experiment. The first three measurements made showed that a constant pCO_2 was maintained when the animal was respired with air. 0.5% carbon monoxide was then added to the air breathed until the haemoglobin became 55% saturated with carbon monoxide. At this time the animal was again respired with air alone and acid-base measurements made until carboxyhaemoglobin was no longer detectable in the blood.

The results are shown in table 2. The pCO_2 was 28 mm Hg. at the outset of the experiment and varied by only $\pm$ 2 mm Hg. throughout. It seems reasonable to conclude that the presence of carboxyhaemoglobin in the blood does not alter the blood pH per se, nor detract from the accuracy of measurements of pCO_2 made by the Astrup technique.

Although no inaccuracy is introduced in the measurement of arterial pCO_2 by the addition of carbon monoxide to the blood, the values given for venous pCO_2 will be slightly low since reduced haemoglobin is more alkaline than oxyhaemoglobin.

RESPIRATORY AND METABOLIC CHANGES DURING CARBON MONOXIDE POISONING.

Following the introduction of mixtures of carbon dioxide and oxygen, - carbogen - for resuscitation (Henderson and Haggard, 1920, 1922, Sayers and Yant , 1923), carbogen mixtures were almost universally adopted for the treatment of carbon monoxide poisoning. In 1955, however, the use of carbon dioxide in resuscitation was challenged by the Committee for Research on Breathing Apparatus for Protection against Dangerous Fumes and Gases in its report to the Medical Research Council (Donald and Paton, 1955). The argument of this Committee was that a patient in severe respiratory depression was already suffering from the effects of an excess of carbon dioxide and was in urgent need of oxygen alone. While the use of carbon dioxide in the treatment of respiratory depression due to many causes is illogical, Marriott (1955 a, b) has urged that carbon monoxide poisoning is a special type of asphyxia in which it is vital that the body should be rid of carbon monoxide by the most rapid and effective means possible and that is, he contends, by the use of carbogen mixtures.

The assumption that the tension of carbon dioxide in the blood rises during poisoning with carbon monoxide and that there will be a considerable excess of carbon dioxide in the blood when respiratory depression supervenes appears to have been made on purely theoretical grounds and has not been supported by experimental evidence. It therefore seemed desirable to study the respiration of dogs as they were being gassed with carbon monoxide and to measure the pCO_2 together with the other significant parameters of acid-base metabolism at various stages of the procedure.

METHODS

Three groups of experiments have been carried out. In each group the dogs were anaesthetised, intubated and gassed with a mixture of coal-gas and air in the standard manner described above.

In the first group of experiments (Group A) 10 dogs were used. Each animal was gassed with a coal-gas/air mixture containing 0.37% carbon monoxide until the blood level of carboxyhaemoglobin was 70% or apnoea occurred. This was repeated on two further occasions at intervals of weeks or months. For any one animal the same dose of anaesthetic (sodium pentobarbitone) was used each time. The respiratory and cardiac rates were recorded as were the ventilatory volumes per minute and the level of carboxy-haemoglobin in mixed venous blood was estimated at intervals using the Hartridge reversion spectroscope. Alveolar gas samples were aspirated into a 20 ml. syringe by the technique described above.

In the second group of experiments (Group B), five dogs from Group A were used. By diluting the supply of coal-gas further with air, lower concentrations of carbon monoxide (0.28%) were obtained in order to prolong the period of

gassing. These dogs were gassed slowly until they became apnoeic. The same parameters were measured except that alveolar gas sampling was omitted. Samples of mixed venous blood were analysed for pH, pCO_2 and bicarbonate content by the semi-micro technique of Astrup (1956). These samples were removed at intervals during the course of gassing and in each case a sample was removed just after apnoea supervened.

In the third group of experiments (Group C) five new dogs were again gassed slowly as before with a mixture of coal-gas and air containing 0.28% carbon monoxide: one became apnoeic. The mean arterial blood pressure was recorded using a mercury manometer and heart and respiratory rates were again recorded as was ventilatory minute volume. Centralaortic blood samples were collected by a catheter inserted through the femoral artery and these were analysed by the semi-micro Astrup technique for pCO_2, pH and standard bicarbonate. In addition the arterial lactate level was assayed using the method of Barker and Summerson (1941).

RESULTS

In Group A five dogs, on each of three separate gassings, reached a carboxyhaemoglobin level of precisely 70% when inhaling 0.37% carbon monoxide in air. The times taken to reach this level are shown in Table 3. Again, in Group A, apnoea occurred in five dogs - in one animal on two occasions. The times taken to reach apnoea and the carboxyhaemoglobin level at that time are set out in Table 4, together with the times taken by animals of Group B which became apnoeic at a slower rate of gassing. From these latter two tables it appears that whether gassed rapidly (87 - 110 min.) or slowly (120 - 270 min.) the eventual blood-levels of carboxyhaemoglobin were the same - 70.5% and 69% respectively. Also, in spite of as near identical conditions as possible, the time to reach apnoea in any one aminal when gassed on three separate occasions, varied to a considerable extent. It was, therefore, necessary in the subsequent analyses of the various data recorded, to refer each particular parameter to the level of carboxyhaemoglobin in the blood at the time.

Dog	1st gassing Min.	2nd gassing Min.	3rd gassing Min.
16572	169	109	101
16026	135	100	101
17433	120	144	101
17431	107	118	96
14732	135	97	185

TABLE 3.

Times taken to reach constant carboxyhaemoglobin level by 5 dogs gassed on three occasions with the same concentration of carbon monoxide.

Dog.	Gassing Time Min.	HbCO at Apnoea %
16548	87	72
16548	100	65
16572	169	65
16992	88	72
17433	146	71
17431	101	73
17431	270	71
16547	222	64
14732	222	70
17433	166	70
16998	200	70

Table 4.

Times taken to reach apnoea by 5 dogs of group A gassed with 0.37% carbon monoxide in air and also times taken by dogs of group B, gassed with 0.28% carbon monoxide in air.

CHANGES IN RESPIRATORY RATE AND MINUTE VOLUME.

As the level of carboxyhaemoglobin rose the minute volume and respiratory rate increased until the blood-level of carboxyhaemoglobin was somewhere between 50% and 60%. The respiratory rate and minute volume then fell rapidly towards apnoea as respiratory depression supervened.

In five of the experiments of Group A the level of carboxyhaemoglobin reached 70% in precisely 3 hours and in another five in precisely 2 hours. In figure 5 the mean values of all the readings of minute volume and respiratory rate made during each half-hour period of each of these two groups of five experiments is shown. It can be seen that both respiratory rate and minute volume increased as the level of carboxyhaemoglobin rose and then, in the last half-hour of gassing, both respiratory rate and minute volume fell as respiratory depression occured. The pattern is essentially the same whether it took 2 or 3 hours for the carboxyhaemoglobin level to reach 70%.

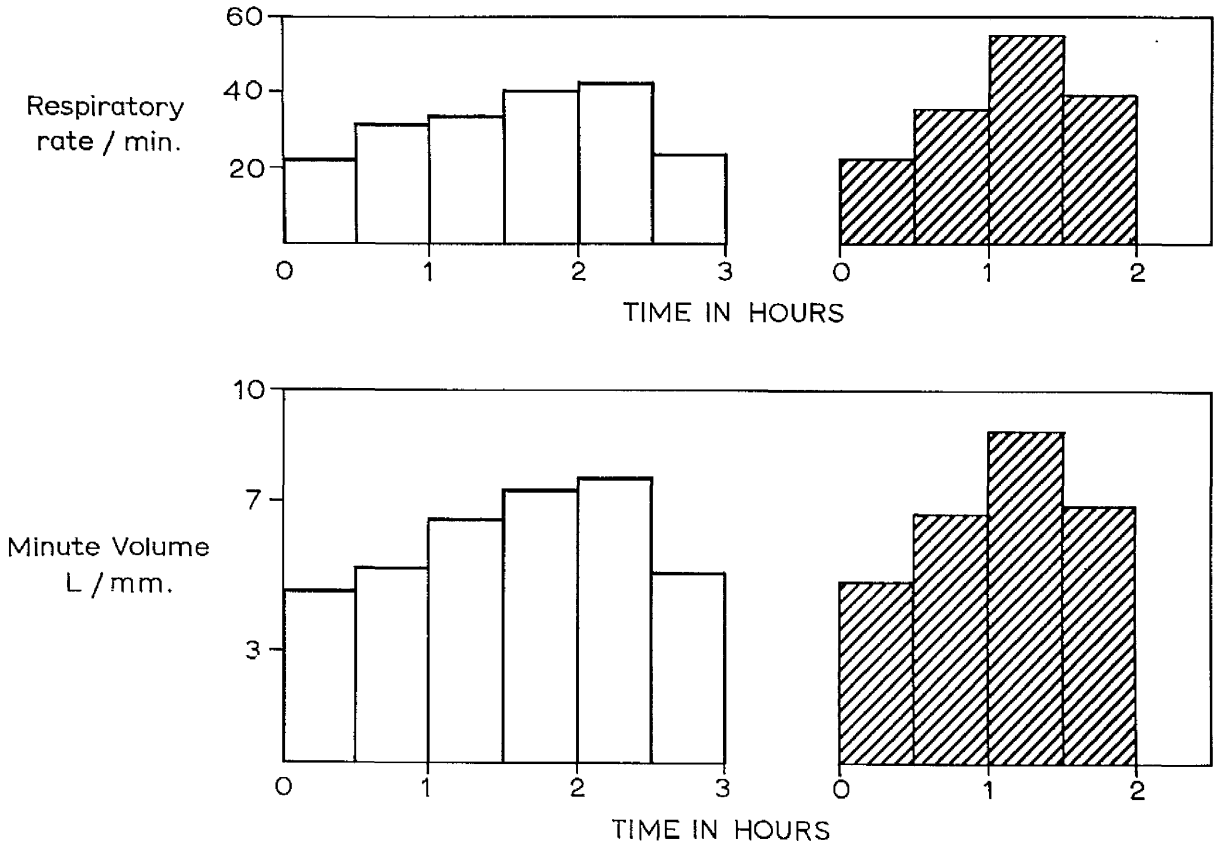

Figure 5.

Mean values of respiratory rate and minute volume for each half-hour period of the gassings which lasted 3 hours and those which lasted 2 hours.

CHANGES IN pCO_2

In Figure 6 can be seen the results of all the measurements of alveolar pCO_2 made in the dogs of Group A. Each reading is referred to the level of carboxyhaemoglobin present when the sample was obtained. The measurements of pCO_2 of mixed venous blood made on the animals of Group B may be seen in Figure 7, and the measurements made at the point of apnoea are included. In Figure 8, the measurements of arterial pCO_2 made in the dogs of Group C are shown. These figures show no evidence of carbon dioxide retention at any point during gassing and it can be seen that the mean value of venous pCO_2 of the four readings made at the point of apnoea is 39 mm Hg., while the animal of Group C which became apnoeic showed an arterial pCO_2 of 34 mm Hg., at that time.

CHANGES IN HEART RATE AND BLOOD PRESSURE

Central aortic blood pressure tended to fall as the level of carboxyhaemoglobin rose but heart rate did not vary in a consistent manner with the level of carboxy-haemoglobin.

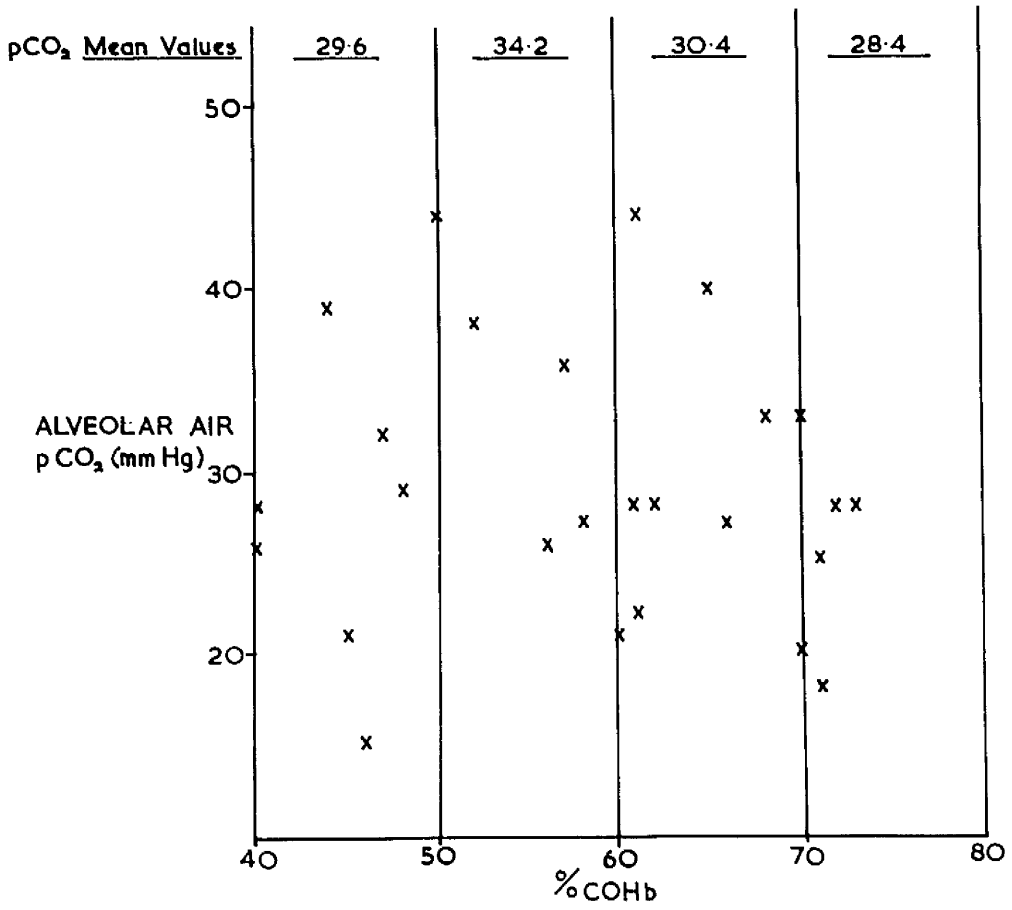

Figure 6.

Measurements of alveolar pCO_2 made on animals of Group A. Each value is related to the level of carboxyhaemoglobin at the time of sampling.

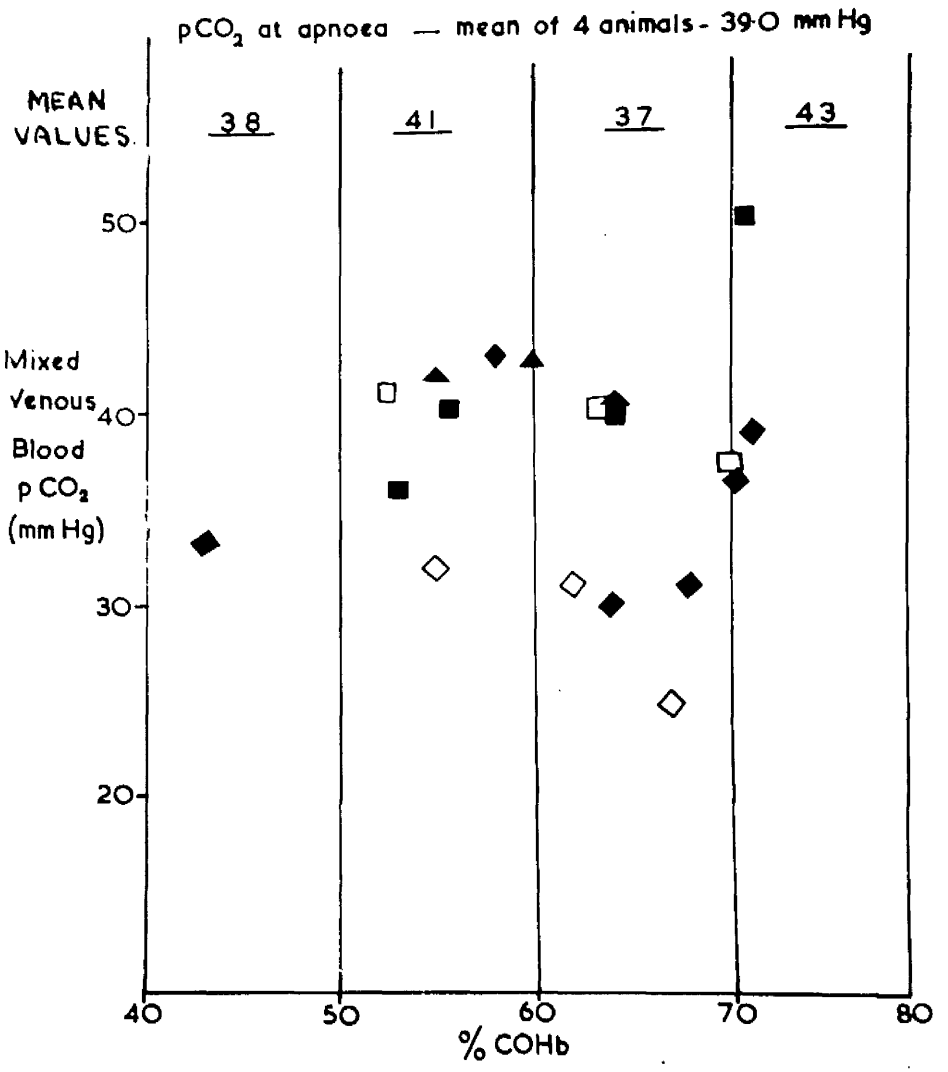

Figure 7

Measurements of venous pCO_2 made on animals of Group B including those when apnoea occured.

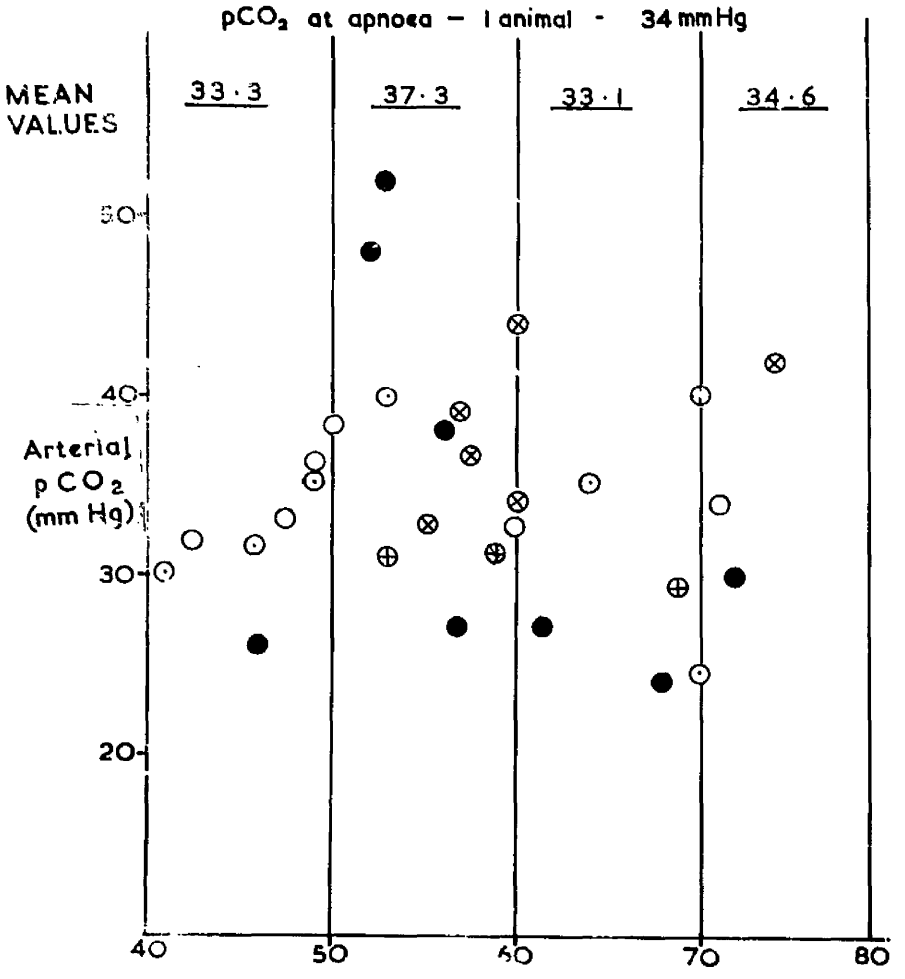

Figure 8.

Measurements of arterial pCO_2 made on animals of Group C.

CHANGES IN ACID-BASE METABOLISM

In Table 5 the measurements of pH, bicarbonate and total carbon dioxide of venous blood made on the animals of Group B are shown and Table 6 shows the measurements of pH, standard bicarbonate, total carbon dioxide and lactic acid made on the arterial blood in the animals of Group C. It can be seen that as the level of carboxyhaemoglobin rises metabolic acidosis develops.

DOG 16547

Time Min.	HbCO %	Blood pCO_2 mm. Hg.	Blood pH	Plasma Bicarbonate m.Eq/l.	Total CO_2 m.Eq./l.	RR/min.	M.V. l/min.	HR/min.
0	0	27	7.360	14.74	15.65	12	3.0	132
20	5	44	7.250	18.70	20.02	16	6.4	124
48	13	39	7.250	16.53	17.70	22	8.0	148
73	28	44	7.255	18.86	20.18	28	11.0	168
128	55	42	7.265	18.42	19.68	34	5.8	108
170	60	43	7.232	17.49	18.78	46	11.2	110
226	64	40.6	7.279	18.40	19.62	0	0	96
		DOG 17431						
0	0	37	7.337	19.16	20.27	42	4.8	160
25	16	30	7.430	19.24	20.14	46	5.8	98
60	33	32	7.391	18.79	19.75	82	11.6	98
80	43	33	7.381	18.90	19.89	84	11.0	132
115	58	43	7.292	20.07	21.36	84	12.4	154
180	64	30	7.394	17.71	18.61	86	13.4	150
220	68	30.5	7.376	17.28	18.20	85	14.4	155
255	70	36.5	7.265	16.09	17.19	72	12.4	176
270	71	39	7.227	15.67	16.84	0	0	192
		DOG 17433						
0	0	24	7.331	12.27	12.99	34	5.7	130
70	53	27.5	7.402	16.54	17.07	62	10.8	150
110	56	33	7.310	16.06	17.05	60	10.4	148
130	64	34.5	7.305	16.59	17.63	60	10.4	140
166	71	44.0	7.236	18.06	19.41	0	0	144
		DOG 16998						
0	0	26	7.314	13.77	14.58	18	4.8	176
80	55	32	7.255	13.72	14.68	36	11.0	172.
110	62	31	7.277	13.98	14.91	42	13.0	142
135	67	24.7	7.261	11.74	12.48	48	12.2	136
		DOG 14732						
0	0	33	7.252	14.05	15.04	22	8.2	
37	3	36.8	7.182	13.29	14.39	22	8.0	
62	11	39	7.248	16.46	16.63	14	3.6	
130	63	37	7.280	16.80	17.91	42	5.2	
200	64	35.7	7.270	15.83	16.90	31	4.6	
222	70	32.5	7.180	11.35	12.33	0	0	

Table 5.

Measurements of mixed venous pH, bicarbonate and total CO_2 made on dogs of Group B.

DOG NO. 1

Time Min.	COHb. %	Blood pCO_2 mm. Hg.	Blood pH	Plasma Bicarbonate m. Eq./l.	ToT CO_2 m.Eq./l.	Lactic Acid mg.%	PR/min.	M.V. l/min.	HR/min.	
0	0	23	7.50	18	18.7	21.4	20	4	131	125
20	23	29	7.55	24.5	25.4	13.4	14	2.1	124	143
43	53	28	7.56	24.5	25.3	12.0	46	6.8	146	118
68	58	38	7.50	28.0	29.1	16.9	40	4.3	154	100
91	59	30	7.57	26.5	27.4	16.1	74	6.5	162	105
111	55	47	7.41	28.0	29.4	17.9	30	4.2	160	110
131	59	45	7.44	29.0	30.4	16.1	44	5.8	148	105
148	64	30	7.56	25.5	26.4	21.6	34	4.6	152	90
168	72	27	7.56	23.5	24.3	25.7	36	5.0	148	75
181	74	31	7.52	25.5	26.4	39.8	10	2.0	134	55
				DOG NO. 2.						
0	0	59	7.43	30	31.5	10.0	30	10	128	105
20	24	48	7.38	26	27.4	12.7	16	4.0	146	110
40	48	52	7.41	31	32.6	15.9	30	6.0	154	123
60	63	38	7.44	23	24.1	24.9	32	8.0	184	-
80	59	36	7.40	21.5	22.6	39.1	36	11.2	144	100
100	59	34	7.44	20.5	21.5	42.1	38	11.4	144	98
120	59	34	7.44	22.0	23.0	38.7	34	8.4	152	108
140	69	33	7.45	22.5	23.5	54.1	40	11.4	142	84
163	70	34	7.35	18.5	19.5	82.3	0	0	-	-
				DOG NO. 3.						
0	0	39	7.59	36	37.2	9.8	22	4.1	194	154
20	14	30	7.62	29.5	30.4	4.9	48	7.0	140	152
40	38	29	7.66	32	32.9	9.6	80	11.2	200	152
60	55	33	7.62	32	33.0	14.7	28	4.4	174	105
80	59	32	7.60	31	32.0	19.4	48	7.4	136	68
94	65	39	7.52	30	31.2	28.8	68	11.0	164	80
120	58	36	7.51	27	28.1	28.8	80	12.6	162	18
180	68	36	7.54	29	30.1	25.4	50	8.6	190	75
200	77	27	7.58	25	25.8	39.7	22	7.8	164	85
				DOG NO. 4.						
0	0	35	7.54	29	30.5	8 .0	22	3.4	204	123
24	21	46	7.51	33	34.8	7.6	32	3.6	224	127
44	42	38	7.57	32	33.1	5.0	30	4.1	240	125
64	55	32.5	7.53	27.5	28.6	8.3	54	6.0	204	112
84	65	39	7.51	29	30.2	4.5	54	6.4	180	102
104	64	41	7.45	29	30.2	5.5	56	6.8	170	92
124	59	31	7.63	31	32.9	9.4	54	7.9	176	90
144	64	37	7.55	31	32.2	11.4	60	7.2	172	82
164	65	35	7.59	32	33.1	7.0	52	6.4	160	80
184	72	42	7.50	31	32.3	10.3	26	1.8	156	80

DOG NO. 5.

Time Min.	COHb %	Blood pCO_2 mm. Hg.	Blood pH	Plasma Bicarbonate m. Eq./l.	ToT CO_2 m.Eq./l.	Lactic Acid mg.%	RR/min	M.V. l/min.	HR/min	B.P. mm./g.
0	0	39	7.40	23	24.2	16.1	30	4.8	236	130
20	5	34	7.45	22.5	23.5	19.4	52	5.4	230	135
40	4	40	7.42	25	26.2	20.9	30	5.0	210	130
60	4	40	7.37	22	23.2	16.6	28	4.4	194	130
80	8	36	7.39	22	23.1	14.7	28	4.4	184	132
100	54	32	7.43	21	22.0	15.7	70	11.4	-	135
120	73	30	7.35	16.5	17.4	48.2	44	7.8	180	90
140	69	39	7.23	15.5	16.7	62.3	44	6.0	220	110

TABLE 6.

Measurements of arterial pH bicarbonate and total CO_2 made on dogs of Group C.

DISCUSSION

The increased ventilatory response to breathing a coal-gas/air mixture noted in the present series of experiments is probably the same as that noted by Haldane (1895 b) in humans when exposed to mixtures of carbon monoxide and air in which the carbon monoxide was present in excess of 0.1%. Asmussen and Chiodi (1941) also noted this response but stated that it did not occur when the saturation of haemoglobin with carbon monoxide exceeded 40%. In many cases, in these experiments, the hyperpnoea has continued even when the carboxyhaemoglobin content of the circulating blood has exceeded 50%. This hyperpnoeic response has also been noted in dogs by Henderson and Haggard (1920); Haggard and Henderson (1922); Kamei (1931a,b); Swann and Brucer (1949); Lilleheі, Wilks and Carter (1954) and Killick and Marchant (1959).

It is generally held that the increasing combination of available haemoglobin with carbon monoxide does not produce an anoxic drive to respiration during gassing, since the tension of oxygen present in the arterial blood is normal and, therefore, will not elicit stimulation of

the respiratory centre through the carotid and aortic chemoreceptors. Moreover, carboxyhaemoglobin itself is apparently without effect on these latter receptors since Comroe and Schmidt (1938) showed in anaesthetised dogs that 8% (V/V) of carbon monoxide in the blood did not produce increased ventilation when perfused through the carotid body if the tension of oxygen was kept within normal limits. This was confirmed in cats by Duke, Green and Neil (1952).

Killick and Marchant (1959) determined the blood pH, pCO_2 and lactate levels in dogs after death from carbon monoxide poisoning or in the early phases of resuscitation following severe gassing. The pH was low, the lactate level was raised and the total carbon dioxide was below normal levels. They have suggested that acidaemia is the stimulus to increased ventilation in this case. These findings confirmed those of Hikami (1927), , Kemel (1931 a, b) and Swann and Brucer (1949). The latter workers noted a fall in total carbon dioxide and a rise in blood lactate in four dogs rapidly gassed with 1% carbon monoxide.

In the present series of experiments there is no evidence of carbon dioxide retention in the blood of the

animals even when at the point of apnoea. The occurrence of hyperventilation during the process of gassing tends to cause a respiratory alkalosis so that finally when respiratory depression occurs the pCO_2 gradually rises towards normal levels.

The rising levels of lactate and the fall in bicarbonate suggest that the stimulus to ventilation is the occurrence of metabolic acidosis, which, in turn, is presumably caused by the tissue hypoxia which occurs as the oxygen transporting function of the haemoglobin becomes progressively blocked and anaerobic metabolism takes place. Metabolic acidosis has been found to cause considerable hyperventilation and is usually compensated for by well marked respiratory alkalosis, (Norman and Clark, 1964). In these experiments blood pH was not abnormal since the metabolic acidosis was compensated for by the hyperventilation.

Since it has not been possible to demonstrate carbon dioxide retention in any of these experiments there can be no contraindication to the use of carbon dioxide mixtures in resuscitation from carbon monoxide poisoning on the basis of the existence of an already high level of carbon dioxide before resuscitation is begun.

RESUSCITATION WITH CARBOGEN

Killick and Marchant (1959) clearly showed that 5% Carbogen lowered the level of carboxyhaemoglobin in acutely gassed dogs more rapidly than oxygen alone and they were able to find no dangerous side-actions. Following this work the Medical Research Council Committee for Research on Breathing Apparatus for Protection against Dangerous Fumes and gases (Brit. Med. J., 1958) gave official sanction to the re-introduction of 5% carbogen as the treatment of choice for carbon monoxide poisoning but stated that there was no point in using higher concentrations. Hill (1956) had indeed shown that the mortality rate was not increased during the years that 5% carbogen was not used. There were still clinicians, however, who believed that the best results could only be obtained by the use of 7% carbogen (Marriott, 1958) and they strongly advocated the use of the higher concentrations of carbon dioxide.

Since it has been shown in the previous section that the pCO_2 is not elevated even at the stage of respiratory depression in carbon monoxide poisoning, there can be no

contra-indication to the administration of carbogen mixtures even at this stage. Thus it seemed reasonable to compare the relative efficiency of 5% and 7% carbogen in resuscitation.

METHODS

Ten mongrel dogs weighing from 14 to 25 Kg. were used. Anaesthesia was induced with minimal doses of sodium pentobarbitone and the animals were gassed slowly with a mixture of coal-gas and air containing 0.37% carbon monoxide, until the blood-level of carboxyhaemoglobin was 70%. The technique of gassing and resuscitation was the standard method described above. When the blood-level of carboxyhaemoglobin reached 70% the dog was given 5% carbogen to breathe and the time required for the gas to be excreted was noted. Several weeks later the same dog was gassed under identical conditions but on this occasion the animal was given 7% carbogen to breathe when the blood-level of carboxyhaemoglobin reached 70%. Each dog therefore acted as its own control and the time required to reduce the level

of carboxyhaemoglobin by half, when 5% and when 7% carbogen was used for resuscitation, was found in each animal. 5% carbogen was used for resuscitation from the first gassing episode in alternate animals. Care was taken to keep the dogs in good condition between experiments.

Respiratory minute volume, respiratory rate and heart rate were monitored at regular intervals during both gassing and resuscitation. Alveolar gas samples were collected in ten of the experiments during both gassing and resuscitation and they were measured for carbon dioxide content by the Haldane apparatus.

RESULTS

A protocol from one of the experiments may be seen in Figure 9 and this shows the changes in minute volume, respiratory rate, heart rate and alveolar pCO_2 which typically took place while the level of carboxyhaemoglobin was rising during gassing and falling during resuscitation. The minute volume and respiratory rate steadily increased until the level of carboxyhaemoglobin rose above 60% when both fell rapidly towards zero as respiratory depression supervened and the level of carboxyhaemoglobin approached 70%. There was a fall in alveolar pCO_2 during the period of hyperventilation but it rose to normal levels as respiratory depression occured. The heart rate did not show any consistent change during this experiment.

During resuscitation the rapidly diminishing blood-level of carboxyhaemoglobin can be seen, together with the simultaneous increase in minute volume and respiratory rate caused by the carbogen mixture used. The alveolar pCO_2 during resuscitation was closely related to the pCO_2 of the carbogen mixture used.

The time taken to reduce the blood-level of

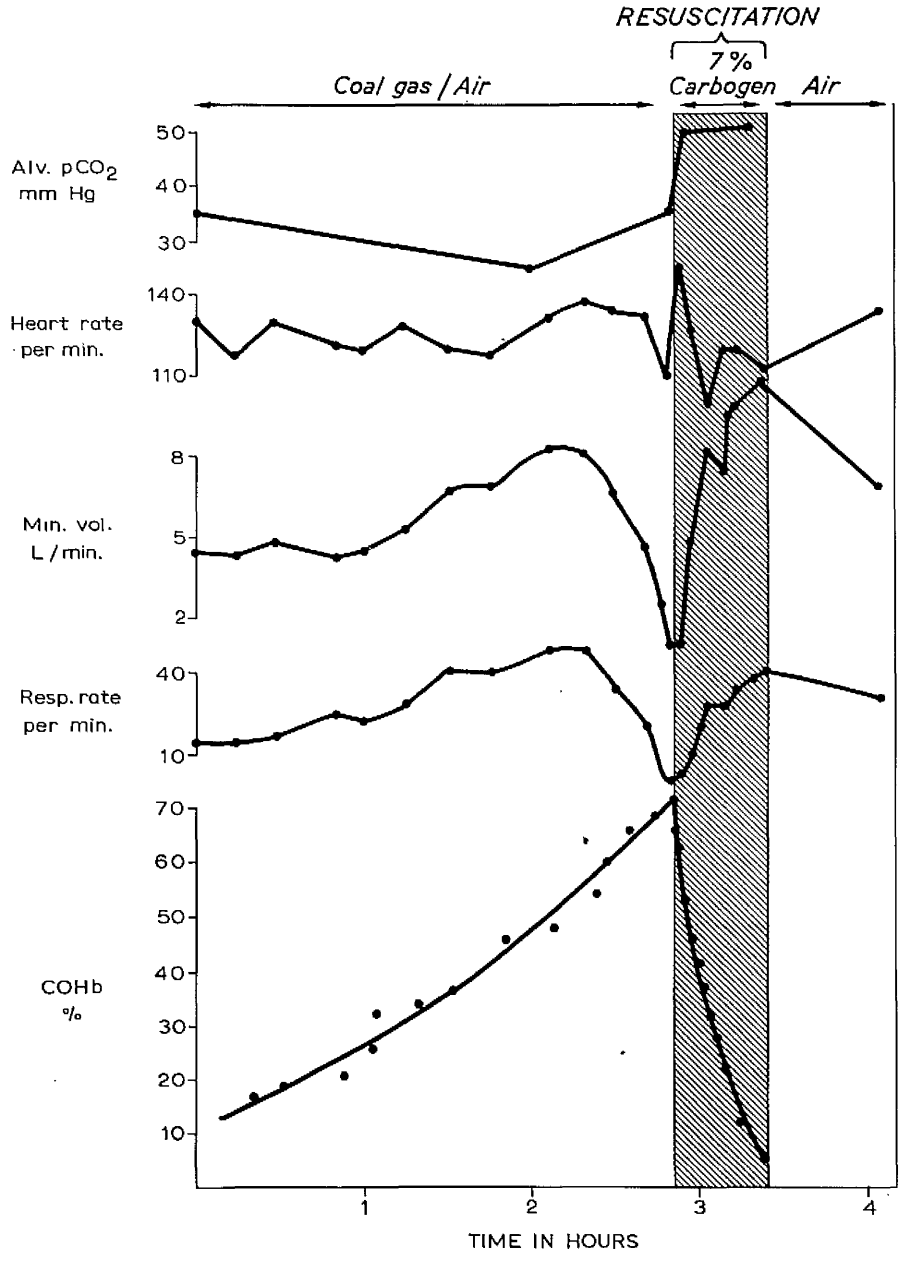

Figure 9

Protocol from one of the experiments showing the manner in which respiratory rate, minute volume, alveolar pCO_2 and heart rate varied with the level of Carboxyhaemoglobin.

carboxyhaemoglobin by half was noted in each case and this has been regarded as the standard of efficiency of the resuscitative gas under test. In Table 7 can be seen the half-clearance time obtained from each experiment. There is little variation in the individual values and the mean value obtained from all the resuscitation procedures using 5% carbogen, is practically identical to that obtained when 7% carbogen was used.

During resuscitation respiratory rate and minute volume were measured every 5 minutes for 35 minutes. Figure 10 shows the mean value of minute volume obtained from the ten dogs at each 5 minute period during resuscitation with 5% carbogen and also the same measurements made under the same conditions during resuscitation with 7% carbogen. There is a rapid increase in minute volume during the first 5 minutes of resuscitation using either gas mixture followed by a more gradual increase. These measurements show that, compared with 5% carbogen, there is a 20% increase in ventilation during resuscitation with 7% carbogen.

The measurements of respiratory rate made during resuscitation were analysed in the same manner as minute

Dog	5% Carbogen. T/2 (min.)	7% Carbogen. T/2 (min.)
A	9	9
B	17	12·5
C	10	15
D	10	12
E	15	15
F	11	6
G	16	15
H	13	14·5
I	21·5	19
J	15	16
Mean	13·75 (S.D. = 3·9)	13·40 (S.D. = 3·7)

Table 7.

Half-clearance times obtained when 5% and 7% carbogen were used for resuscitation.

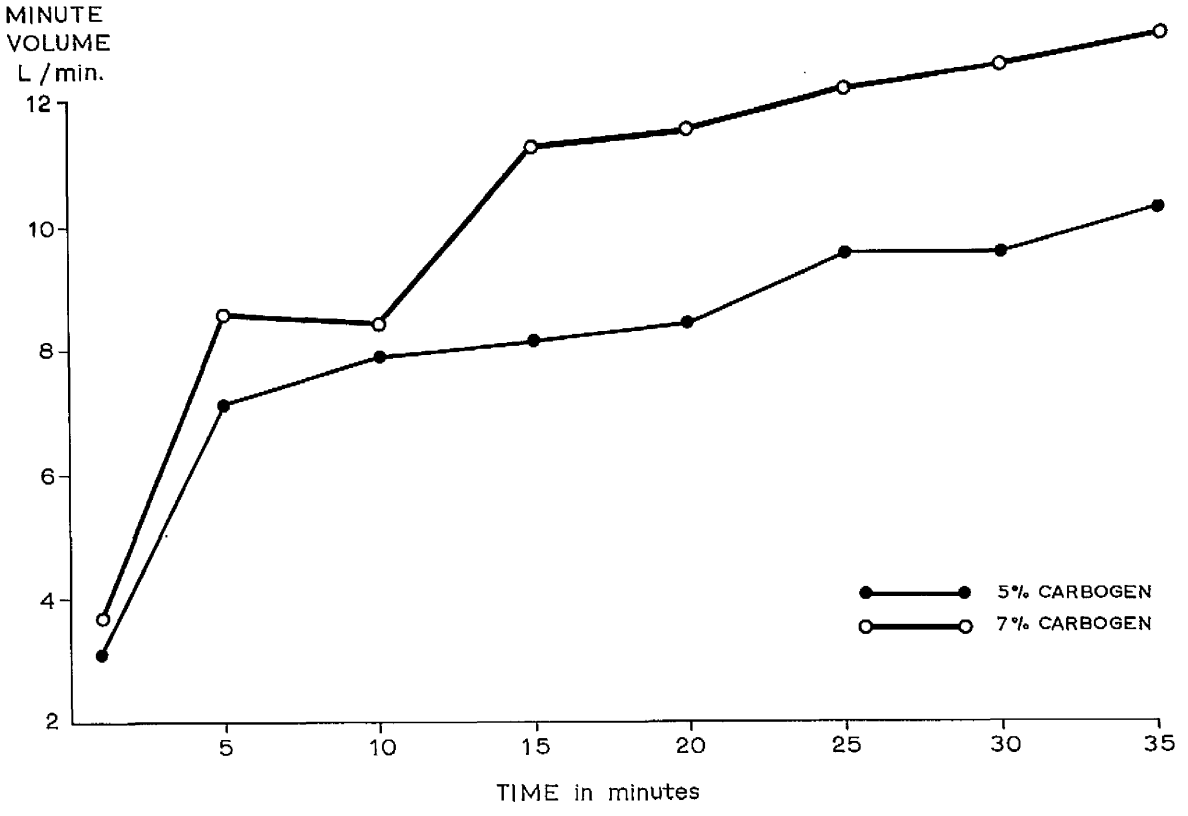

Figure 10.

Mean values of minute volume obtained from the ten dogs at each 5 minute period during resuscitation with 5% carbogen and also with 7% carbogen.

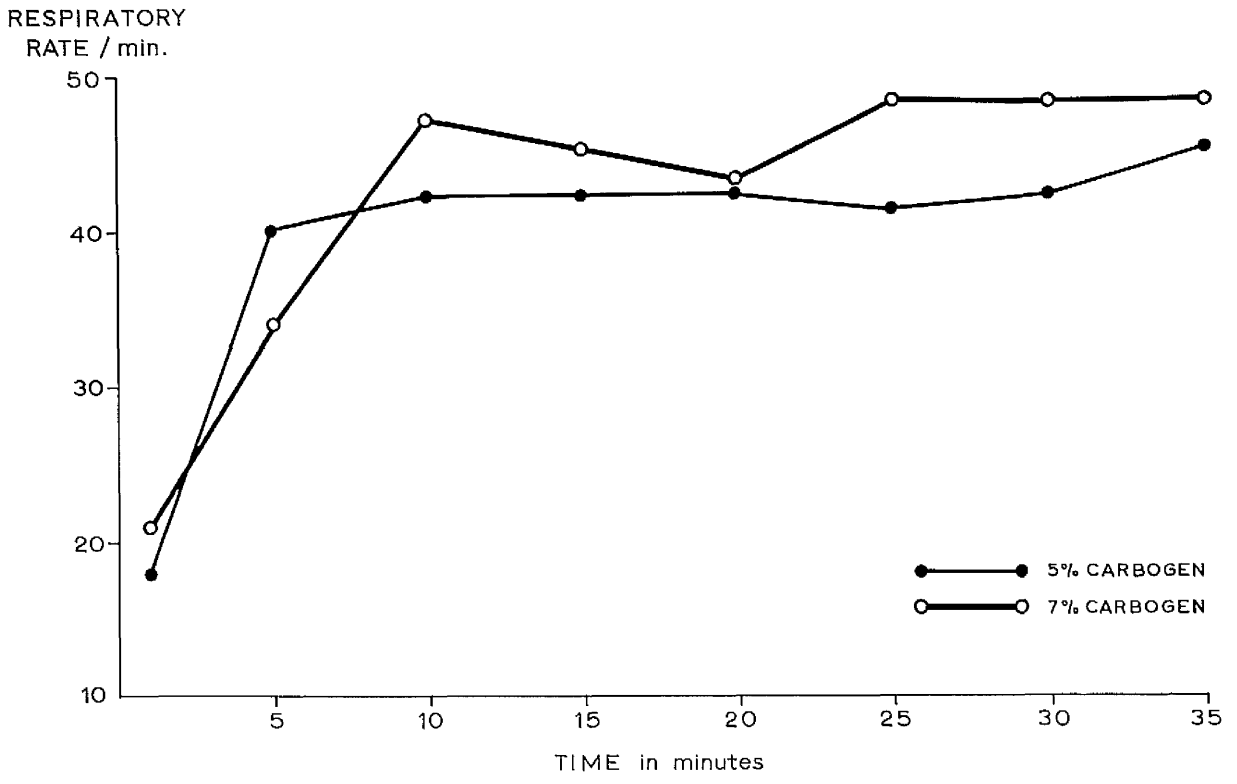

Figure 11.

Mean values of respiratory rate obtained from the ten dogs at each 5 minute period during resuscitation with 5% carbogen and also with 7% carbogen.

volume and they may be seen in Figure 11. There is a rapid increase in respiratory rate during the first 5 minutes of resuscitation by either gas mixture and the respiratory rate then remains at the same high level for the remainder of the procedure. The response of respiratory rate to 5% and 7% carbogen is not significantly different.

In Table 8 can be seen the measurements of alveolar pCO_2 made before gassing, following 1 - 2 hours of gassing, and at two points during resuscitation - one towards the beginning and one towards the end of the procedure. The pCO_2 measurements made during the course of gassing have been related to the blood-level of carboxyhaemoglobin present at the time.

DOG	ALVEOLAR pCO_2					
	GASSING			RESUSCITATION		
	BEFORE mm. Hg.	DURING mm. Hg.	COHb %	GAS USED % Carbogen	MIN 3-7 mm. Hg.	MIN 20-25 mm. Hg.
1	46	29	40	5	43	41
	38	33	66	7	50	45
2	50	46	40	5	49	50
	36	25	71	7	50	51
3	48	27	40	5	65	56
	54	38	40	7	67	72
4	37	34	45	5	40	45
	26	28	50	7	50	59
5	53	51	40	5	41	46
	39	20	70	7	51	54

Table 8

Alveolar pCO_2 measurements made at various points before and during gassing and during resuscitation.

DISCUSSION

This series of experiments fails to demonstrate any difference in the speed of clearance of carbon monoxide from the blood when resuscitation is carried out by either 5% or 7% carbogen. Douglas, Lawson, Ledingham, Norman, Sharp and Smith (1961) found that 7% carbogen cleared the blood of carbon monoxide slightly (but not significantly) more rapidly than 5% carbogen when a Heidbrink valve was used in the circuit instead of a Ruben valve. It seems likely that it is important to use a respiratory valve which does not permit re-breathing when resuscitation is undertaken.

There seems to be little point in using 7% carbogen in preference to 5%, since 5% carbogen will clear the blood of carbon monoxide as efficiently as 7% particularly if a respiratory valve which does not allow re-breathing is placed in the circuit by which the gas is administered.

None of the dogs died in this series during gassing or resuscitation, though many were gassed until apnoea occured - an event which takes place shortly after the blood-level of carboxyhaemoglobin has reached 70%. Respiratory failure always preceeded cardiac arrest and

when respiration ceased it was easily restored by rhythmically squeezing the rubber bag, filled with the carbogen mixture under test, for a few seconds. All the dogs recovered uneventfully and appeared normal in all respects by the following morning. Three months later there was still no evidence of neurological or other damage.

The alveolar pCO_2 measurements (Table 8) made before gassing show a wide scatter and this is probably due to variations in the level of anaesthesia at that time. Anaesthesia was not normally required after the blood-level of carboxyhaemoglobin was around 20 - 30% and the measurements made after the first hour of gassing are not subject to this criticism. There is no evidence of carbon dioxide retention in the measurements made during gassing and indeed many of them show respiratory alkalosis. It is presumed that the respiratory alkalosis, which commonly develops during gassing, is secondary to the hyperventilation that occurs as the level of carboxyhaemoglobin rises. The pCO_2 measurements made during resuscitation give values related to the tension of carbon dioxide in the resuscitative gas used.

In this series of experiments there is a 20% difference between the ventilatory response achieved with 5% and 7% carbogen but there is no difference between the mean half-clearance times. Thus the hyperventilation induced by carbon dioxide does not appear to be the only factor governing the rate of clearance of carbon monoxide from the blood. Comparisons of ventilatory response and rate of clearance of carbon monoxide in individual animals also fails to demonstrate any pattern.

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CARBOGEN IN EXPERIMENTAL CARBON-MONOXIDE POISONING

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The use of carbon dioxide with oxygen (carbogen) for the treatment of carbon-monoxide poisoning was first suggested by Henderson and Haggard (1920) after a series of experiments on dogs in which they used 10% carbon dioxide and 90% oxygen. Later they recommended the use of a mixture of 95% oxygen and 5% carbon dioxide (Haggard and Henderson, 1922). Nicloux, Nerson, Stahl, and Weill (1925) and Walton, Eldridge, Allen, and Witherspoon (1926) were unable to confirm the great increase in the speed of carbon-monoxide elimination which Haggard and Henderson claimed to be due to the presence of carbon dioxide. They therefore advocated the use of pure oxygen only as the treatment of choice. Carbogen mixtures, how-

ever, were almost universally adopted throughout the world.

The Medical Research Council Committee for Research on Breathing Apparatus for Protection against Dangerous Fumes and Gases condemned the use of mixtures of oxygen and carbon dioxide in resuscitation (Donald and Paton, 1955). This was done on the hypothesis that a patient in severe respiratory depression was inevitably already suffering from the effects of an excess of carbon dioxide in his tissues and was in urgent need of oxygen alone. In this country carbogen was therefore replaced by oxygen in the first-aid treatment of carbon-monoxide poisoning by ambulance men, by mine-rescue teams, and by other first-aid groups. This change provoked vigorous criticism by certain experienced clinicians, among whom was Marriott (1955a, 1955b), who had successfully treated large numbers of cases of carbon-monoxide poisoning with 7% carbogen. Marriott agreed that the use of carbon dioxide in the treatment of respiratory depression from most causes was illogical, but he urged that carbon-monoxide poisoning was a special case where it was vital that the body should be rid of carbon monoxide by the most rapid and effective means possible, and that was by the use of carbogen.

The work of Killick and Marchant (1959) on dogs clearly demonstrated that 5% carbogen cleared the blood of carbon monoxide significantly faster than did oxygen alone: carbogen produced no dangerous side-actions. The use of 5% carbogen was then given official sanction by the Medical Research Council (1958). The Council also stated that they did not consider that there was anything to be gained by the use of a higher percentage of carbon dioxide in oxygen.

Marriott (1958) still maintained, however, that the best results could only be obtained by the use of 7% carbogen rather than 5%. He emphasized his point by quoting the percentage of deaths from carbon-monoxide poisoning in New York over a period of eight years. During the first three years 5% carbogen was used: in this period there was a higher percentage of deaths than during the succeeding five years when 7% carbogen was used.

In view of all this it seemed desirable to compare experimentally the relative efficiencies of 5% and of 7% carbogen in the treatment of carbon-monoxide poisoning. This was done by gassing a dog under

standard conditions until the blood level of carboxyhaemoglobin was 70%. The dog was then given 5% carbogen to breathe and the time required for the gas to be excreted was noted. Several weeks later, under identical conditions, the experiment was repeated in the same dog using 7% carbogen.

Method

The animals were anaesthetized by the intravenous route with minimal doses of pentobarbitone sodium to allow the insertion of a cuffed Magill endotracheal tube: a "polythene" catheter was passed down the external jugular vein to the right atrium to permit sampling of mixed venous blood. Two groups, A and B, each of 10 dogs, were used.

Group A

The circuit shown in Fig. 1 was attached to the endotracheal tube. A T-junction was applied close behind the Heidbrink valve, and through one limb of this passed a supply of oxygen to replace that used by the animal. The carbon dioxide produced by the dog was removed by a to-and-fro soda-lime absorber of the Waters type. Through the other limb of the T-junction measured amounts of pure carbon monoxide were admitted to the circuit. After the addition of each increment of carbon monoxide the concentration of carboxyhaemoglobin in the blood was estimated. The level rose in a stepwise

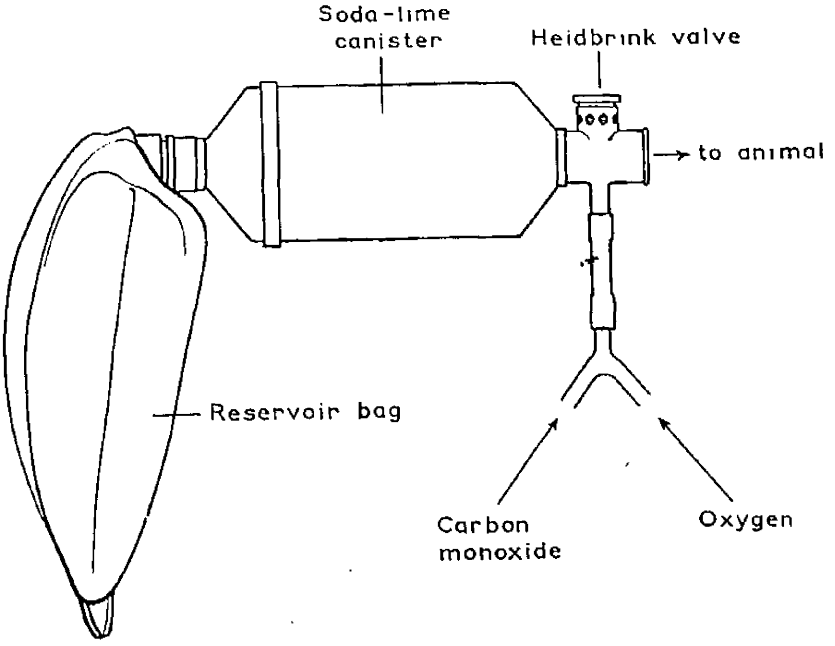

FIG. 1.—Circuit used in group A dogs.

fashion until 70% saturation was reached, taking an average of 45 minutes to do so. At this point gassing was stopped and the resuscitating mixture was applied direct to the inspiratory side of the Heidbrink valve. This latter was now set with the minimal amount of tension on the spring which retains the valve disk in its seating. The soda-lime canister was removed, retaining the bag, which was allowed to fill with the resuscitating mixture and was emptied frequently during the process of resuscitation.

Blood samples were removed at 1, 3, 5, 7, 9, 12, and 15 minutes, and thereafter at five-minute intervals from the beginning of resuscitation until carboxyhaemoglobin could be no longer detected. Thereafter the animals breathed air.

In three dogs of this group the procedure was repeated after several weeks, substituting a Ruben non-return valve for the Heidbrink valve. Again 5% and 7% carbogen were tested. This was done because there is reason to believe that the Heidbrink valve, even with the minimum spring-loading possible, allows a degree of rebreathing while the Ruben valve does not.

Group B

In this series coal-gas and air were withdrawn from cylinders of these gases and passed through a system of flowmeters. The gas mixture then passed into a large reservoir bag and finally on to the dog through a Ruben non-return valve (Fig. 2).

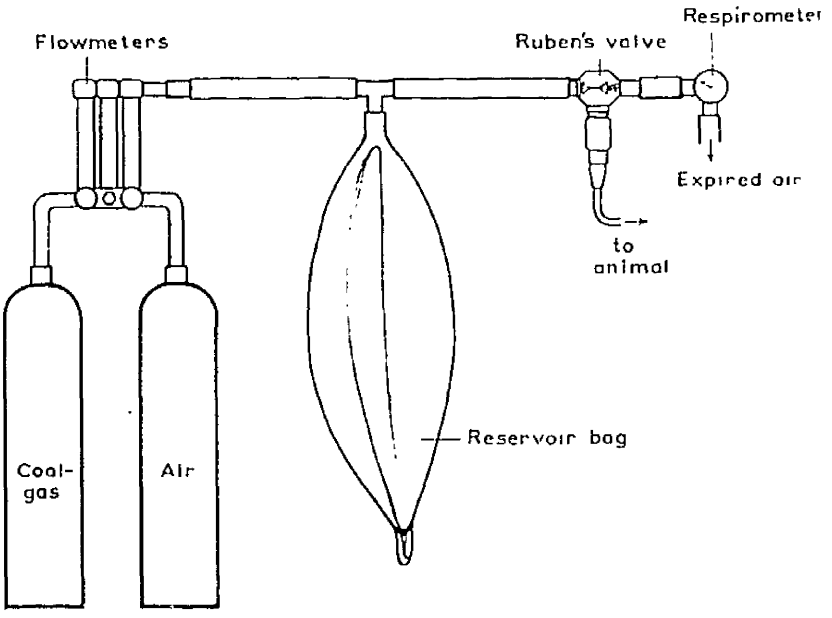

FIG. 2.—Circuit used in group B dogs.

Since the coal-gas in the cylinder contained 18.8% carbon monoxide and the gases were delivered at rates of 100 ml. gas/min. and 5 l. air/min., the gas delivered to the dog contained 0.37% carbon monoxide. The use of the Ruben valve ensured that the gas mixture delivered to the animal was of known composition and prevented rebreathing.

The rising carboxyhaemoglobin levels were again recorded during the period of gassing, and when the 70% level was reached, after an average period of two hours, the carbogen mixture under test was fed into a 20-litre rubber bag which was connected to the inspiratory side of the Ruben valve. The carboxyhaemoglobin levels were followed in the same manner as in group A until the carbon-monoxide content of the blood was negligible.

Estimation of Carboxyhaemoglobin

All estimations of carboxyhaemoglobin levels were performed by Harrison's (1957) quantitative method, using a Hartridge reversion spectroscope. In each group all the observations were made by one observer using his own calibration curve, constructed from the mean values obtained from measurements made on the blood of six dogs.

This method had the advantage of speed and simplicity, but in order to confirm the results obtained by it two other methods of determining carboxyhaemoglobin were carried out in certain cases. They were: (1) the spectrophotometric method of Heilmeyer and Krebs as described by Heilmeyer (1943), using a Unicam SP. 600 spectrophotometer; and (2) the manometric method of Van Slyke and Neill (1924) as modified by Horvath and Roughton (1942).

TABLE I.—*Estimations of Carboxyhaemoglobin Percentage on the Same Blood Samples by Three Methods*

Reversion Spectroscope	Manometric Method	Spectrophotometric Method
72	80	81
69	78	80
62	64	74
61	58	58
53	53	59
45	49	57
44	43	50
37	41	44
22	38	39
20	29	33
19	27	30
3	23	25

Table I shows the results obtained when the three methods were applied to the same samples of blood. It will be seen that there is good agreement among the methods down to a level of 35% as recorded by the reversion spectroscope.

It was therefore decided to take the time for the carboxyhaemoglobin percentage to fall from 70% to 35%—that is, the half-clearance time (T/2)—as a parameter with which to compare the efficiency of treatment of one group with another.

Results

Table II shows the half-clearance times obtained in animals of group A when resuscitated with 5% and 7% carbogen on the circuit utilizing the Heidbrink valve.

TABLE II.—*Half-clearance Times of 10 Dogs Resuscitated with 5% and 7% Carbogen, Using a Heidbrink Valve in the Circuit*

Dog	5% Carbogen. T 2 (min.)	7% Carbogen. T 2 (min.)
1	17	14
2	21	17
3	18	11
4	21	18·5
5	19	19
6	13	12
7	21	13
8	27	15·5
9	30	27
10	18·5	16
Mean	20·55 (S.D. = 4·9)	16·3 (S.D. = 4·6)

The difference between the means of the half-clearance times suggests that 7% carbogen clears the blood of carbon monoxide faster than does 5%—in 16.3 minutes as compared with 20.6 minutes—although the difference is not statistically significant.

In the three animals on which the experiment was repeated, substituting the Ruben for the Heidbrink valve, the increased efficiency of the 7% carbogen mixture disappears: 5% and 7% carbogen appear to be about equal in their effect as judged by the time taken to lower the concentration of carboxyhaemoglobin from 70% to 35%. This is shown in Table III.

In the animals of group B (Table IV) where only the Ruben valve was used, the difference between the means of the half-clearance times for animals resuscitated by 5% and by 7% carbogen again no longer exists—13.8 and 13.4 minutes.

TABLE III.—*Half-clearance Times from Three Dogs when Resuscitated with 5% Carbogen and Then with 7%, Using a Heidbrink Valve and Then a Ruben Valve in the Circuit*

Dog	Heidbrink Valve		Ruben Valve	
	5% Carbogen T/2 (min.)	7% Carbogen T/2 (min.)	5% Carbogen T/2 (min.)	7% Carbogen T/2 (min.)
4	21	18·5	10	8
5	19	19	15	12
8	27	15·5	17	24
Mean	22·3	17·7	14	14·7

TABLE IV.—*Half-clearance Times of 10 Dogs Resuscitated with 5% and 7% Carbogen with the Ruben Non-return Valve in the Circuit*

Dog	5% Carbogen. T/2 (min.)	7% Carbogen. T/2 (min.)
A	9	9
B	17	12·5
C	10	15
D	10	12
E	15	15
F	11	6
G	16	15
H	13	14·5
I	21·5	19
J	15	16
Mean	13·75 (S.D. = 3·9)	13·40 (S.D. = 3·7)

Discussion

Although the results of the first series of experiments (Table II) demonstrate that 7% carbogen clears the blood of carbon monoxide more rapidly than does 5% on the same animals, the second series (Tables III and IV) shows no such difference. The only alteration in the technique of resuscitation is the use of the Heidbrink valve for the first group and the Ruben valve for the second. Further, the difference in mean half-clearance time shown in Table II when 5% and 7% carbogen are used with the Heidbrink valve disappears when the Ruben valve is used. This clearly demonstrates that the difference is a function of the respiratory valve used in the circuit and indicates the importance of using a respiratory valve which does not permit rebreathing when resuscitation is undertaken.

There seems to be little point in using 7% carbogen in preference to 5%, since 5% carbogen will clear the blood of monoxide as efficiently as 7% if a respiratory valve which does not allow rebreathing is placed in the circuit by which the mixture is applied.

None of the dogs in either series died during gassing or resuscitation, though many were gassed to apnoea—

an event which occurs shortly after the 70% level of carboxyhaemoglobin is recorded by the reversion spectroscope. Respiratory failure always occurred before cardiac arrest. When respiration ceased, artificial respiration was undertaken by rhythmically squeezing the rebreathing bag filled with the appropriate carbogen mixture for the experiment. All the dogs recovered uneventfully and seemed perfectly well by the following day. Up to three months later there was no evidence of neurological or other damage.

Summary

Two groups of 10 dogs were gassed with carbon monoxide until the level of carboxyhaemoglobin was 70%. The animals were then resuscitated using 5% and 7% carbogen in turn. In group A a Heidbrink valve was placed in the resuscitating circuit and there was a difference in efficiency of resuscitation in favour of 7% carbogen. In group B a Ruben non-return valve was placed in the resuscitating circuit and no difference between the efficiency of 5% and 7% carbogen was demonstrated. The choice of a respiratory valve which prevents rebreathing when resuscitation is undertaken in carbon monoxide poisoning is thus more important than the choice of a 5% or a 7% carbogen mixture.

Our thanks are due to Professors R. C. Garry, Sir Charles F. W. Illingworth, and W. L. Weipers for their interest and help.

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RESUSCITATION WITH OXYGEN AT TWO ATMOSPHERES PRESSURE.

The treatment of choice for carbon monoxide poisoning indicated by the preceding sections, is 5% carbogen administered by means of a circuit, in which re-breathing is prevented. Following experimental work on rodents by Lawson, McAllister and Smith (1959, 1961), however, the successful use of oxygen at two atmospheres pressure in the treatment of two patients suffering from severe coal-gas poisoning was described by Smith and Sharp (1960). The series of experiments detailed below was designed to ascertain whether oxygen at two atmospheres pressure would rid the blood more speedily of carbon monoxide than carbogen mixtures. (Douglas, Lawson, Ledingham, Norman, Sharp and Smith, 1962).

METHODS

The same ten dogs in which the efficiency of 5% and 7% carbogen in resuscitation was compared were again used in this series of experiments since the speed with which carbon monoxide was removed from the blood by both carbogen mixtures was already known for these animals.

The half-clearance times obtained when oxygen at twice atmospheric pressure was used in resuscitation could thus be compared directly with the known efficiency of carbogen mixtures in the same animals.

The ten animals were anaesthetised and gassed with a coal-gas/air mixture containing 0.37% carbon monoxide, in precisely the same manner as before. When the blood-level of carboxyhaemoglobin reached 70% the dog was given pure oxygen to breathe in the pressure chamber when the ambient pressure was two atmospheres absolute. The pressure within the chamber was raised to two atmospheres during the final half hour of gassing so that resuscitation could take place as soon as the blood-level of carboxy-haemoglobin reached 70%. Thus, resuscitation was begun at the same juncture of the experiment as in the experiments conducted at normal atmospheric pressure. The blood samples removed during the course of resuscitation were all analysed for carboxyhaemoglobin content before the pressure was reduced.

The apparatus used in this series of experiments was mounted on a trolley to enable the whole preparation to be moved into the pressure chamber without interruption of

gassing. This trolley may be seen in Figure 3.

Ventilatory minute volume, respiratory rate, heart rate and alveolar pCO_2 were recorded at intervals during both gassing and resuscitation. In seven experiments respiratory rate, minute volume and alveolar pCO_2 were observed following decompression. Gas samples collected in the pressure chamber were allowed to expand over mercury during decompression and analysed for carbon dioxide content at normal atmospheric pressure.

RESULTS

Figure 12 shows a protocol of one of the experiments in which hyperbaric oxygen was used for resuscitation. The level of carboxyhaemoglobin, respiratory rate, minute volume, heart rate and alveolar pCO_2 is plotted against time. The minute volume can be seen to rise with the rising level of carboxyhaemoglobin and to fall when the carboxyhaemoglobin level had exceeded 55%. Respiratory rate did not increase during gassing, in this experiment, but it fell in sympathy with minute volume at the higher levels of carboxyhaemoglobin. In this case the heart

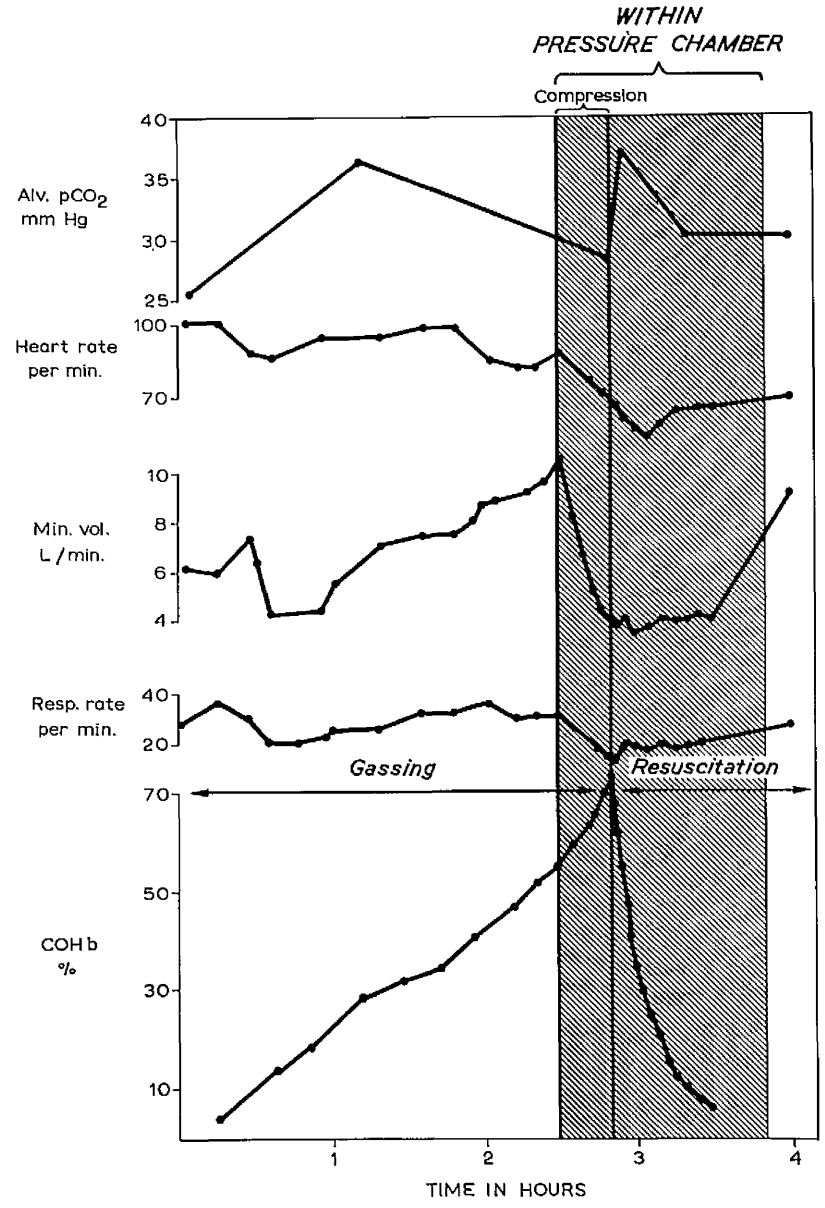

Figure 12.

Protocol of one of the experiments. Variations in respiratory rate, minute volume, heart rate and alveolar pCO_2 with the changing level of carboxyhaemoglobin are shown against time.

rate fell also at this stage, but this was not a constant finding. During resuscitation with hyperbaric oxygen respiratory rate and minute volume did not alter distinctly though both increased following decompression.

Table 9 shows the half-clearance times obtained from the ten animals when resuscitated with oxygen at two atmospheres pressure and the results are compared with those obtained from the same animals when resuscitated with 7% carbogen. The mean half-clearance times show that carbon monoxide is removed nearly twice as fast when hyperbaric oxygen is used as compared to 7% carbogen.

In Figure 13 can be seen the mean clearance curves obtained from the animals when resuscitated with 5% carbogen, 7% carbogen and oxygen at two atmospheres pressure. It can be seen that there is little difference between the curves obtained for 5% and 7% carbogen but that the rate of clearance is much more rapid when hyperbaric oxygen is used.

Figure 14 shows the mean values of minute volume obtained from the ten dogs during resuscitation at minutes 1, 5, 10, 15, 20, 25, 30 and 35. These values are compared with similar readings made during resuscitation of the same dogs with 5% and 7% carbogen.

Dog	With oxygen at 2 atmospheres T/2 (min.)	With 7% carbogen T/2 (min.)
A	6	9
B	9	12.5
C	7	15
D	5	12
E	4	15
F	5.5	6
G	8	15
H	13	14.5
I	10	19
J	8	16
Mean	7.6 (S.D. $\pm$ 2.7)	13.4(S.D. $\pm$ 3.7)

Table 9

Half clearance times obtained when 7% Carbogen and when oxygen at two atmospheres pressure were used for resuscitation of the same dogs.

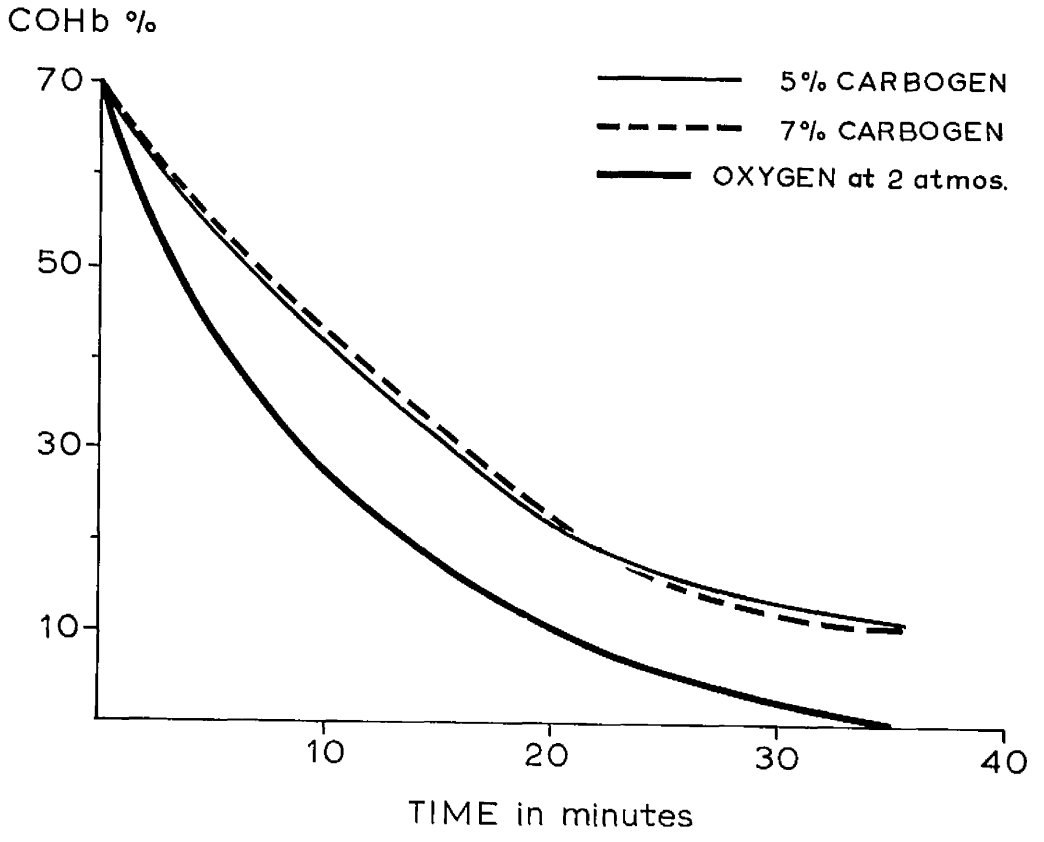

Figure 13.

Clearance curves obtained from 10 animals resuscitated with 5% and 7% carbogen and with oxygen at two atmospheres pressure.

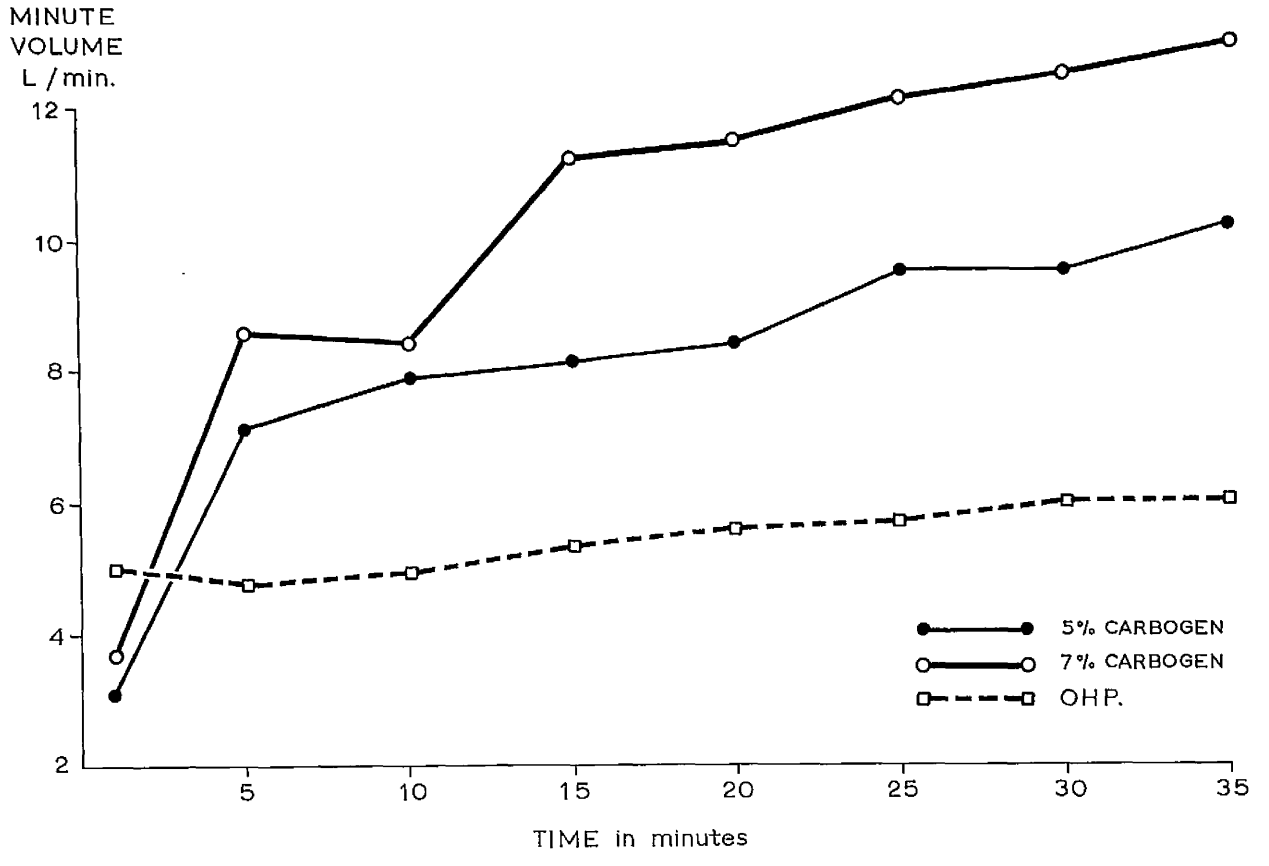

Figure 14.

Mean values of minute volume obtained from the same ten dogs when resuscitated with 5% and 7% carbogen and with oxygen at two atmospheres pressure.

In Figure 15 the mean values of respiratory rate, measured at the same times during resuscitation, are presented in the same manner. It can be seen that the ventilatory response found with carbogen is absent when hyperbaric oxygen is used for resuscitation and in this case there is little change in ventilation throughout the procedure.

The alveolar pCO_2 falls as the carboxyhaemoglobin level increases and it rises to normal values towards the end of gassing in the same manner as in the previous experiments. The measurements made during resuscitation were not abnormal and the pCO_2 appears to be little affected by this relatively short exposure to 100% oxygen at two atmospheres pressure. These results may be seen in table 10.

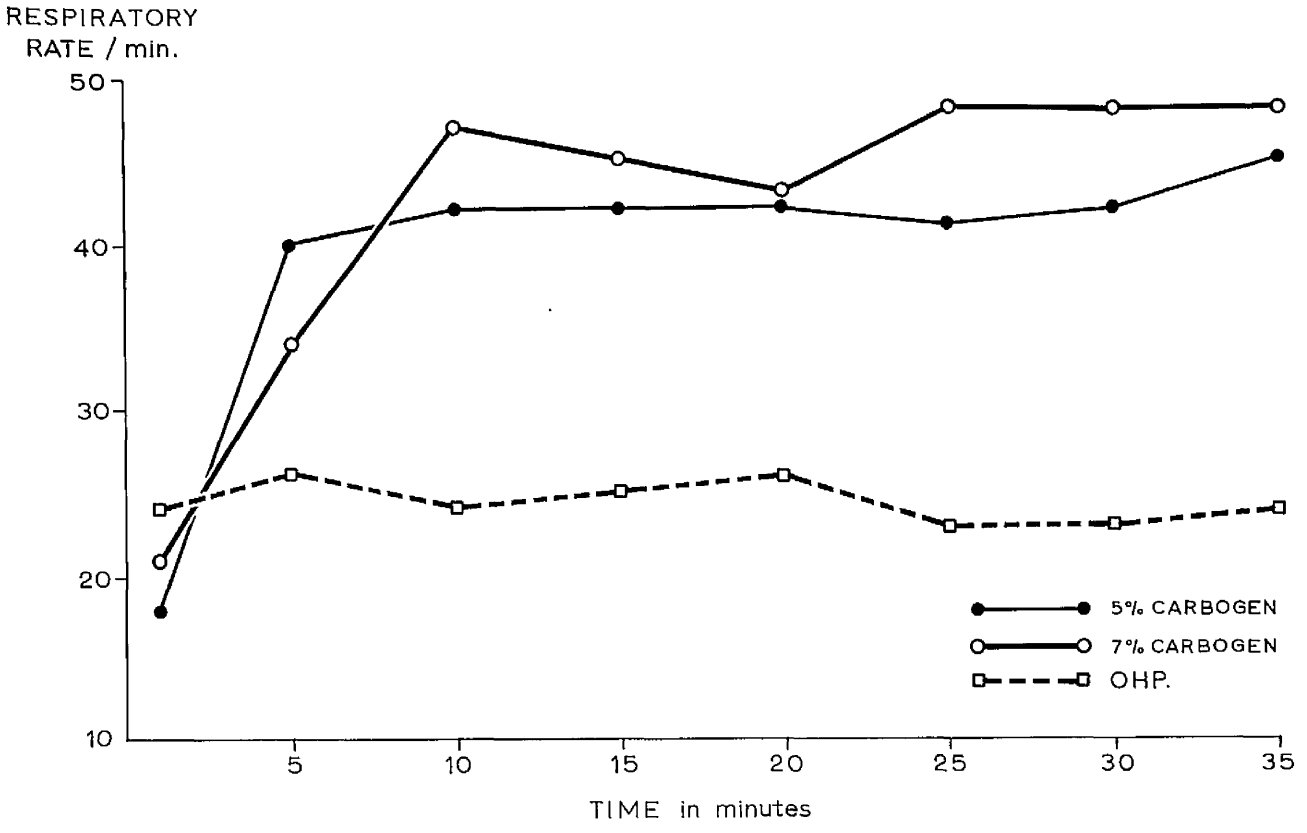

Figure 15

The mean values of respiratory rate obtained from the same ten dogs when resuscitated with 5% and 7% carbogen and with two atmospheres pressure.

DOG	ALVEOLAR pCO_2							
	GASSING					RESUSCITATION		
NO	BEFORE mm. Hg.	DURING mm. Hg.	COHb %	END mm. Hg.	COHb %	MIN 3-7 mm. Hg.	MIN 20-25 mm. Hg.	Post-Decompression mm. Hg.
1	25	36	28	36	75	37	30	31
2	29	39	45	31	69	26	20	38
3	42	21	32	38	60	47	36	32
4	46	47	42	40	66	55	44	49
5	34	30	25	30	63	34	30	31

Table 10.

Alveolar pCO_2 measurements made at various times during gassing and resuscitation with oxygen at 2 atmospheres pressure.

DISCUSSION

There is no doubt that oxygen at a pressure of two atmospheres will remove carbon monoxide from the body more rapidly than any other method considered. It is commonly accepted that in carbon monoxide poisoning it is vital to rid the body of carbon monoxide by the most rapid and efficient means possible if anoxic damage is to be avoided. Hyperbaric oxygen fulfills this criterion but the immediate correction of the tissue anoxia brought about by administering oxygen at a pressure of two atmospheres is probably a more important factor in advocating its use. Thus the oxygen in physical solution by-passes the blocked haemoglobin mechanism and oxygenates the tissues directly. Boerema, Meyne, Brummelkamp, Bouma, Mensch, Kamermans, Stern Hanf and Van Aalderen (1959; 1960) have shown that life can be maintained in animals deprived of haemoglobin by giving them oxygen at a pressure of three atmospheres to breathe. Although rapid reduction in the level of carboxyhaemoglobin with the restoration of normal oxygen transport by the haemoglobin is important it is likely that the immediate correction of the tissue anoxia is of greater value.

THE TREATMENT OF COAL-GAS POISONING WITH OXYGEN AT TWO ATMOSPHERES PRESSURE.

Following the experimental demonstration of the efficiency of hyperbaric oxygen in the treatment of coal-gas poisoning and the report of its use in two patients (Smith and Sharp, 1960) it was decided to treat all severely gassed patients admitted to the Western Infirmary, Glasgow, during a period of one year with oxygen at two atmospheres pressure.

During the year of the study thirty-two patients were admitted to the hospital from the area of Glasgow which it serves. Of these patients twenty-two were judged ill enough to warrant treatment in the pressure chamber, and none of the thirty-two patients died. One further patient was transferred from another hospital where he had been treated for several hours, and had not responded to orthodox therapy. Treatment with hyperbaric oxygen removed the carbon monoxide from his blood but he did not regain consciousness and died three days later.

PROCEDURE.

When an ambulance was despatched to a suspected gassing incident the hospital team was alerted so that they would be at the hospital before the arrival of the patient. If the patient was conscious oxygen was given in the ambulance. If the patient was unconscious and respiration much depressed oxygen was given by a Stephenson cycling resuscitator.

On arrival at the hospital the patient's clinical condition was rapidly assessed and a sample of venous blood withdrawn for the estimation of its carboxyhaemoglobin content. Treatment with hyperbaric oxygen was used in those cases who were semi-conscious or comatose on admission, and these showing respiratory and/or cardiac depression.

The percentage saturation of the blood with carboxyhaemoglobin was determined with the Hartridge Reversion Spectroscope, partly in order to maintain continuity with the research programme and also since the Reversion Spectroscope has the advantage of rapidity and facility of use for following the progress of any case inside the

pressure chamber. A reasonable degree of accuracy was obtained by one observer making all the measurements and using his own calibration curve, which was constructed from the meaned results obtained from the blood of six different people. In case of emergency the other members of the team constructed their own calibration curves also.

When a patient arrived at the hospital, he was transported rapidly to the pressure chamber. Oxygen could be given or respiration assisted with the Stephenson Respirator in transit. Once inside the pressure chamber, the pressure was raised to two atmospheres absolute as rapidly as possible.

While in the chamber the patient breathed oxygen delivered through a well-fitting face mask, fitted with a Ruben valve, (Figure 16.). If respiration was not adequate, however, then the oxygen was led into a two litre rubber bag and assisted respiration carried out by rhythmical compression of the bag.

Treatment was continued until carboxyhaemoglobin was no longer detectable in the blood, and the patient showed signs of returning consciousness.

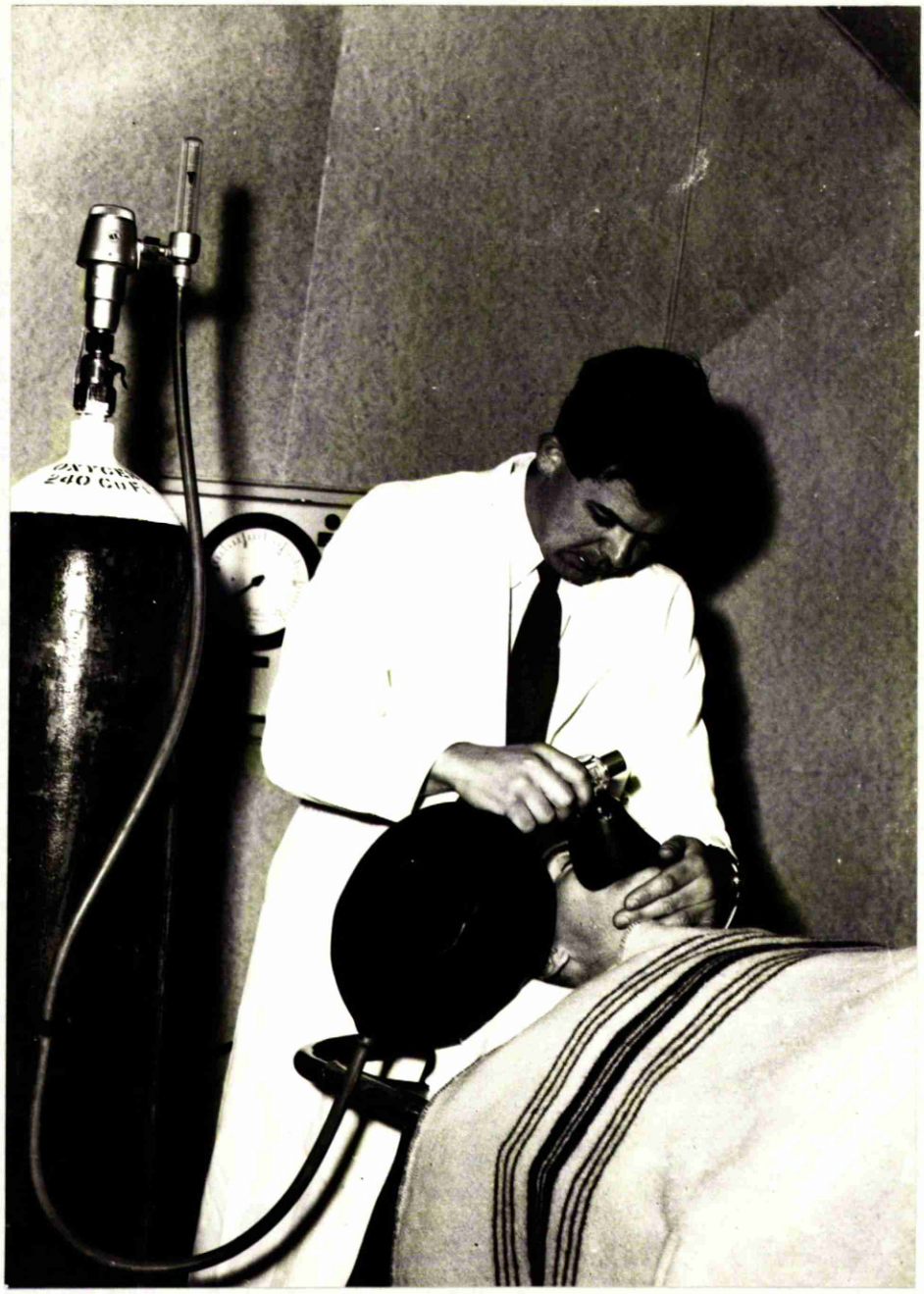

Figure 16.

Patient receiving oxygen in pressure chamber through face mask with Ruben Valve.

RESULTS.

In all cases treated during the year of this study consciousness has returned within thirty to ninety minutes at two atmospheres pressure; they have all survived and shown no neurological or cardiac sequelae. Table 11 gives details of a selection of cases from each group.

Since the year of this study and during three years of routine treatment of all severely gassed patients entering the hospital 70 patients were treated and there have been three who did not conform to the usual picture.

Case 1: A 45 year old woman was admitted to the pressure chamber with a history of at least eight hours exposure to coal gas. This woman was deeply unconscious with pupils fixed in the mid-position; she did not respond to painful stimuli and showed decerebrate rigidity. Both plantar responses were extensor. Respiration was deep but not stertorous and the pulse was feeble, irregular and rapid. Carboxyhaemoglobin level on admission was 34%.

The patient was admitted to the pressure chamber and given oxygen at two atmospheres pressure to breathe

Age & Sex	% Hb CO on Admission	Condition on Admission	Time on O_2 2 Atmos.	% Hb CO after treatment	Condition of Patient after treatment
F 48	67%	Comatose	35 min.	0%	
F 49	68%	Depressed Respiration	35 "	0%	
M 47	50%		60 "	0%	
F 50	50%	Cardiac and Vasomotor Depression	30 "	0%	(1) Fully conscious
F 60	40%		30 "	0%	
F 19	+ 30%	Diminished or Absent Reflexes	60 "	0%	
F 65	+ 28%		65 "	0%	
F 62	50%	Comatose	35 "	0%	(2) Adequate Spontaneous Ventilation
F 57	41%	No Respiratory or Cardiac Depression	25 "	0%	
M 28	28%		35 "	0%	
M 59	50%		15 "	24%	
F 13	52%	Conscious But with either depressed respiration or poor pulse	30 "	0%	(3) Good Cardiac Action
F 11	-		30 "	-	
M 15	-		30 "	-	
M 8	-		30 "		
F 75	26%		15 "	5%	(4) Normal ECG. Pattern
F 19	26%		60 " +	0%	
F 70	25%	Deeply comatose Localising neurological signs	20 "	0%	Remained comatose and found subsequently to have cerebro-vascular accident

TABLE 11.

Details of a selection of patients suffering from carbon monoxide poisoning and treated with hyperbaric oxygen.

and serial samples of blood were removed for measurement of carboxyhaemoglobin. Unlike the other cases 2½ hours elapsed before the level of carboxyhaemoglobin was reduced to zero, as measured by the reversion spectroscope. At this time respiration was still deep and regular, but the pulse was strong, regular and slower. The patient now responded to painful stimuli but was still unconscious and the other neurological signs persisted. Treatment with hyperbaric oxygen was continued for a further hour and the patient was then admitted to one of the wards and oxygen given at normal pressure through a B.L.B. mask at a flow rate of 10 litre/min. When seen two hours later the patient's condition had deteriorated markedly. Systolic blood pressure was 70 mm. Hg., the pulse feeble and respiration periodic. She was rapidly returned to the pressure chamber and kept there for the next six hours by which time respiration was normal, the pulse strong and regular and the B.P. 150/90. Consciousness had not returned, but the level of consciousness was much lighter, there was a brisk, purposeful response to painful stimuli, the limbs were less rigid but the plantar responses still extensor.

The patient was once again returned to the ward where

consciousness gradually returned during the subsequent 24 hours, but she showed severe extrapyramidal damage, with tremor, rigidity and expressionless features. She was completely disorientated and speech was slow and slurred. During the succeeding 4 weeks the patient gradually improved and eventually made a full recovery. There have been no sequelae.

Case 2: A 35 year old man was admitted to another hospital following a relatively short exposure to a high concentration of carbon monoxide. He was treated by conventional methods, failed to regain consciousness following three hours of treatment and was then transferred for treatment in the pressure chamber. On admission the level of carboxyhaemoglobin was 40% and in the course of an hour no further carboxyhaemoglobin could be detected. Respiration was stertorous on admission to the pressure chamber and remained so. The pulse and blood pressure were normal. He was deeply unconscious and showed no response to painful stimuli. There was decerebrate rigidity and the plantar responses were extensor. Despite 6 hours treatment with hyperbaric oxygen the signs did not alter,

and he died three days later.

At autopsy ischaemic lesions of the globus pallidus areas of the brain were present but no other abnormalities were detected.

Case 3: A 30 year old man was admitted to the pressure chamber with a history of at least 8 hours exposure to coal gas. He was deeply unconscious with depressed respiration, feeble pulse and blood pressure of 90/68. He responded slightly to painful stimuli but not in a purposeful manner. The limbs were spastic and the plantar responses extensor. The level of carboxyhaemoglobin on admission was only 20%. Following 5 hours treatment with hyperbaric oxygen the level of consciousness was lighter but the other neurological signs were unchanged. Respiratory and cardiac function were normal.

He remained unconscious for three days and showed the neurological signs of mid-brain damage. Subsequently he regained consciousness and was able to speak sluggishly, but shortly afterwards unconsciousness again occurred and he died a week following the incident. The only autopsy finding was severe arteriolitis of the mid-brain and ischaemia of the globus pallidus.

DISCUSSION

Apart from the three cases detailed above all cases treated with hyperbaric oxygen have made a full and complete recovery. (Smith, Ledingham, Sharp, Norman and Bates, 1962). In the cases which recovered there have been no neurological or cardiac sequelae and they have been unusual in that they all claimed to feel well immediately following resuscitation. There were no complaints, in the post-resuscitation phase, of headaches, nausea or vomiting.

The three patients described in whose case resuscitation was difficult or impossible show that in some cases anoxia has persisted for too long before discovery of the patient and the institution of treatment for recovery to take place. Case 1 was border-line and it is reasonable to suppose that any form of therapy other than the rapid correction of tissue anoxia by hyperbaric oxygen would be insufficient to save life or to prevent permanent neurological damage. In Case 2 the time spent on conventional treatment may have been responsible for the persistence of a severe degree of cerebral anoxia so that neurological damage became irreversible. This view is supported by the finding of a blood-level of carboxyhaemoglobin

of 40% on admission to the pressure chamber.

In this series which contains some cases in which the patients were very ill, the half clearance times have shown a wide scatter between 20 and 40 minutes. This may be attributable to physiological factors such as poor circulation and perhaps inadequate ventilation, which in turn are the result of anoxia. A further possible factor in long exposures is the combination of carbon monoxide with other pigments than haemoglobin, such as the myglobin of muscle, so that the final mass of carbon monoxide to be excreted is increased. This is suggested by the inhibition of contractility of heart muscle exposed to a small quantity of carbon monoxide in a Burn-Dale bath and the low-voltage pattern found typically in the E.C.G. of severely gassed patients. (Smith et. al. 1962). It has also been shown that the effects are unlikely to be due to a histotoxic effect of carbon monoxide in the concentrations met clinically.

Sluijter (1963) states that the influence of the carbon monoxide that is combined outside the vascular bed on the rate of elimination of carbon monoxide is considerable. Only 60 - 70% of the carbon monoxide that disappears from the blood during the first hour of resuscitation can be traced

in the expired air. (Killick and Marchant, 1959; Roughton and Root, 1945). After the first hour the converse is the case and more carbon monoxide is found in the expired air than disappears from the blood. Since the combination of carbon monoxide outside the vascular bed is a slow process, the quantitative importance of it can be expected to correlate with the period during which carboxyhaemoglobin is present in the blood. (Sluijter, 1963).

The blood-level of carboxyhaemoglobin is of little value in prognosis - indeed one of the fatal cases had a blood-level of 20% COHb on admission. The clinical examination is likewise not particularly helpful and many of the patients who have made rapid and complete recoveries have had high levels of carboxyhaemoglobin and have been deeply unconscious on admission, with severely depressed cardiac and respiratory function. The only information which appears to be of value is the duration of gassing and this is, unfortunately, often difficult to elicit. It has frequently been observed during this study that patients exposed to a high concentration of carbon monoxide for a short period of time normally regain consciousness rapidly and completely following treatment even though the level of carboxyhaemoglobin may have been

high, whereas those exposed to a low concentration of carbon monoxide for several hours and who may have a relatively low blood-level of carboxyhaemoglobin on admission tend to eliminate the gas slowly and to remain comatose for several hours. This agrees with the experience of Sluijter (1963) and he has extended this clinical observation to an experimental situation by gassing dogs until the blood-level of carboxyhaemoglobin was 70% and then maintaining it at this level for several hours while observing the E.E.G. He found several cases where the pathological pattern of the E.E.G. did not revert to normal following the maintenance of a high blood-level of COHb for several hours.

It is obvious that there is a requirement for the minimum of delay in the institution of therapy with hyperbaric oxygen in patients suffering from severe coal-gas poisoning. Deaths in ambulances as gassed patients are being transported to hospital and the occurrence of irreversible neurological damage in those who have reached hospital alive indicate that the logical extension of therapy should include the development of a small pressure vessel, capable of being fitted into an ambulance and transported to the site of the gassing incident. (Smith, 1962). Such a chamber has been designed by

Smith and built, the Medical Division of Vickers Research Ltd. It may be seen in Figures 17 and 18. This chamber is made of perspex and is pressurised from an oxygen cylinder, so that it should be possible for ambulance teams to provide therapy with hyperbaric oxygen for severely gassed patients as soon as they are discovered and to continue it during transportation to hospital. A further advantage of the development of this small chamber is its economy. It should be possible for small hospitals or mine rescue teams to possess such a facility, thus lessening the time during which the patient is at risk from anoxia and making the best treatment more widely available.

The diagnosis of coal-gas poisoning presents some problems since it is frequently complicated by other pathology. Cases of suicidal gassing have frequently also taken large overdoses of barbiturates and many old people have been gassed following their collapse from a cerebro-vascular incident when a pot has boiled over on a gas stove and extinguished the flame. Ambulance men are frequently mistaken in believing that coal-gas poisoning is the only problem when they find collapsed patients in gas filled rooms. It is unlikely, however, that any harm would result from the emergency treatment of a

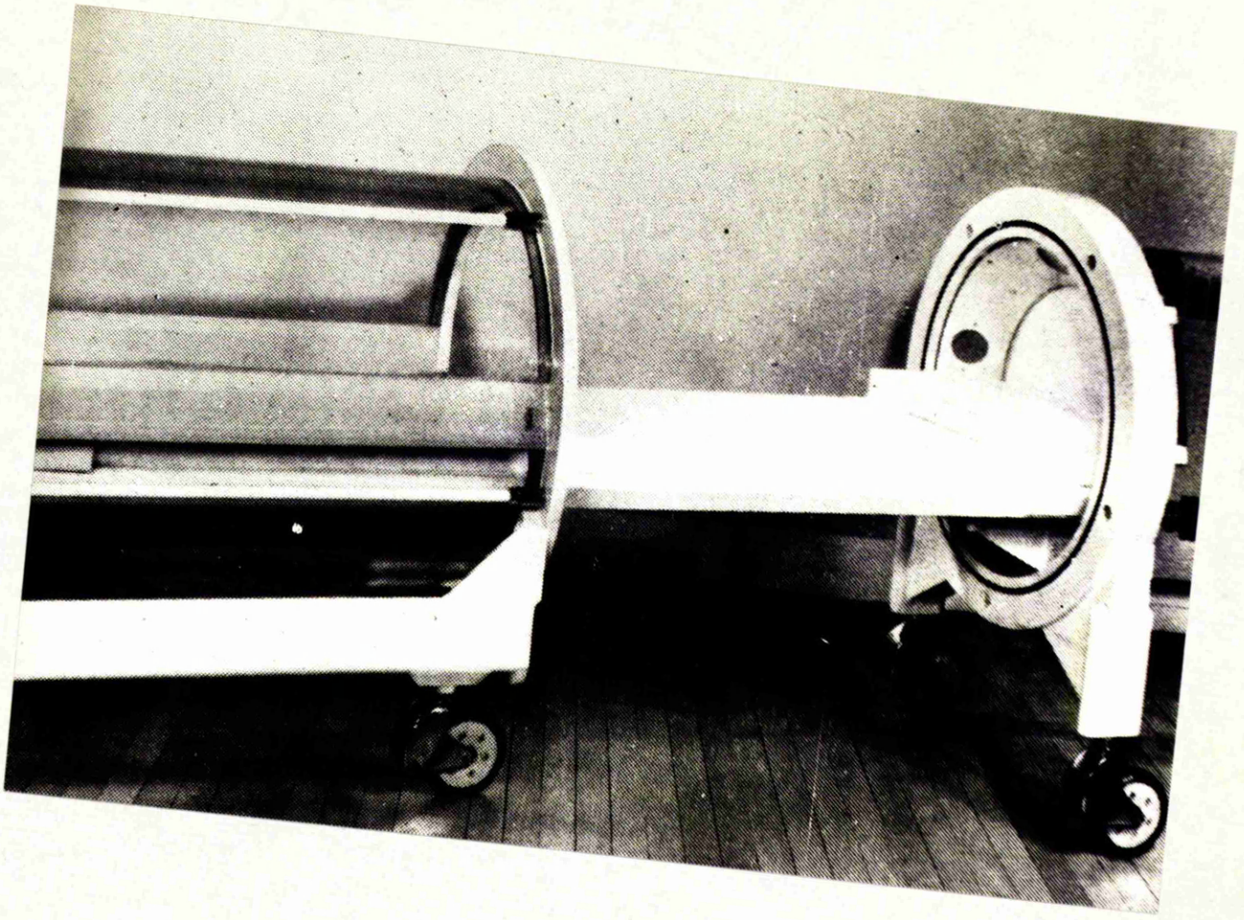

Figure 17.

Pressure vessel capable of being housed within ambulance.

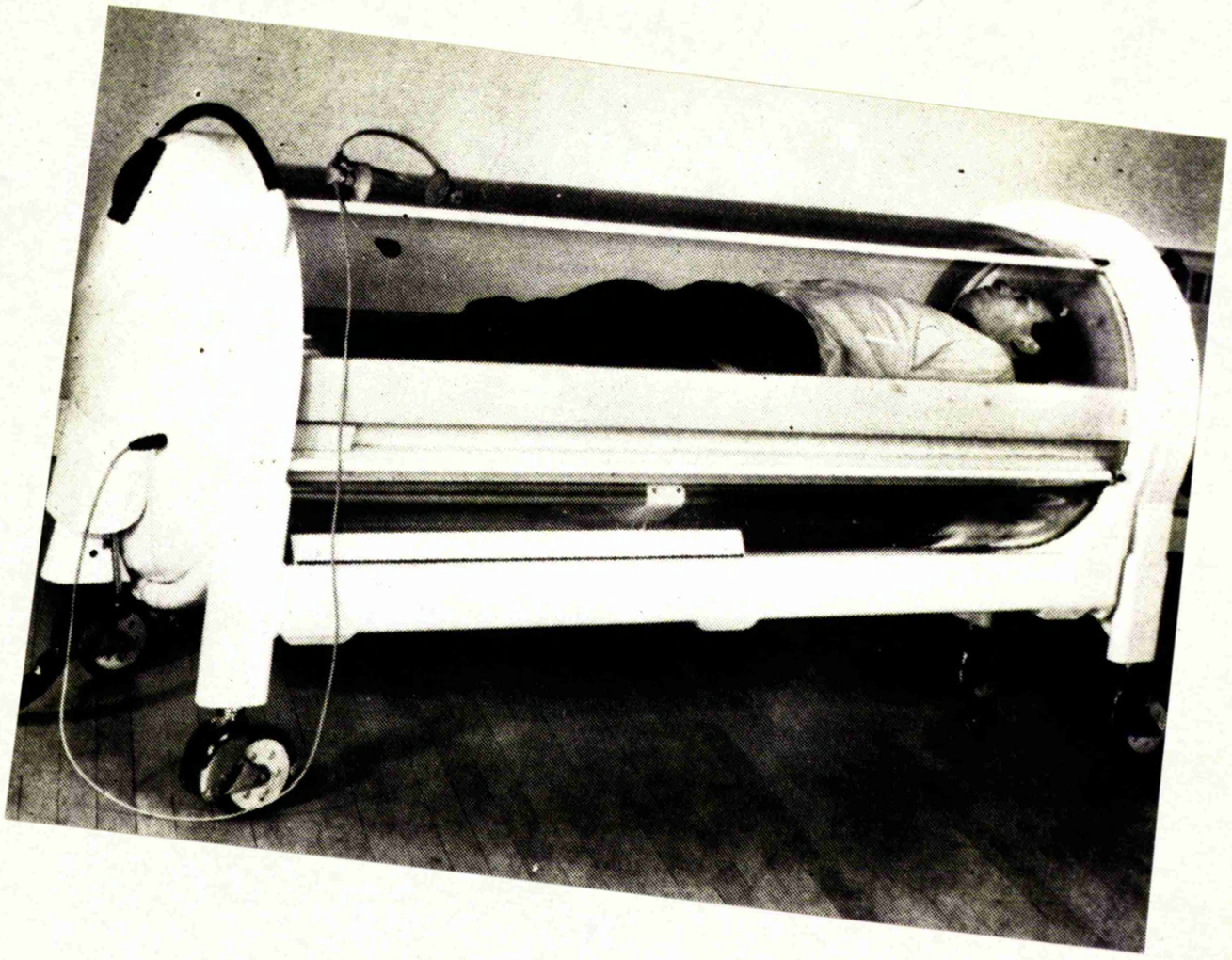

Figure 18.

Pressure vessel showing patient in place.

collapsed patient, wrongly diagnosed as suffering from coal-gas poisoning only, with hyperbaric oxygen since it has been shown that this form of therapy is beneficial in patients suffering from barbiturate overdosage (Sharp, Ledingham and Norman, 1962; Illingworth, Smith, Lawson, Ledingham, Sharp, Griffiths, 1961) and from cerebral anoxia, (Smith, Lawson, Renfrew, Ledingham and Sharp, 1961).

On the question of the most desirable pressure of oxygen to use for coal-gas poisoning Smith et. al., (1962) have shown from the data of Roughton (1945 a, b,) and Pace, Strajman and Walker (1950) that only small decreases in the time for half-clearance of carboxyhaemoglobin from the blood are to be expected by increasing the tension of oxygen above 2 - 2½ atmospheres absolute. Donald (1947a) moreover, has reported oxygen toxicity at 3.7 atmospheres in healthy, naval ratings after 6 - 96 minutes exposure, and Sluijter (1963) has encountered oxygen toxicity while treating patients for coal-gas poisoning with oxygen at 3 atmospheres pressure. This would indicate that there is no advantage to be gained from exceeding 2 atmospheres pressure and there are dangers in using higher pressures. Sluijter (1963) in fact, now uses 2 atmospheres of oxygen instead of 3, for he has noted signs

of oxygen poisoning in a few patients suffering from carbon monoxide poisoning who were exposed to oxygen at 3 atmospheres pressure for a relatively short period of time. Haldane (1927) also observed that the addition of carbon monoxide to the atmosphere when rats were breathing oxygen at 3 atmospheres pressure caused hyperventilation, convulsions and death but this did not happen if nitrogen was added instead of carbon monoxide. The presence of carbon monoxide thus appears to predispose to oxygen poisoning and there seems to be little point in exposing patients to higher pressures of oxygen than necessary. On the other hand there is no evidence that any of the patients treated in this series was harmed by the hyperbaric oxygen breathed during resuscitation. A pressure of oxygen of 2 - 2½ atmospheres absolute allows sufficient oxygen to be dissolved in the plasma that the state of the haemoglobin can be disregarded. This is adequate to correct the tissue anoxia and bring cardiorespiratory function to a more nearly normal state. The outstanding benefit of this type of therapy lies not only in the rapid removal of carbon monoxide from the blood but also in the rapid correction of tissue anoxia when the patient breathes

oxygen at 2 atmospheres pressure. Patients who have not already suffered irreversible tissue damage should not die or be further affected following the institution of treatment with hyperbaric oxygen.

About the year when Claud Bernard (1875) discovered the affinity of carbon monoxide for haemoglobin and postulated the disturbance in oxygen transport that results from it, Paul Bert (1878) published the first scientific account of the biological effects of high pressures of oxygen but it was not until nearly a century later that the investigation of those two subjects united in the treatment of coal-gas poisoning in man.

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TREATMENT OF COAL-GAS POISONING WITH OXYGEN AT 2 ATMOSPHERES PRESSURE

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EIGHTEEN months ago we described the use of oxygen at 2 atmospheres absolute pressure for the treatment of two cases of coal-gas poisoning (Smith and Sharp 1960). We report here the further use of this method during the ensuing twelve months when 32 cases were admitted *directly* to this hospital from the sector of Glasgow which it serves. 22 of these patients appeared ill enough to merit treatment in the pressure chamber. None of these 32 patients died. 1 further patient was transferred from another hospital where he had been treated for several hours and had not responded to orthodox therapy. Pressure treatment removed the carbon monoxide from his blood, but he did not regain consciousness and died three days later.

Procedure

These results have been made possible by the collaboration of the Glasgow division of the Scottish Ambulance Association. The hospital team manning the chamber has been on call 24 hours a day. When an ambulance team is dispatched to a suspected gassing incident the hospital team is alerted. On arrival at the incident the ambulance crew radios to confirm that the patient is likely to need treatment and will be brought forthwith to hospital. If the patient is conscious, oxygen is given in the ambulance. When respiration is somewhat depressed and consciousness is not complete, inhalation of 5%

FINDINGS ON ADMISSION IN 23 CASES

Clinical state	No.	HbCO(%)	
		Mean	Range
Comatose: with respiratory and cardiac depression	8	51	69–40
Comatose: no pronounced respiratory or cardiac depression	5	34	50–26
Semicomatose: with respiratory or cardiac depression	10	35	52–27

carbon dioxide in oxygen is applied if it appears clear that the patient is suffering solely from carbon-monoxide poisoning. If the patient is unconscious and respiration is much depressed or if the patient is apnœic when found, oxygen is given by a Stephenson respirator. The average time elapsing between finding the patient and his admission to hospital has been about 30 minutes.

On arrival at hospital the patient's clinical condition is rapidly appraised and a sample of venous blood is withdrawn for determination of carboxyhæmoglobin content. Pressure treatment has been used in those cases showing respiratory and/or cardiac depression with or without semicoma or coma. The numbers in the various clinical categories, together with the range and mean values for carboxyhæmoglobin level in the venous blood of each, are shown in the accompanying table.

The percent saturation of the blood with COHb was determined by Harrison's quantitative method, using a Hartridge reversion spectroscope (Harrison 1957). We have already published (Douglas et al. 1961) the results of this method compared with those obtained from two other techniques—namely, the spectrophotometric method of Heilmeyer and Krebs (Heilmeyer 1943) using the Unicam S.P. 600 spectrophotometer and the manometric method of Van Slyke and Neil (1924) as modified by Hovarth and Roughton (1942). There is good agreement between all three methods in the range 40–60% COHb. Readings above and below these levels tend to be underestimated using the reversion spectroscope when compared with the two other methods. Thus in the table the values over 60%, especially in 2 patients with 67 and 69% COHb in the peripheral venous blood on admission, are probably underestimates. Similarly those below 30–40% in the last two classes are certainly underestimates of the actual amount of COHb present. Nevertheless, for following the progress of any case inside the pressure chamber the reversion spectroscope has the advantages of rapidity and facility of use.

While in the chamber the patient, if ventilatory exchange has been adequate, has breathed oxygen delivered at 5 litres a minute through a well-fitting facepiece fitted

with a Ruben valve. Where ventilation has been deficient the oxygen has been led into a 2 litre bag and thence to the patient's facepiece, so that assisted or artificial respiration could be carried out by rhythmical compression of the bag. The chamber has been maintained at a pressure of 2 atmospheres absolute by compressed air. Thus only the patient, and not the attendants, breathes oxygen at pressure. Treatment has been stopped when no detectable COHb remained and the patient's clinical condition has improved pari passu with the disappearance of this substance. In these cases, fortunately the patients who were unconscious have all come round after 35 to 90 minutes at 2 atmospheres pressure. Since this series, however, we have had to keep a patient in the chamber for several hours; she regained consciousness only slowly, but eventually made a full recovery. In the patient who had been referred from another hospital because he was not regaining consciousness under more orthodox methods of treatment, the COHb level was only 40% on admission to the tank, and in the course of an hour no further COHb could be detected.

He did not regain consciousness and died 3 days later. At necropsy ischæmic lesions of the globus pallidus areas of the brain were present; and in the opinion of Dr. Hume Adams, neuropathologist of the university Department of Pathology, Western Infirmary, the appearances were those of the brain lesions of carbon-monoxide poisoning.

Both these patients were known to have been exposed to high concentrations of gas for many hours and apparently by intent. They illustrate what was anticipated at the start of this study—namely, that in some cases anoxia before discovery and treatment would have lasted too long for the patient to survive.

As for the patients admitted directly to this hospital for pressure treatment, the improvement has been maintained on return to the wards. There the patients' general wellbeing, in contrast to the lengthy malaise and sometimes unexpected death after apparent successful resuscitation by other methods, encourages us to continue its use. In the follow-up of these patients we have not seen any changes in the electrocardiographs which have been reported as sequelæ of carbon-monoxide poisoning, nor has there been any apparent mental deterioration.

Discussion

In 1895 J. S. Haldane showed that a mouse would remain apparently normal in a mixture of two parts of

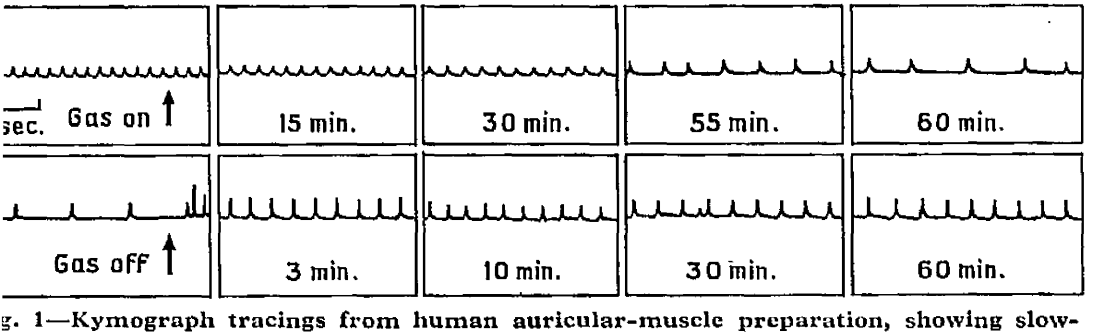
oxygen to one of carbon monoxide at a total pressure of 2 atmospheres of oxygen and 1 of carbon monoxide. He thus appeared to demonstrate that carbon monoxide had no toxic effects apart from producing anoxia by combining more readily with hæmoglobin than did oxygen. This had already been postulated by Claude Bernard as the cause of death in monoxide poisoning. While this is not the whole story, as was indicated by J. B. S. Haldane (1927), Haldane senior in the ingeniously simple mouse experiment did show that enough oxygen was dissolved in physical solution to greatly diminish or even eliminate the need for oxygen transport by hæmoglobin. Further, there is implicit in this experiment the idea of using oxygen at higher pressures than atmospheric for the treatment of carbon-monoxide poisoning. This idea seems to have lain fallow for some years. In 5 volunteers breathing carbon monoxide until the blood level was 20% saturated with carboxyhæmoglobin, Pitts and Pace (1949) showed that half-clearance levels in the blood could be attained in 19·8 minutes when oxygen was breathed at 2·5 atmospheres pressure, compared with 68·3 minutes when air was breathed at the same pressure. Prior to our report (Smith and Sharp 1960), however, the logical extension to the treatment of patients does not seem to have been made.

Work in this department has shown that, compared with methods of resuscitation involving administration of oxygen or carbogen mixtures, oxygen at pressure shortens the time to reach half-clearance from apnœa levels of COHb in the blood (Lawson et al. 1961, Douglas et al. 1962a). On the assumption that the shorter the duration of any anoxic state the better the outlook for the patient, this present method of treatment must rank higher. Further in some cases of carbon-monoxide poisoning other significant factors may be present. Thus the patient may have had a cerebral vascular accident which led to the exposure to gas, or barbiturate may have been taken. It is clear both from studies by Killick and Marchant (1959) and from our investigations (Douglas et al. 1961, 1962a and b) that there is no carbon-dioxide retention even with severe levels of monoxide poisoning. Carbogen mixtures therefore can be used with benefit. This, however, is not necessarily so in the presence of complications such as cerebrovascular accident or barbiturate intoxication, where there may be carbon-dioxide retention. In either cerebral depression from barbiturate overdose

or states of diminished cerebral blood-flow we have shown that oxygen at 2 atmospheres is beneficial (Smith et al. 1961).

By this technique anoxia is rapidly corrected, even in the presence of high levels of carboxyhæmoglobin, by the carriage of some 4 volumes % of oxygen in physical solution. This goes far towards correcting tissue anoxia and appears to speed restoration of adequate myocardial function. The effect of carbon monoxide on heart-muscle does not seem to be simply anoxic. Thus if small pieces of human left-auricular muscle obtained during the operation for mitral stenosis are put up in a Burn-Dale bath in oxygenated Ringer's solution, rhythmic contractions are maintained. These contractions are abolished by addition of small amounts of coal-gas to the oxygen going into the bath; and when this addition is discontinued, rhythmic contractions are regained (fig. 1). This suggests that carbon monoxide may either bind with the myoglobin of the heart-muscle cells or interfere with some enzyme system involved in the energy production of the cells. The K value of monoxide for myoglobin is only 17, compared with over 200 for hæmoglobin; hence the increased tension of oxygen attained by the pressurisation treatment will greatly enhance the splitting off of monoxide from the myoglobin, with improved cardiac action and output. The superiority of oxygen under pressure over other methods is also partly attributed to the fact that the speed at which monoxide is removed from the lungs depends on the volume of blood circulated through these organs. This factor is illustrated by the improvement in the state of the electrocardiograph in a patient under such treatment (fig. 2).

Lastly there is the question of the optimum increase



g. 1—Kymograph tracings from human auricular-muscle preparation, showing slowing of frequency of contraction when coal gas is added to the oxygen being bubbled into the organ bath.

The slow rate of recovery over a period of an hour is shown in the lower set of tracings.

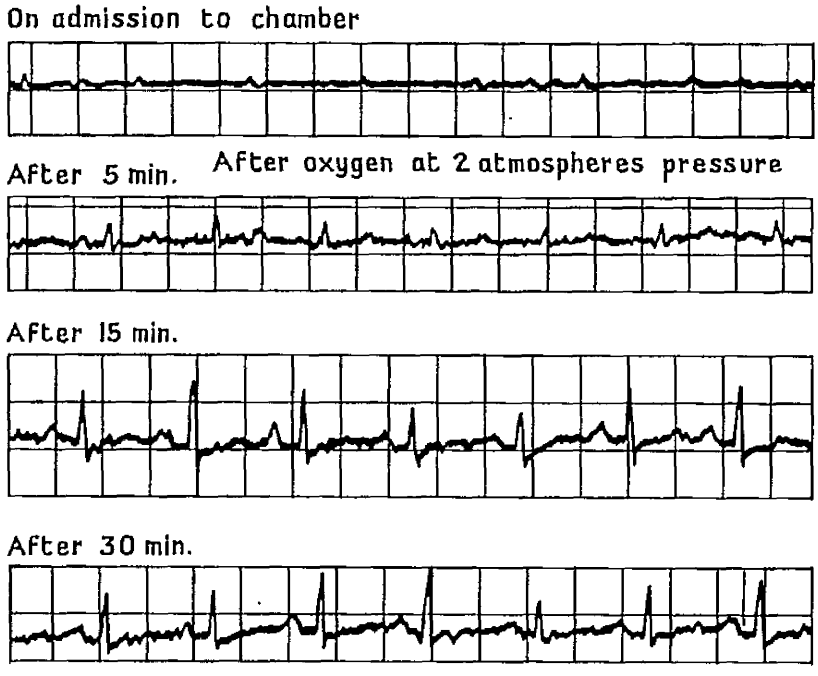


Fig. 2—Electrocardiographic tracings of a woman with severe coal-gas poisoning, breathing oxygen at 2 atmospheres absolute pressure.

Progressive improvement is evident.

in pressure. Oxygen toxicity has been reported (Donald, 1947) at 3·7 atmospheres in healthy naval ratings after 6 to 96 minutes exposure; and this level should probably not be exceeded, although such a pressure is safely used during irradiation of patients with malignant neoplasms.

From the work of Roughton (1945a) on the kinetics of the reaction $CO+O_2Hb \rightleftharpoons O_2+COHb$ in human blood at body-temperatures, the velocity constant of the reaction $CO+O_2Hb \rightarrow O_2+COHb$ was found to be about 21. If the velocity constant for the reverse reaction, $O_2+COHb \rightarrow O_2Hb+CO$ be m, and the equilibrium constant of the reaction $CO+O_2Hb \rightleftharpoons O_2+COHb$ as determined by Sendroy et al. (1929) is 210, then $m=21/210=0{\cdot}1$. The time for half-dissociation of COHb will be $ln2/0{\cdot}1=6{\cdot}9$ sec. This dissociation of COHb in the red cell is, however, only effective as far as ridding the body of carbon monoxide is concerned when the cell is in the capillary of the lung alveolus. Thus to arrive at some estimate of the minimum time needed to rid the blood of half the CO which it is carrying, it is necessary to multiply 6·9 sec. by the ratio of time which the red cell spends in the rest of the body circulation to the time which it spends in the alveolar capillary. Again from the work of Roughton

(1945b) this ratio is in the order of 1/0·01. Thus the theoretical rate of maximal elimination of CO from COHb is 690 sec. or $11^1/_2$ min.

In our observations on animals gassed to 70% COHb saturation (Douglas et al. 1962a) it was found that the time taken to reach a half-saturation of 35% COHb in mixed venous blood was a mean of 8·6±1·9 min. when the animals were breathing oxygen at 2 atmospheres absolute. This time thus approaches the maximal speed of elimination possible when the factors of the speed of chemical dissociation and transit-time of red cells through the lung capillaries are taken into account. It follows that, although theoretically the rate of chemical breakdown of COHb in the presence of oxygen can be written rate = constant x (COHb) (O_2), and if the concentration of O_2 be increased, the rate of breakdown of COHb will vary inversely as the oxygen concentration, a physiological limit is imposed by the time spent by the red cell in the rest of the body and the time spent giving up CO in the lung capillary.

To examine further the pressure which might suitably be used for patients, data from Roughton (1945b) and Pitts and Pace (1949) were plotted (fig. 3). Fig. 3 suggests that only small decreases in the time for half-clearance of COHb from the blood are to be expected by increasing the tension above $2–2^1/_2$ atmospheres absolute. These data were obtained from healthy volunteers gassed, naturally enough, to relatively low levels of COHb.

In the present series, containing as it does some cases

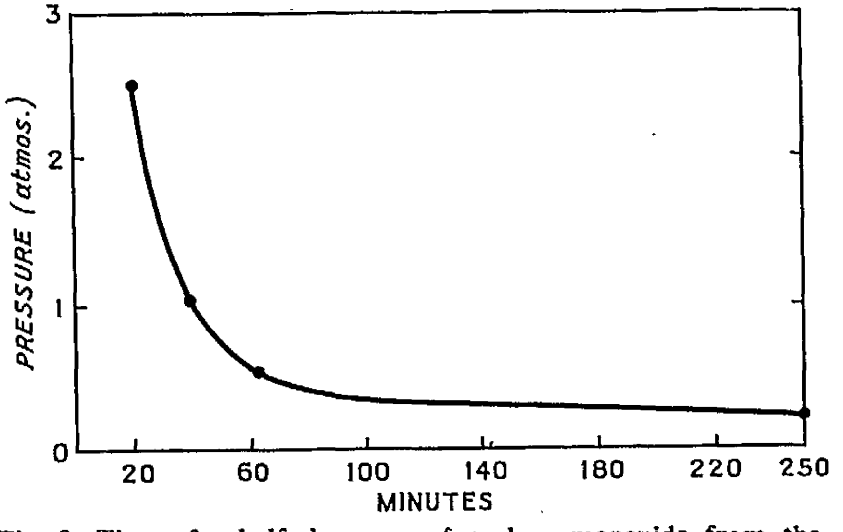


Fig. 3—Times for half-clearance of carbon monoxide from the blood of volunteers, plotted against the absolute pressure, in atmospheres, of oxygen breathed.

in which the patients were very ill, the half-clearance times have shown a much wider scatter between 20 and 30 minutes. This must be attributed mainly to physiologically important components such as poor circulation and perhaps inadequate ventilation, which in turn are the result of anoxia. Thus a pressure of 2–2$^1/_2$ atmospheres absolute, allowing enough oxygen to be dissolved in the blood independent of the state of the hæmoglobin, seems to be adequate to correct this anoxia and bring cardiorespiratory function to a more nearly normal state.

Summary

32 patients with coal-gas poisoning admitted directly to the Western Infirmary, Glasgow, during a twelve-month period all recovered completely.

22 of these, who appeared to be severely gassed, were treated in a pressure chamber where they breathed oxygen at 2 atmospheres absolute pressure.

This form of treatment rapidly corrects the anoxia and increases the speed at which carbon monoxide is removed from the blood and the tissues.

On theoretical grounds, 2–2$^1/_2$ atmospheres absolute pressure is probably the most useful range.

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THE EFFECT OF OXYGEN ON METABOLISM

Lavoisier demonstrated that the active biological component of air was oxygen and at once interest arose in the effect of various concentrations of oxygen on metabolism. Seguin and Lavoisier (1789) had concluded, however, that breathing pure oxygen did not alter any of the vital processes and they propounded the concept, with which most of the early literature agrees, that respiratory exchange is not a function of oxygen tension.

Regnault and Reiset (1849) could find no change in the oxygen consumption of the dog or the rabbit following exposure to 46 - 72% oxygen for 23 hours and Lukjanow (1884) and Wood and Cerna (1890) agreed. Fredericq (1884) found no increase in the oxygen consumption of either rabbits or himself when breathing oxygen enriched air and Loewy (1894) stated that respiratory gas exchange was independent of the oxygen content of respired air and that doubling the oxygen concentration breathed did not alter oxygen consumption.

Despite these findings, however, Bert (1878) noted an increase in oxygen consumption when 49% oxygen was breathed

compared to that found when higher or lower concentrations were used and he concluded that there was an optimum oxygen concentration for biological oxidations of about 45%. Rosenthal (1898) agreed with Bert and stated that oxygen rich mixtures caused a distinct and large increase in the uptake of oxygen and propounded the hypothesis that there may be oxygen storage in the tissues.

Most other authors of this time and later continued to oppose Bert's view, however, and Terray (1897) found no difference in oxygen consumption between 10 and 87% oxygen while Hill and McLeod (1902; 1903 a, b.) and Hill and Greenwood (1906) stated that, "Nothing conclusive can be asserted as to the influence of oxygen on the gaseous metabolism". Campbell (1927) kept rabbits in 80% oxygen for six weeks and found no difference in their oxygen consumption, while Richards and Barach (1934) found the metabolic rate of two normal men unchanged by one week's residence in 40% oxygen.

Stadie, Riggs and Haugaard (1944), however, found a 30% decrease in the oxygen consumption of canine lung slices exposed for 48 hours to one atmosphere of oxygen and Bean (1929, 1931) found a decrease in the oxygen consumption of dogs exposed to 5 atmospheres of air. These two groups

of workers thus agreed that oxygen consumption is reduced when one atmosphere of oxygen is breathed and Cruickshank and Trotter (1956) also found a decrease in the oxygen consumption of guinea pig skin on exposure to one atmosphere of oxygen for 24 hours but none on exposure to 0.5 or 0.75 atmospheres of oxygen.

Many technical criticisms can, however, be levelled against much of this work and particularly the whole animal studies performed under general anaesthesia. Oxygen consumption, for example, varies with the anaesthetic agent used and with the depth of anaesthesia (McDowall, Harper and Jacobson, 1963). In general anaesthesia, moreover, wide variations are found in the alveolar/arterial pO_2 difference due to the degree of shunting which takes place in the pulmonary vasculature (Nahas, Morgan and Wood, 1952). Variable differences in alveolar and arterial pO_2 even occur with change of position of the animal and they are due to differences in the ventilation/perfusion ratio which is dependant upon the position of the thorax (West, 1963).

Unless measurements of arterial pO_2 are made it is not possible to estimate the quantity of oxygen which is actually crossing the alveolar membrane. Since it has been shown

that blood-flow through organs varies with increasing oxygen tension (Kety and Schmidt, 1948; Lambertson, Kough, Cooper, Emmal, Loeschicks and Schmidt, 1953 a,b.; Jacobson Harper and McDowall, 1963) it would also be necessary to measure the venous pO_2 if the actual pO_2 to which the tissues were exposed was to be estimated.

In view of these factors it is not surprising that there are differing opinions regarding the effect of partial pressures of oxygen of less than one atmosphere on metabolism, particularly as the effect is not likely to be marked. The observations made on isolated tissues are, however, free from many of these criticisms and the consensus of opinion suggests that when in vitro measurements are made on tissues exposed to one atmosphere of oxygen there is a depression of oxygen consumption. There is, however, no uniformity of opinion regarding the effect of partial pressures of oxygen of less than one atmosphere.

The metabolic effects of tensions of oxygen in excess of one atmosphere cause little argument, however, and these were succintly summarised by Bert (1878):

"One finds clearly demonstrated the apparently paradoxical

result that under the influence of very high oxygenation of the blood, the tissues oxidise less, organic combustions diminish in energy, production of carbon dioxide, excretion of urine, the destruction of sugar in the blood are diminished, and that as a result the temperature falls".

Bert interpreted this inhibition of metabolism as evidence of oxygen toxicity and he was convinced that oxygen at high pressures was "toxic to every living thing." This has been the conclusion reached by others (Bean, 1929; Stadie, Riggs and Haugaard, 1944).

Dickens (1946 a) observed a marked depression in oxygen consumption of slices of rat brain exposed for 3 hours to 3 atmospheres of oxygen in a Warburg apparatus and Jacobson, Harper and McDowall (1963) noted a 40% reduction in oxygen consumption of dog brain exposed, in vivo, to 2 atmospheres of oxygen. Dickens interpreted his findings as evidence of oxygen toxicity and he stated that the time of exposure necessary to produce a given degree of poisoning was inversely proportional to the pressure of oxygen from 1 - 5 atmospheres. Restoration of normal brain metabolism did not occur when the tissue was returned to normal pressures. He also noted that the order of sensitivity to oxygen was

brain>spinal cord>liver>testis>kidney>lung. The explanation advanced by Dickens (1946 b.) to account for this phenomenon was inactivation of certain enzymes notably the pyruvate oxidase system, so that both CO_2 and lactate production are affected and both aerobic and anaerobic metabolism inhibited. Depression of lactate production when tissues are exposed to high pressures of oxygen has also been observed by Ishikawa, (1939); Bean and Haldi, (1932); Mann and Quastel, (1946) and Cruickshank and Trotter, (1956).

Pyruvate oxidase contains a thiol group and Stadie, Riggs and Haugaard (1945), Stadie and Haugaard (1945 a,b.) and Haugaard (1946) in extensive tests on the effects of oxygen at 8 atmospheres on a large range of enzymes, have clearly shown that all enzymes which contain a thiol group are inactivated by high pressures of oxygen. No enzyme which did not contain a thiol group was shown to be affected.

Cruickshanks and Trotter (1956) noted a reduction in the oxygen consumption of guinea pig skin following exposure to 1.5 atmospheres of oxygen for 24 hours and Donald (1954) noted very low consumption of oxygen in "Booted and Fin" divers, with little difference between minimal and maximal activity.

There seems little doubt that exposure to oxygen at high

pressures will result in a disturbance of metabolism if tissues are exposed to it for sufficiently long and there is evidence that the clinical and biochemical effects appear in a progressively shorter period of time as the pressure of oxygen is raised. Dickens (1946a) did not observe a marked fall in the oxygen consumption of his brain slices until the third hour of their exposure to 3 atmospheres of oxygen, and clinical effects of oxygen poisoning have also been observed following 3 - 4 hours exposure to 3 atmospheres of oxygen (Sluijter, 1963). Clinical effects have also been observed in a much shorter time at high pressures (Donald, 1947 a,b; Haldane, 1941, Behnke, Johnson, Poppen and Motley, 1935) and Thomas, Neptune and Sudduth (1963) observed a depression of oxygen consumption in rat brain homogenates within 10 minutes of exposure to 5 atmospheres of oxygen.

In view of the growing interest in the therapeutic uses of hyperbaric oxygen it seemed desirable to study the effects on metabolism of oxygen at various tensions. The succeeding section deals with the effect of oxygen at tensions up to 1520 mm. Hg. on the oxygen consumption of homogenates of rat liver and its metabolism of succinic acid;

it also deals with the combined effects of hypothermia and oxygen at various pressures.

THE EFFECT OF HYPERBARIC OXYGEN ON THE METABOLISM OF TISSUE AT NORMAL AND REDUCED TEMPERATURES

Hyperbaric oxygen alone (Bernhard and Tank, 1963) and in conjunction with hypothermia (Boerema, Knoll, Meijne, Lokin, Kroon and Huiskes 1956; Smith Ledingham, Norman, Douglas, Bates and Lee, 1963; Barclay Ledingham and Norman 1964) has been used to prolong the safe period of total circulatory arrest as an aid to cardiac surgery. It has been shown that high pressures of oxygen reduce the oxygen consumption of tissues following long exposures at normal temperatures (Dickens, 1946 a; Cruickshanks and Trotter, 1956). Little is known, however, of the effects of oxygen at two atmospheres pressure on tissues exposed to it for the relatively short periods of time required for heart surgery. Moreover, nothing has been reported of the effects on tissue metabolism of hyperbaric oxygen in combination with hypothermia.

This study was designed to assess the effect on oxygen

consumption of pressures of oxygen up to 2 atmospheres absolute and measurements of this have been made, over a 2 hour period, at 37° C, 28° C and 15° C.

METHODS

Homogenates of rat liver in Krebs ringer phosphate solution were prepared and 2.5 ml. placed in each of 12 Warburg respirometer flasks. 0.2 ml. 10% KOH was added to the centre well along with 1 sq. cm. of filter paper designed to increase the surface area available for carbon dioxide absorption. 0.5 ml. 0.05 M. succinic acid was placed in the side-arm of six of the flasks while 0.5 ml. Krebs ringer phosphate solution was added to the remaining six side-arms.

The 12 flasks were divided into two groups of six so that the side-arms of 3 flasks in each group contained succinate while the other 3 contained Krebs ringer phosphate solution. One group of flasks was then placed in one Warburg apparatus, maintained constantly at 37° C, and the results obtained used as control values for the other group of flasks which was placed in a second Warburg

apparatus in which the conditions varied with the experiment.

In the first group of experiments the gas phase was air at a pressure of 1 or 2 atmospheres absolute and in the second group it was oxygen at a pressure of 1 or 2 atmospheres. Twice atmospheric pressure was obtained by placing one of the Warburg apparatuses in the pressure chamber (Plate 1) and allowing 15 minutes for the gas to equilibrate with the fluid phase before commencing the experiment. The control measurements were made in the laboratory and the observer inside the pressure chamber communicated with the observer in the laboratory by telephone so that identical time relationships were observed. The homogenates were thus exposed to four different oxygen tensions, namely, air at 1 atmosphere pressure (PO_2 = 150 mm. Hg.), air at 2 atmospheres pressure (PO_2 = 300 mm. Hg.), oxygen at 1 atmosphere pressure (PO_2 = 760 mm. Hg.) and oxygen at 2 atmospheres pressure (PO_2 = 1520 mm. Hg.).

In the first group of experiments all the control measurements, in the first Warburg apparatus, were made on tissue exposed to 37° C and 1 atmosphere of air and this was compared with the oxygen consumption of the tissue, in the second Warburg apparatus, submitted to the following

conditions:

(1) air at 1 atmosphere pressure; temp. 28° C.
(2) " " 1 " " ; temp. 15° C.
(3) " " 2 " " ; temp. 37° C.
(4) " " 2 " " ; temp. 28° C.
(5) " " 2 " " ; temp. 15° C.

In the second group of experiments all the control measurements were made on tissue exposed to oxygen at 1 atmosphere pressure at 37° C and this was compared with the following:

(1) oxygen at 1 atmosphere pressure; temp. 28° C.
(2) " " 1 " " ; temp. 15° C.
(3) " " 2 " " ; temp. 37° C.
(4) " " 2 " " ; temp. 28° C.
(5) " " 2 " " ; temp. 15° C.

Endogenous metabolism was followed in all flasks for 30 minutes and the contents of the side-arms was then added to the flask and the oxygen consumption was followed for the next 90 minutes, measurements being made at 10 minute intervals. The oxygen consumption of the rat liver

homogenates was thus measured for a total period of two hours.

A sample of each homogenate was analysed for nitrogen content by the micro-Kjeldahl technique (Prunty, McSwiney and Hawkins, 1959) and the results were finally expressed in terms of micro-litres of oxygen consumed per mg. nitrogen in the homogenate.

Each of the experiments was repeated at least six times and thus for each combination of oxygen tension and temperature the endogenous oxygen consumption has been observed in 18 flasks containing liver from six different rats and the rate of metabolism of succinate has also been studied on each occasion from the same number of experiments.

RESULTS

Figure 19 shows the oxygen consumption of rat liver homogenate at 37° C. when exposed to air at one atmosphere pressure (pO_2 = 150 mm. Hg.) air at two atmospheres pressure (pO_2 = 300 mm. Hg.) oxygen at one atmosphere pressure (pO_2 = 760 mm. Hg.) and oxygen at two atmospheres pressure (pO_2 = 1520 mm. Hg.). The measurements have been made at ten minute intervals for a total period of two hours. It can be seen that the consumption of oxygen decreases as the tension of oxygen, to which the tissue is exposed, rises. Each of these curves is determined from the means of the six experiments performed at each pressure level and there is a highly significant difference between each curve at the two hour point. ($P > 0.05$ between air at one and two atmospheres pressure and $P > 0.001$ between oxygen at one and two atmospheres pressure).

Figures 20 and 21 show the oxygen consumption of rat liver homogenates at 28° C. and 15° C. plotted in the same manner as the results obtained at 37° C. At 28° C. (Figure 20) there is no difference between the

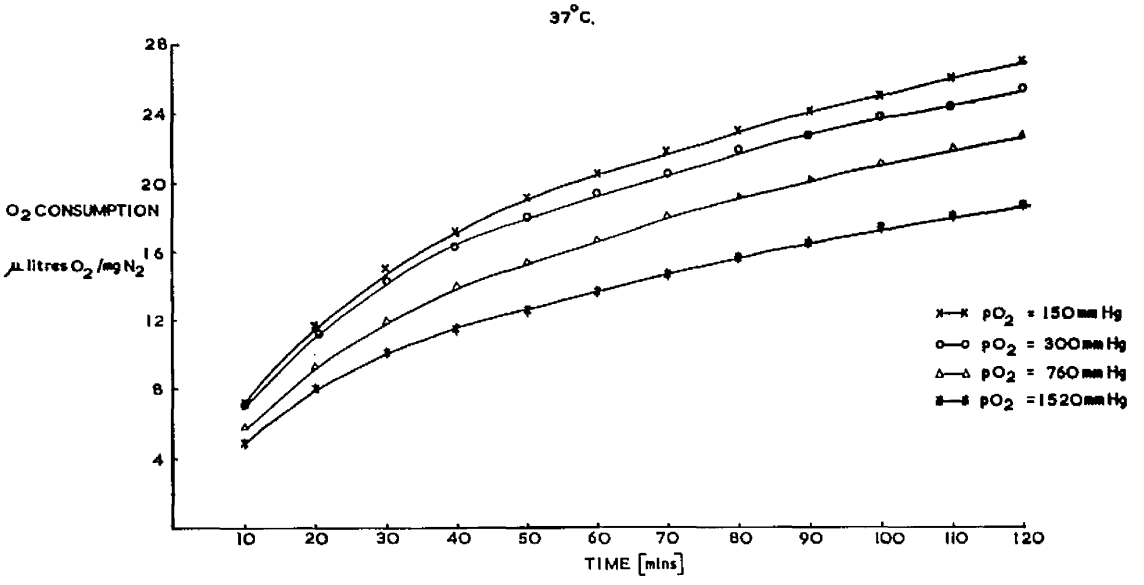


Figure 19.

Oxygen consumption of rat liver homogenates at 37° C. when exposed to various tensions of oxygen.

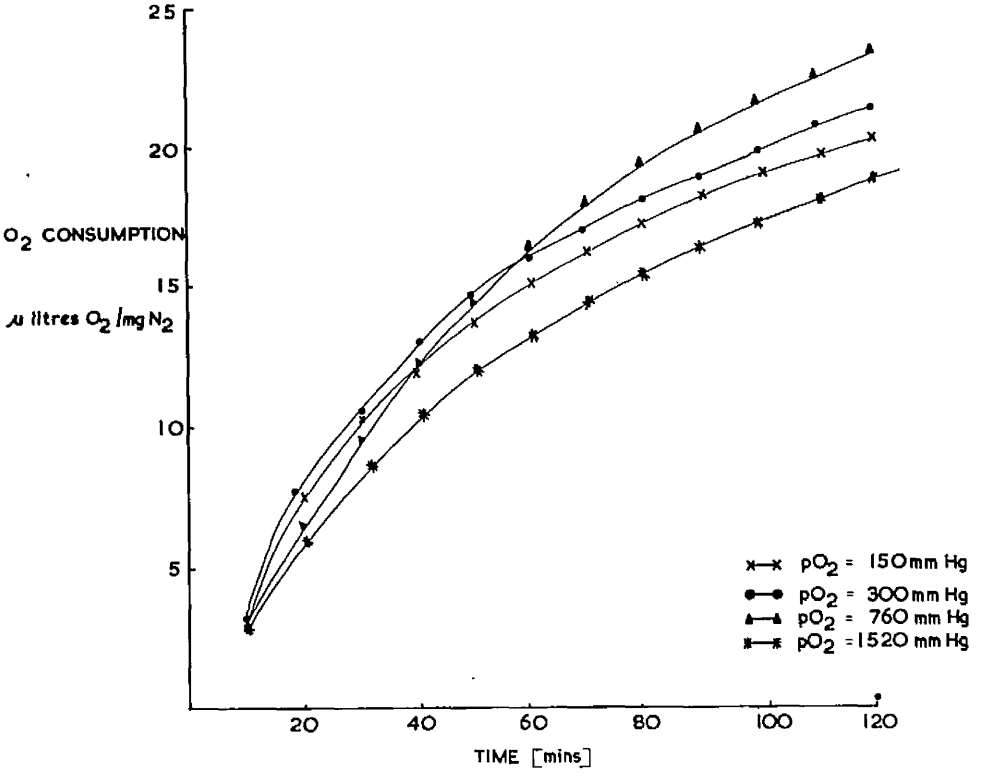


Figure 20.

Oxygen consumption of rat liver homogenates at 28° C. when exposed to various tensions of oxygen.

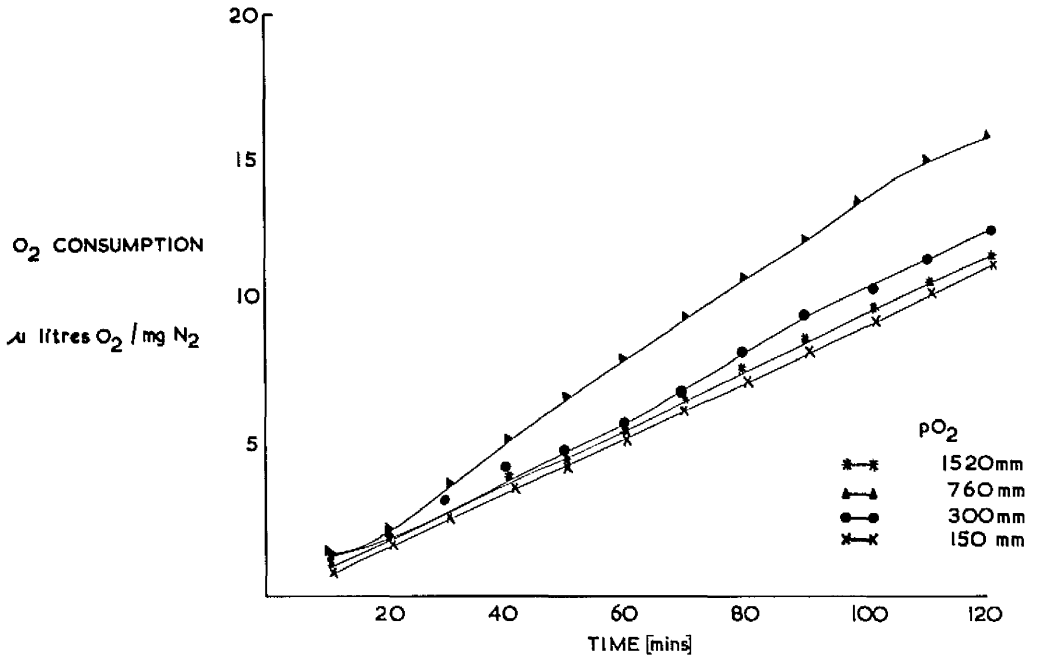


Figure 21.

Oxygen consumption of rat liver homogenates at 15° C. when exposed to various tensions of oxygen.

oxygen consumption of tissue exposed to a pO_2 of 300 mm. Hg. or 760 mm. Hg. but it is significantly less than that exposed to a pO_2 of 150 mm. Hg. ($P > 0.05$) and greater than that exposed to a pO_2 of 1520 mm. Hg. ($P > 0.001$). At 15° C. there is no significant difference between the oxygen consumption of the tissue when the pO_2 is 150 mm. Hg. or 1520 mm. Hg. but the consumption of oxygen is increased when the pO_2 to which the tissue is exposed is 300 mm. Hg. and still further increased when it is 760 mm. Hg.

Figure 22 shows the results obtained at 37° C. over the two hour period, plotted in a different manner. In this case the oxygen consumption found when the tissue was exposed to a pO_2 of 150 mm. Hg. is arbriterily taken at 100% and the oxygen consumption found when the tissue was exposed to the other oxygen pressures considered is expressed as a percentage of the value found when the pO_2 was 150 mm. Hg. In this case it can be seen again that the consumption of oxygen falls as the pressure of oxygen to which the tissue is exposed rises. When the pO_2 is raised from 150 mm. Hg. to 760 mm. Hg. the consumption of oxygen is reduced by 14%

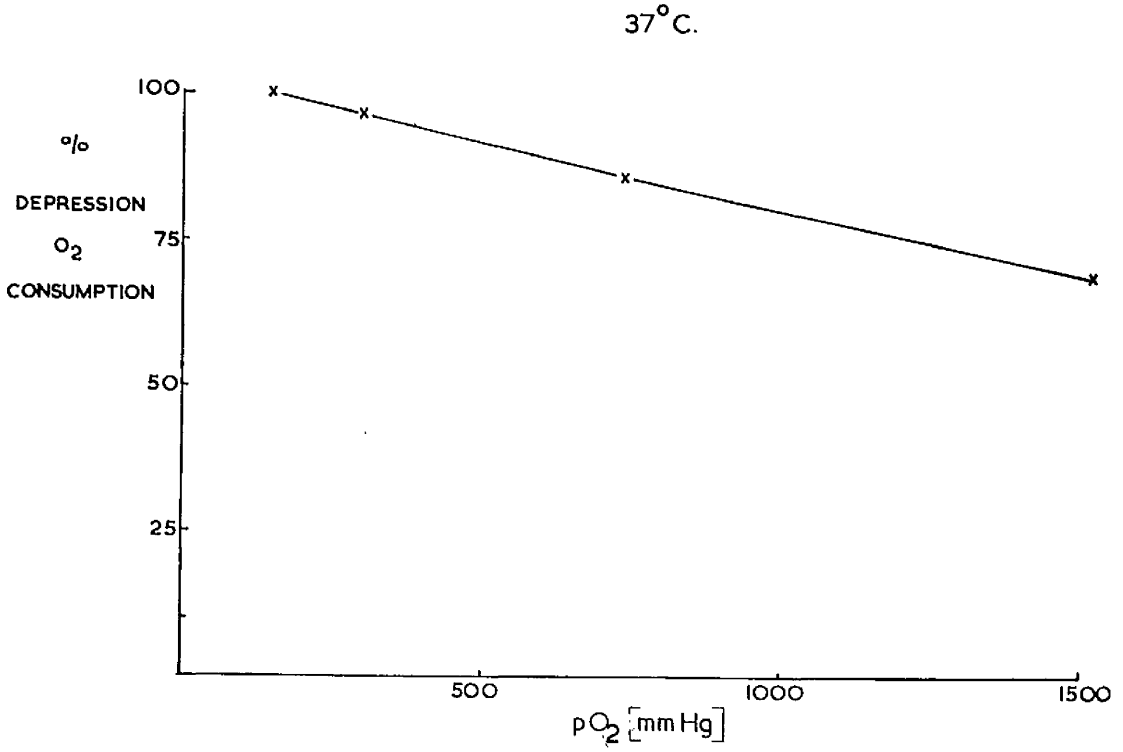


Figure 22.

Percentage change in oxygen consumption of rat liver homogenates as the tension of oxygen to which the tissue is exposed rises. The measurements were made at 37° C. during a period of 2 hours.

and when the pO_2 is raised from 150 mm. Hg. to 1520 mm. Hg. the oxygen consumption is reduced by 32%.

In Figure 23 can be seen the results of the observations made at 28° C. set out in the same manner as the results from the experiments conducted at 37° C. shown in Figure 22. In this case there is an initial rise in oxygen consumption when the pO_2 is raised from 150 mm. Hg. to 300 mm. Hg. which is maintained when the pO_2 is raised to 760 mm. Hg. but there is a fall in oxygen consumption when the pO_2 is raised to 1520 mm. Hg. The overall depression in oxygen consumption between a pO_2 of 150 mm. Hg. and 1520 mm. Hg. is 10%.

The results of the observations made at 15° C. can be seen in Figure 24. In this case there is also a rise in oxygen consumption when the pO_2 is raised from 150 mm. Hg. to 300 mm. Hg. and a further rise when the pO_2 is increased from 300 mm. Hg. to 760 mm. Hg. There is a final fall, however, when the pO_2 is increased from 760 mm. Hg. to 1520 mm. Hg. Oxygen consumption between a pO_2 of 150 mm. Hg. and 1520 mm. Hg. is increased by 1% at this temperature level.

Extrapolation of these curves suggest that oxygen

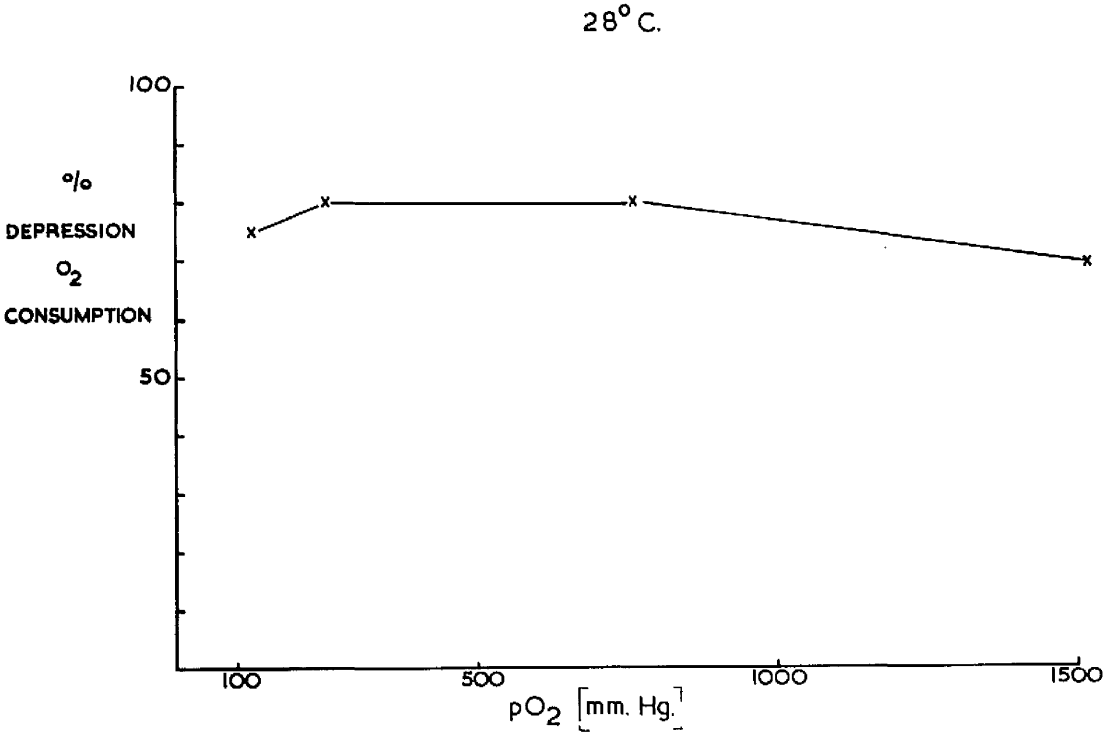


Figure 23.

Percentage change in oxygen consumption of rat liver homogenates as the tension of oxygen to which the tissue is exposed rises. The measurements were made at 28° C. during a period of 2 hours.

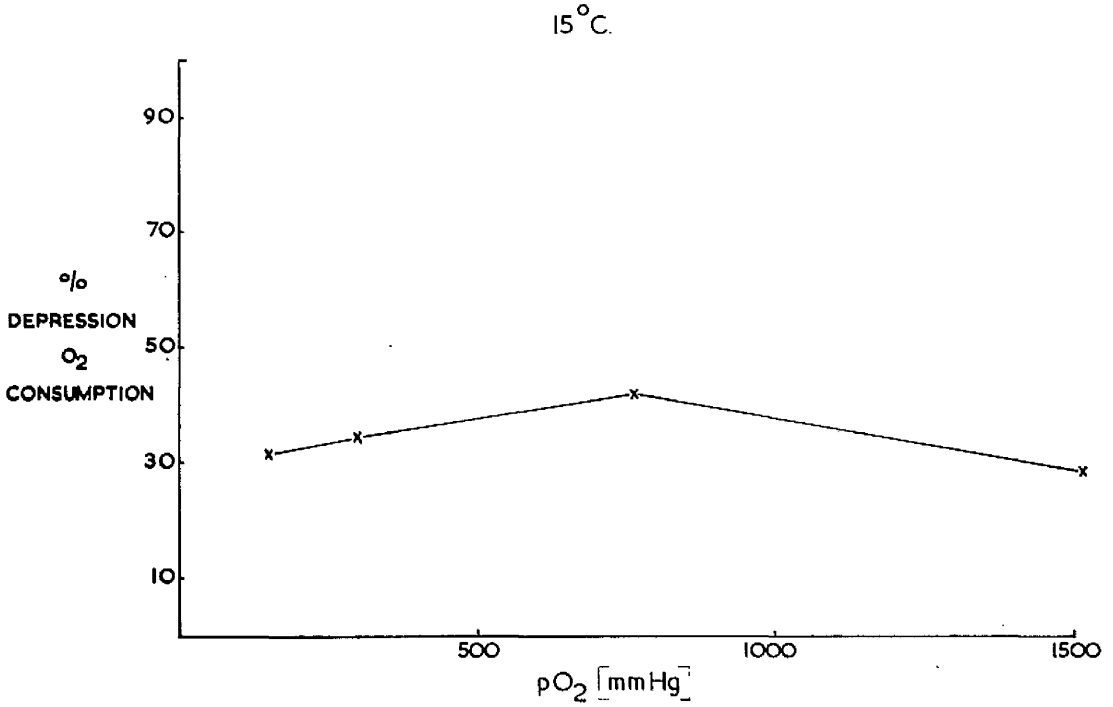


Figure 24.

Percentage change in oxygen consumption of rat liver homogenates as the tension of oxygen to which the tissue is exposed rises. The measurements were made at 15° C. during a period of 2 hours.

Oxygen Pressure (mm. Hg.)

Temp. °C.	150	300	760	1520
37	12.1	11.7	11.1	13.0
28	16.7	14.8	16.1	17.0
15	24.0	23.7	22.2	26.3

TABLE 12.

Average time (in minutes) taken to metabolise a standard quantity of succinate by rat liver homogenate exposed to a variety of temperatures and pressures.

consumption reaches a peak, at 28° C., when the pO_2 is in the region of 500 mm. Hg. and at 15° C. when the pO_2 is in the region of 1000 mm. Hg.

Table 12 shows the time taken at each combination of temperature and pressure to metabolise a standard quantity of succinate. In general the results mirror the changes noted in endogenous metabolism but they are less well defined.

DISCUSSION

The depression of oxygen consumption observed by Dickens (1946a) on exposure of rat brain slices to three atmospheres of oxygen and by Cruickshanks and Trotter (1956) in guinea pig skin subjected to 1.5 atmospheres of oxygen has also been found in homogenates of rat liver exposed to partial pressures of oxygen up to two atmospheres absolute. Jacobson, Harper and McDowall (1963) have shown that the oxygen consumption of canine brain in vivo is reduced by 40% when the animal breathes oxygen at twice atmospheric pressure and Dickens (1946 a) has shown that the order of tissue sensitivity to hyperbaric oxygen is brain $>$ spinal cord $>$ liver. The reduction of 34% in the oxygen consumption found in rat liver homogenates exposed to two atmospheres of oxygen is thus not at variance with the existing data.

It can be seen from Figure 19 that the reduction in oxygen consumption is most marked when the pO_2 is raised from one to two atmospheres pressure, but there is nevertheless a significant reduction in oxygen

consumption when the pO_2 is raised from 150 mm. Hg. to 300 mm. Hg. and also to 760 mm. Hg. The relatively small magnitude of this effect at pressures of oxygen less than one atmosphere may have been responsible for the failure to recognise this change in the past. Cruickshanks and Trotter (1956) nevertheless noted a depression in the oxygen consumption of guinea pig skin when the pO_2 was raised from 0.75 to 1 atmosphere.

Jacobson, Harper and McDowall (1963) noted a 12% reduction in canine cerebral blood flow when the animal breathed oxygen at one atmosphere pressure and a 21% reduction when it breathed oxygen at two atmospheres pressure. They postulated that the cerebral vasoconstriction observed and the relatively small increments of venous pO_2 found were evidence of a homeostatic mechanism "to maintain tissue oxygen levels within fairly close limits, and thus to mitigate against the possible deleterious effects of hyperbaric oxygen on the central nervous system". It appears that exposure of tissues to pressures of oxygen higher than those to which they are

normally exposed, viz. 1/5 atmosphere, results in an alteration in their metabolism, which becomes more marked the higher the oxygen tension is raised. This phenomenon is part of the syndrome of oxygen poisoning.

The addition of hypothermia to the system modifies the tissue response to increase in oxygen tension in that the oxygen consumption increases until the pO_2 exceeds about 500 mm. Hg. at 28° C. and about 1000 mm. Hg. at 15° C. This finding is in accord with the observation of Grossman and Penrod (1949) and Campbell (1937) that hypothermia prolongs the period during which rats can be exposed to high pressures of oxygen before signs of oxygen poisoning occur.

The stimulation of oxygen consumption at hypothermia in response to moderate increase in oxygen tension suggests that the reduction in oxygen consumption brought about by hypothermia is due not only to a reduction in the requirement of oxygen by the tissues but also in a progressive inability of the tissues to utilise oxygen at low temperatures. Thus a high tension of

oxygen may be necessary to ensure adequate oxygenation at low tissue temperatures but when the oxygen tension is raised above the optimum pO_2 for the temperature under consideration then oxygen consumption falls as oxygen poisoning supervenes. Norman, Douglas, Smith and Henderson (1963) showed that after human cardiac muscle had been maintained at reduced temperatures for two hours there was an increase in the oxygen consumption of the rewarmed tissue compared to that which had been maintained at 37° C. throughout. It is possible that this could have been due to the formation of an oxygen debt when the tissue was at low temperature. The development of metabolic acidosis commonly observed during rewarming following hypothermia (Bunker, 1962) may also be due to increased demands by the tissues for oxygen, at this time, in addition to the circulatory changes caused by the induction of hypothermia.

These results indicate that preliminary saturation of the tissues, at normothermia, with oxygen at high pressure should make it possible to prolong the period

of time during which the circulation can be arrested with safety, both by increasing the amount of oxygen available and also by reducing the tissue's requirement for oxygen.

At hypothermia it may be necessary to deliver oxygen to the tissues at high pressures if adequate oxygenation is to be ensured. Since there is an initial increase in oxygen consumption at 28° C. as the tension of oxygen is raised, and a greater increase at 15°C. it may be necessary to raise the tension of oxygen progressively higher as the temperature is reduced if the same relative increase in the safe duration of total circulatory arrest is to be obtained at different temperatures. Thus by a skilful choice of oxygen tension and tissue temperature it should be possible to ensure both adequate oxygenation of the hypothermic tissues and also considerable periods of "safe" circulatory arrest.

Hyperbaric Oxygen in Experimental Circulatory Arrest in Dogs.

The use of hyperbaric oxygen to extend the period during which the circulation may be arrested with safety, as an aid to open heart surgery, was suggested by Boerema, Kroll, Meyne, Lokin, Kroon and Huiskes (1956, 1957) and by Smith, Ledingham, Norman, Douglas, Bates and Lee (1961, 1963). It was postulated that the additional oxygen dissolved in the plasma, when hyperbaric oxygen is breathed, would act as an oxygen store which would provide the tissues with sufficient oxygen to cover an extended duration of total circulatory arrest with safety. Smith et. al. (1961, 1963) and Meijne, Vermeulen-Cranch, Sluijter, Eloff, Schripsema, Deen, Schoemaker and Boerema (1962) also suggested that considerable advantage might accrue from combining hyperbaric oxygen with hypothermia since oxygen requirements would be reduced by hypothermia and an increased amount of oxygen would also be supplied. It was hoped that these measures would result in providing a sufficiently prolonged period of suspended circulation to allow open heart surgery to be performed,

in infants, without the use of cardio-pulmonary by-pass techniques.

EXPERIMENTAL METHODS.

Adult mongrel dogs weighing between 14 and 25 Kg. were anaesthetised with minimal doses of sodium thiopentone to allow the insertion of a cuffed Magill endotracheal tube and respired with oxygen by means of a positive pressure respirator. These dogs were divided into three groups, one of which was maintained at normothermia. The second group was cooled to 28° C. and the third to 20° C. Cooling was accomplished with the aid of dry ice or a mixture of ice and water applied to the surface according to the method described by Ledingham and Norman (1963, 1964). In each group, the dogs which acted as controls were given oxygen at one atmosphere pressure to breathe while the others were given oxygen at two atmospheres pressure to breathe.

When the dog had reached the required temperature a right thoracotomy was performed through the bed of the fifth rib and slings placed around the inflow tracts of the heart. The circulation was then arrested for a pre-determined period of time and was then restored using

vasopressor drugs, cardiac massage and electrical defibrillation where indicated. The experiments were conducted under strict acid-base control according to the methods of Ledingham and Norman (1962) and Norman and Ledingham (1964). Following cardiac resuscitation the chest was formally closed and the animal rewarmed and allowed to recover.

The criterion of recovery was based upon the condition of the animal 24 hours after the procedure. If an animal showed any neurological defect 24 hours following the procedure, then the duration of circulatory arrest which had been practised was considered to be beyond the limit of safety.

RESULTS.

The results obtained are shown in tables 13 - 15. It can be seen that at normothermia it was possible to arrest the circulation for five minutes with safety when the dogs breathed oxygen at one atmosphere pressure and for eight minutes when the animals breathed oxygen at two atmospheres pressure. Further increase in the duration of circulatory arrest beyond this time led to the occurrence of neurological sequelae.

At 28° C. the permissable duration of total circulatory arrest was increased from 20 minutes to 30 minutes when the dogs breathed oxygen at two atmospheres pressure instead of one atmosphere, but at 20° C. it was possible to arrest the circulation for 40 minutes with safety when the animal breathed oxygen at one atmosphere pressure and for no longer than this when the animals breathed oxygen at two atmospheres pressure.

CIRCULATORY ARREST AT 37° C.

Dogs No.	Duration of Circulatory Arrest (Min)	Pressure O_2 Breathed Atmos.	Survivors No.	Deaths No.	Condition 24 hrs. later.
1	3	1	1	0	Normal
2	4	1	2	0	Normal
5	5	1	5	0	Normal
2	6	1	2	0	1 Spastic 1 Normal
2	7	1	2	0	1 Spastic & blind 1 Normal
1	6	2	1	0	Normal
2	7	2	2	0	Normal
5	8	2	5	0	Normal
2	9	2	2	0	1 Normal:1 blind

TABLE 13.

Survival and post-operative condition of dogs subjected to total circulatory arrest at 37° C. for various periods of time while breathing oxygen at one or two atmospheres pressure.

CIRCULATORY ARREST AT 28° C.

Dogs No.	Duration of Circulatory Arrest (Min)	Pressure O_2 Breathed Atmos.	Survivors No.	Deaths No.	Condition 24 hrs. Later.
2	12	1	2	0	Normal
3	15	1	3	0	Normal
5	20	1	5	0	Normal
3	25	1	2	1	1 Normal 1 Atoxic & blind
1	20	2	1	0	Normal
3	25	2	3	0	Normal
5	30	2	5	0	Normal
5	35	2	3	2	1 Spastic 1 Normal
5	40	2	1	4	1 Normal

TABLE 11.

Survival and post-operative condition of dogs subjected to total circulatory arrest at 23° C. for various periods of time while breathing oxygen at one or two atmospheres pressure.

CIRCULATORY ARREST AT 20° C.

Dogs No.	Duration of Circulatory Arrest (Min)	Pressure O_2 Breathed Atmos.	Survivors No.	Deaths No.	Condition 24 hrs. Later.
2	30	1	2	0	Normal
2	35	1	2	0	Normal
8	40	1	8	0	Normal
2	45	1	0	2	-
2	30	2	2	0	Normal
2	35	2	2	0	Normal
8	40	2	8	0	Normal
3	45	2	1	2	Normal

TABLE 15

Survival and post-operative condition of dogs subjected to total circulatory arrest at 20° C. for various periods of time while breathing oxygen at one or two atmospheres pressure.

DISCUSSION.

It has been shown, in the preceding section, that the oxygen consumption of tissue maintained at 37° C. falls as the tension of oxygen to which it is exposed rises. It seems unlikely that the extra 2 - 3 vols.% oxygen carried in the plasma when the animal breathed two atmospheres of oxygen instead of one would be sufficient to account for considerable increase in the time during which the circulation could be arrested with safety. It seems reasonable to conclude that the increase in time is due partly to the extra oxygen carried in solution and also to the depression in oxygen consumption brought about by the metabolic response of the tissues to hyperbaric oxygen.

It is not possible to relate closely, the results of these whole animal experiments to the in vitro measurements shown in the previous section since nothing is known of the absolute values of tissue pO_2 in these dogs nor is it possible to estimate the gradients of tissue pO_2 which would result from changing the inspired

gas from oxygen at one atmosphere pressure to oxygen at two atmospheres pressure, in view of the alterations brought about in the cerebral, pulmonary, renal and portal circulations by altering the inspired tensions of oxygen (Jacobson, et. al. 1963, Bain, 1963, Bloor et al. 1963). As the temperature is reduced, however, the absolute duration of safe circulatory arrest is lengthened but the relative increase in time obtained when the animal breathes two atmospheres of oxygen instead of one decreases as the temperature falls. These findings are not at variance with the results of the in vitro studies, however, since the permissable duration of total circulatory arrest at hypothermia, when the animal has been exposed to oxygen at two atmospheres pressure is less than expected by considering the duration of circulatory arrest obtained at normothermia by pre-oxygenation with oxygen at two atmospheres pressure.

It is possible that the permissable duration of circulatory arrest at hypothermia could be greatly increased, with safety, by increasing the pressure of oxygen to, say, three atmospheres absolute at 28° C.

and to about four atmospheres absolute at 20° C. Considerable increase in oxygen pressure at normothermia would, of course, be limited by oxygen poisoning and the logical extension of this study is the investigation of the role of higher pressures of oxygen at low temperatures.

OXYGEN TOXICITY

In 1884 Paul Bert was the president of the Societe de Biologie de Paris and this may have been the reason for the considerable interest shown in the biological effects of high atmospheric pressures by the French scientists of that year. Regnard (1884 a,c.) investigated the effects of pressures of 100 - 600 atmospheres on numerous micro-organisms and found that some died and some were unaffected while others went into a state which he termed "vie latente". Presumably these high pressures were obtained by means of water and, when Regnard (1884,b) observed that muscles became rigid when subjected to 600 - 1000 atmospheres pressure, he suggested that the toxic effect might be related to water forcing itself between the cells and he concluded that "L'eau en effet est un poison des tissus: elle tue les cils vibratiles, les spermatozoides, la fibre musculaire et la cellule nerveuse". Two other discoveries of note were made during this year; Quinquand (1884) showed that exposure of an animal to 1 atmosphere of pure oxygen raised the arterial oxygen content by 2.2 vols. per cent and, more important to the economy

of France, Certes and Cochin (1884) observed that at 300 - 400 atmospheres pressure alcoholic fermentation always produced 'un bout d'un certain temps'.

It was Bert (1878), however, who first pointed out that the toxic substance in high pressures of air was oxygen itself. The other constituents of air have each been shown to cause effects at elevated pressures and these, together with the mechanical effects of change of pressure alone, have been summarised by J.B.S. Haldane (1941). High atmospheric pressure imparts a nasal twang to the voice and whistling becomes impossible at 3 atmospheres pressure while, at a pressure of 10 atmospheres, the air becomes thick and resists stirring. Violent earache occurs during rapid compression if the subject is not trained but rapid decompression is more dangerous since breath holding or bronchial obstruction from any cause may result in such a rise of intra-pulmonary pressure that air embolism into the pulmonary circulation occurs, (Liebow, Stark, Vogel and Schaefer, 1959). This latter event was the cause of death in early escapes from submarines, (Case and Haldane, 1941). Trained subjects have, nevertheless, been compressed to 7 atmospheres in 90 seconds by Haldane (1941) without apparent

discomfort and he states that he has compressed 4 workmen to 10 atmospheres in 5 minutes. Behnke, Thomson and Motley (1935) have shown that nitrogen is narcotic at high pressures: it causes mental changes, a decrease in normal skill and intellectual ability and finally, narcosis. Poulton, Carpenter and Cotton (1963) have also reported slight intellectual deterioration at pressures of only two to three atmospheres. The effects of high pressures of nitrogen are two-fold, however, and its behaviour during decompression is more dangerous than its narcotic effect. Rapid and uncontrolled decompression causes nitrogen to bubble from the blood and block the smaller blood vessels with the production of caisson disease. The bubbles tend to persist since nitrogen is an inert gas and the only effective treatment for caisson disease is re-compression. 'Bends' are thought to arise, in the first instance, from nitrogen bubble formation in the vascular net-work of the medulla and cortex of bone, and Behnke and Stephenson (1942) state that the high fat content of the medullary marrow of bone, with its peculiar arrangement of blood vessels and vascular spaces and its sluggish circulation makes it probable that this tissue is highly susceptible to the formation of gaseous embolism following rapid decompression.

These workers, however, were unable to detect changes in the bones of deep sea divers, but Davidson (1963) has reported numerous foci of aseptic bone necrosis in men working in caissons while constructing tunnels and bridges. Protection against caisson disease is not obtained by breathing oxygen during decompression since nitrogen is only eliminated from the lungs after breathing oxygen for abou nine hours (Behnke and Stephenson, 1942) and Donald (1955) claims to have observed 'oxygen bends' in goats decompressed rapidly from $5\frac{1}{2}$ atmospheres while breathing 64% oxygen.

High concentrations of carbon dioxide are also narcotic, but the concentration of this gas in air is so small that very high pressures would be reached before it could have a narcotic effect. An increase in the partial pressure of carbon dioxide is, however, known to hasten the onset of oxygen poisoning (Gesell, 1923; Bean, 1929; Hill, 1933; Bean, 1945; Taylor, 1949).

It has been known since the time of Bert that high pressures of oxygen are toxic yet the fundamental nature of the syndrome of oxygen poisoning is still unexplained. At pressures of oxygen greater than three atmospheres, Bert

observed that the central nervous system was soon damaged irreparably so that his experimental animals did not recover. Lorrain Smith (1899), however, stated that oxygen at less than three atmospheres pressure produced no neurological disturbances, yet prolonged exposure to as little as three quarters of an atmosphere of oxygen may produce fatal pneumonia. Oxygen poisoning is thus described as having a pulmonary component - usually encountered at oxygen pressures below three atmospheres and a neurological component - usually encountered at oxygen pressures greater than three atmospheres.

The pulmonary damage may be acute or chronic and the picture of acute oxygen poisoning is essentially that of massive atalectasis (Penrod 1956). Behnke, Shaw, Shilling, Thomson and Messer (1934) report that in chronic oxygen poisoning there is hypertrophy and hyperplasia of the pulmonary epithelium with thickening and hyalinisation of the pulmonary vessels. These changes were caused by prolonged exposure to three quarters of an atmosphere of oxygen and other effects included loss of weight, stunted growth, and premature death of litters.

The toxic effects of oxygen on the central nervous system have been more widely recognised than the pulmonary effects

and Behnke and Stephenson (1942) have described oxygen toxicity as essentially the induction of "transient idiopathic epilepsy in the apparently normal individual." There are few warning symptoms and the convulsions are sudden in onset and severe in nature (Haldane, 1941). If the high concentration of oxygen is not removed death soon follows. Lambertson, Kough, Cooper, Emmel, Loeschcke and Schmidt (1953 a) suggested that the cause of the convulsions may be one of the following:

1. Direct toxic effect of oxygen at high pressure on certain constituents of brain cells.
2. Accumulation of carbon dioxide in toxic quantities in the central nervous system because of the break-down of haemoglobin transport of carbon dioxide.
3. Changes in the cerebral circulation.

Mann and Quastel (1946) and Dickens (1946 a, b.) showed that oxygen at three atmospheres pressure inhibited the oxygen consumption of slices of rat brain and they concluded that the respiration of brain is slowly and irreversibly poisoned by oxygen at elevated pressures and that the time of exposure necessary to cause a given percentage of poisoning was inversely proportional to the pressure of oxygen from 1 - 5 atmospheres. The reduction in oxygen consumption was

attributed to the inactivation of certain enzymes, notably the pyruvate oxidase system. Thomson, Neptune and Sudduth (1963) have shown recently that the metabolism of D-glucose by dispersions of rat brain is inhibited by high pressures of oxygen. Clearly, then, the aerobic oxidative metabolism of the brain is affected by oxygen at high pressures and this may play an important part in the aetiology of the neurological signs of oxygen poisoning.

It has been frequently suggested that the loss of the dual function of the haemoglobin, when high pressures of oxygen are breathed, may be responsible for oxygen poisoning (Gesell 1923, 1925; Stadie, Riggs and Haugaard, 1944). Since the oxygen requirements of the tissues can be supplied by the oxygen in physical solution the haemoglobin does not become reduced and the normal mechanism of carbon dioxide transport is interfered with. Gesell (1925) has suggested that there may be a progressive accumulation of carbon dioxide in the tissues causing a mounting tissue acidosis and he attributes oxygen poisoning to this disturbance in acid-base metabolism. While this is a tempting theory, particularly as there is no doubt that the administration of carbon dioxide to subjects breathing oxygen at high pressures

precipitates oxygen poisoning, (Sluijter, 1963). Behnke and Stephenson (1942) were unable to find any reduction in the elimination of carbon dioxide from the tissues and high levels of carbon dioxide have never been convincingly demonstrated in the tissues of animals breathing high pressures of oxygen. Behnke et.al. (1934) also measured venous pCO_2 in animals breathing high pressures of oxygen and found that it rose from a mean value of 43 mm. Hg. to 53 mm. Hg. and they concluded that this was sufficient to account for the elimination of the carbon dioxide from the tissues in physical solution. On the other hand, Shaw, Behnke and Messer (1934) later said that "Carbon dioxide tensions which are wholly innocuous when associated with oxygen pressures of less than 1 atmosphere, prove highly toxic when associated with oxygen at 4 atmospheres of pressure." This is quoted by Bean and Rottschaffer (1938) who adhere to the view that the accumulation of carbon dioxide and increasing acidity of the tissues, consequent upon a failure of reduction of haemoglobin and resultant upset in carbon dioxide carriage, is one of the most important causative factors of oxygen poisoning.

Dautrebande and Haldane (1921) first suggested that the

tissues of the nervous system might be protected from oxygen if their circulation was diminished and Kety and Schmidt (1948) noted a reduction in cerebral blood flow of 13% in man breathing oxygen at one atmosphere pressure compared with air. Lambertson et.al. (1953a,b,c.) measured cerebral blood flow in human subjects breathing oxygen at 3.5 atmospheres and found a reduction of 24%. In these subjects the arterial pCO_2 fell owing to hyperventilation so the effects of oxygen per se could not be precisely defined. Jacobson, Harper, and McDowall (1963), however, measured cerebral blood flow in dogs breathing oxygen at 2 atmospheres pressure and found a reduction in cerebral blood flow of 21%. In this latter series the pCO_2 did not vary significantly. There seems little doubt that the cerebral blood flow is diminished when hyperbaric oxygen is breathed, but it is most unlikely that this reduction would be sufficient to cause cerebral ischaemia and convulsions from anoxia.

The small increase in cerebral venous pO_2 observed by Jacobson et.al. (1963) suggests that the reduction in blood flow is a protective mechanism designed to maintain tissue oxygen levels within fairly close limits and thus to counter the possible harmful effects of hyperbaric

oxygen on the central nervous system. Bloor, Bratten, Jacobson, McCaffrey and McDowall (1964) have suggested that a similar mechanism exists in other organs such as the heart, liver and kidneys. It seems likely that the potentiality of carbon dioxide to precipitate oxygen poisoning is due to its elimination of this protective cerebral vasoconstrictor action, and it is possible that the observation of Shaw et. al. (1934) that tensions of carbon dioxide which are innocuous at pressures of oxygen less than two atmospheres but become highly toxic in association with four atmospheres of oxygen is due to the vasodilatory action of carbon dioxide on the cerebral circulation. Cerebral vasodilation from anoxia in carbon monoxide poisoning may also explain the increased susceptibility of patients suffering from carbon monoxide poisoning to the toxic effects of hyperbaric oxygen.

The pulmonary and neurological manifestations of oxygen poisoning are usually considered as separate entities but it seems possible that the pulmonary effects are secondary to exposure of the brain to excessively high tensions of oxygen and can be regarded, initially, as physiological protective mechanism. Lorrain Smith (1899) noted a falling arterial pO_2 a few hours after exposure of an animal to

high oxygen pressures and suggested that the purpose of the lung changes was to protect the brain but Behnke et. al. (1934) were unable to confirm Lorrain Smith's finding of a falling arterial pO_2. Bain (1963) noted a constant vasoconstriction of the pulmonary vascular bed when the inspired pO_2 rose above 200 mm. Hg.

Penrod (1956) and Bohr and Bean (1942) found that intermittent positive pressure respiration had an ameliorating effect on the pulmonary pathology of oxygen poisoning and this was confirmed by McDowall (1963). Penrod (1956) pointed out that when an animal had been breathing oxygen for some time the normal supporting gas, nitrogen, would have been washed out and this would facilitate the dynamics leading to collapse peripheral to an obstruction. The cause of obstruction is suggested to be increased bronchial secretion or pulmonary oedema in association with narrowed air passages. Thus it seems possible that a neurogenic component may indeed play a part in the production of the pulmonary oedema of oxygen toxicity, and it is conceivable that this may be working with the hormonal influences, shown by Bean and Johnson (1955) to have a profound effect on pulmonary pathology and survival in

elevated pressures of oxygen, through an influence on the calibre of the air passages and thus their patency.

Bean (1951) noted that the adrenal glands were enlarged following exposure to high pressures of oxygen, and Gerschman, Gilbert, Nye, Nadig and Fenn (1954), Bean and Johnson (1954) and Taylor (1958) all showed that adrenalectomy protects rats from oxygen poisoning. The relative importance of adrenal cortical and medullary factors was investigated by Bean and Johnson (1955) and they showed that epinephrine precipitated the occurrence of oxygen poisoning in adrenalectomised rats and they concluded that while adrenal cortical elements had a definite part to play, it was secondary to that of the sympathetic nervous system acting through the adrenal medulla. Taylor (1958), however, while admitting involvement of the adrenal medulla, felt that cortical influences were more important.

Bean (1952) showed that hypophysectomy produced a similar protective effect and believed, initially, that this was due to the removal of adrenal stimulating influences. Administration of A.C.T.H. to hypophysectomised rats did not, however, entirely remove the protective effect of hypophysectomy and it was eventually concluded that the pituitary had an

additional action in the production of oxygen poisoning besides its action on the adrenal cortex and that this method of protection involved more than is known about the action of the hypophysis on the oxidative reactions of the body. That pituitary and hypothalamic centres are directly involved in oxygen poisoning was again suggested by Bean and Rottschaffer (1938) who showed that removal of the cortex and even the whole cerebrum did not influence the appearance of convulsions, when rats were exposed to 5.6 atmospheres of oxygen. They concluded that neither cortex nor basal ganglia were essential for the induction of oxygen poisoning which must arise from sites below the basal ganglia. The overall conclusion of Bean and Johnson (1955) was that there are probably several mechanisms for the pulmonary oedema and damage caused by exposure to high pressures of oxygen, prominent among which are the pituitary-adrenal axis and a neurogenic component of sympathetic or hypothalmic origin. This postulates a final common pathway for the action of the various causative agents.

Oxygen toxicity is obviously a serious limiting factor to the use of hyperbaric oxygen for therapeutic purposes. The following experiment was designed to study the occurrence

of oxygen poisoning in the rat when exposed to two atmospheres of oxygen since this is a pressure of oxygen in common use clinically. In addition the effect of administering hyperbaric oxygen in an intermittent manner was compared with administration of oxygen for the same total period of time but in a continuous manner.

METHODS.

Six groups of ten adult Spragge Dawley rats weighing from 200 - 240 gm. were exposed to oxygen at two atmospheres pressure for periods up to 18 hours. A small pressure chamber was used and each rat was placed in this chamber, in its cage, so that food and water were available. 3 - 4 litres/minute oxygen were allowed to flow through the chamber continuously to prevent accumulation of carbon dioxide or water vapour and the chamber was flushed with oxygen for 10 minutes prior to compression to ensure that the gas breathed was pure oxygen. The gas in the chamber was proved to be pure oxygen by analysis with the Beckmann D2 oxygen analyser. The overflowing gas was estimated

for carbon dioxide prior to decompression in each experiment and the range of carbon dioxide concentrations was 0.05 - 0.2%.

For each total period of time chosen (i.e. 6, 12 and 18 hours), oxygen at 2 atmospheres pressure was administered either continuously or in three divided doses, each separated by 24 hours. Ten rats were thus exposed to oxygen at 2 atmospheres pressure for the following periods of time:

No. of Rats	Group	Duration of each exposure (Hr.)	No. of Exposures
10	A	18	1
10	B	6	3
10	C	12	1
10	D	4	3
10	E	6	1
10	F	2	3

Following decompression, which was always carried out over 10 minutes, each rat was observed clinically until it died or for at least 7 days, after which time it was sacrificed. Those rats which were already dead when the chamber was decompressed were subjected to immediate autopsy. The lungs of all the rats were retained for histological

examination and liver, spleen, brain, heart and adrenal glands were examined histologically in 3 rats from each group. The sections were stained with haematoxylin and eosin.

RESULTS

The rats which survived exposure to hyperbaric oxygen were kept for at least 7 days before sacrifice and those which died before the seven days had elapsed were considered to have died as a result of the exposure. The results obtained, in terms of survival may be seen in Table 16. It can be seen that all 10 rats exposed to oxygen at 2 atmospheres pressure for 18 hours continuously, together with 7 of those exposed intermittently, died. Two rats died in the group exposed to hyperbaric oxygen for 12 hours continuously while only 1 rat died in the group exposed for this period of time in an intermittent manner. All the animals, which were exposed to oxygen at two atmospheres pressure for 6 hours, survived whether the exposure was intermittent or continuous.

Rats No.	Exposure Hrs.	No. of Exposures	Survival	Death	Mortality %
10	18	1	0	10	100
10	6	3	5	5	50
10	12	1	8	2	20
10	4	3	9	1	10
10	6	1	10	0	0
10	2	3	10	0	0

TABLE 16

Mortality of rats exposed to 2 atmospheres of oxygen for various periods of time.

Clinical Observations from Each Group

1. Group A (18 hours continuous exposure).

Only one rat, in this group, survived the exposure to hyperbaric oxygen and when the chamber was decompressed, it was found to be lethargic and ataxic although it was not unduly dyspnoeic. Within 30 minutes of decompression, however, the animal had a convulsion and died.

2. Group B (18 hours intermittent exposure).

9 of the 10 rats of this group appeared clinically normal at the end of the second exposure to hyperbaric oxygen but one showed paralysis of all four limbs together with gross respiratory distress and it died within one hour of decompression. At the end of the third exposure one further rat was already dead and another was quadriplegic, had gross respiratory distress and died within 10 minutes of decompression. A further two rats were in severe respiratory distress and they both had a convulsion and died within minutes of decompression. The remaining 5 rats were lethargic and ataxic and they remained in this state for 7 days following the exposure when two more were sacrificed. The remaining 3 rats were sacrificed 14 days following the exposure when

they appeared clinically normal.

3. Group C (12 hours continuous exposure).

In this group 2 rats were found to be quadriplegic following the exposure and they showed episodic convulsions, with spasms affecting all four limbs together with gross respiratory distress. Although the respiratory signs regressed within the next hour both animals died. The remaining 8 rats were all drowsy and ataxic; they did not move about their cages and did not eat. Respiratory signs, however, were not marked. During the following day or two they all returned to normal and 4 rats were sacrificed on the 7th day following the exposure and the remaining 4 rats were sacrificed on the 14th day.

4. Group D (12 hours intermittent exposure).

At the end of the second exposure to hyperbaric oxygen all the rats of this group appeared normal but at the end of the 3rd exposure they were all drowsy and lethargic. None, however, showed marked evidence of neurological disturbance or respiratory distress. Within 48 hours all the rats had returned to normal, but one died suddenly on the 5th day following exposure. Four of the remaining rats were sacrificed on the 7th day following the exposure

and the other 5 on the 14th day.

5. Group E (6 hours continuous exposure)

All the rats of this group appeared clinically normal and active at the end of the exposure to oxygen at high pressure. There was no lethargy or other clinical evidence of neurological or respiratory disturbance. Five were sacrificed on the 7th day following the exposure and the remaining five on the 14th day.

6. Group F (6 hours intermittent exposure).

All the rats of this group remained lively and normal throughout the experiment. Five were sacrificed on the 7th day following the exposure and the remaining five on the 14th day.

7. Control Group.

A further group of 10 rats from the same batch were kept in the animal house during the period of this experiment to detect mortality from other causes during the period of the experiment. These rats all remained well.

POST-MORTEM APPEARANCES

Post-mortem examinations were carried out in all cases immediately after sacrifice of the rat or as soon as possible

after death. The rats which died during exposure to hyperbaric oxygen or within two days following the last exposure all showed similar post-mortem appearances but the features were more marked in those subjected to 18 hours pressurisation than those exposed for 12 hours.

1. Post-mortem appearances in rats dying following exposure for 18 hours to oxygen at 2 atmospheres pressure.

In most instances there were a few ml. clear fluid in the pleural cavity while the lungs were collapsed and dark red due to congestion. Liver, kidney and spleen all showed marked congestion and the adrenals appeared large and were dark on section.

2. Post-mortem appearances in rats dying following exposure for 12 hours to oxygen at 2 atmospheres pressure.

No pleural effusions were found in this group but the lungs were collapsed and congested. In this batch, however, the collapse was patchy and pink areas remained in the lungs indicating lesions of less severity than those found in the rats exposed to oxygen for 18 hours. The adrenal glands were again dark on section and there was congestion of liver, spleen and kidneys.

3. Post-mortem appearances of rats which survived exposure to hyperbaric oxygen and which were subsequently sacrificed.

There were no pleural effusions. Patchy areas of congestion could be seen in the lungs of most of the rats which had been exposed to hyperbaric oxygen for 12 or 18 hours while other organs showed variable degrees of congestion. No pathological features were noted in any of the animals exposed for 6 hours to hyperbaric oxygen.

HISTOLOGICAL APPEARANCES

Histological sections were examined from the lungs of all sixty rats and liver, heart, kidney, brain and adrenal were examined histologically in three rats from each group.

The chief findings were referable to the lungs and the changes detected were classified into four categories:

GRADE 0 Normal lung. (See Figure 25).

GRADE 1 Thickening of alveolar septa, but no overt collapse. This implies minimal lung changes. (See Figure 26).

GRADE 2 Patchy areas of collapse with areas of focal emphysema. In addition a mild degree of septal oedema was present. This implies moderate lung damage. (See Figure 27).

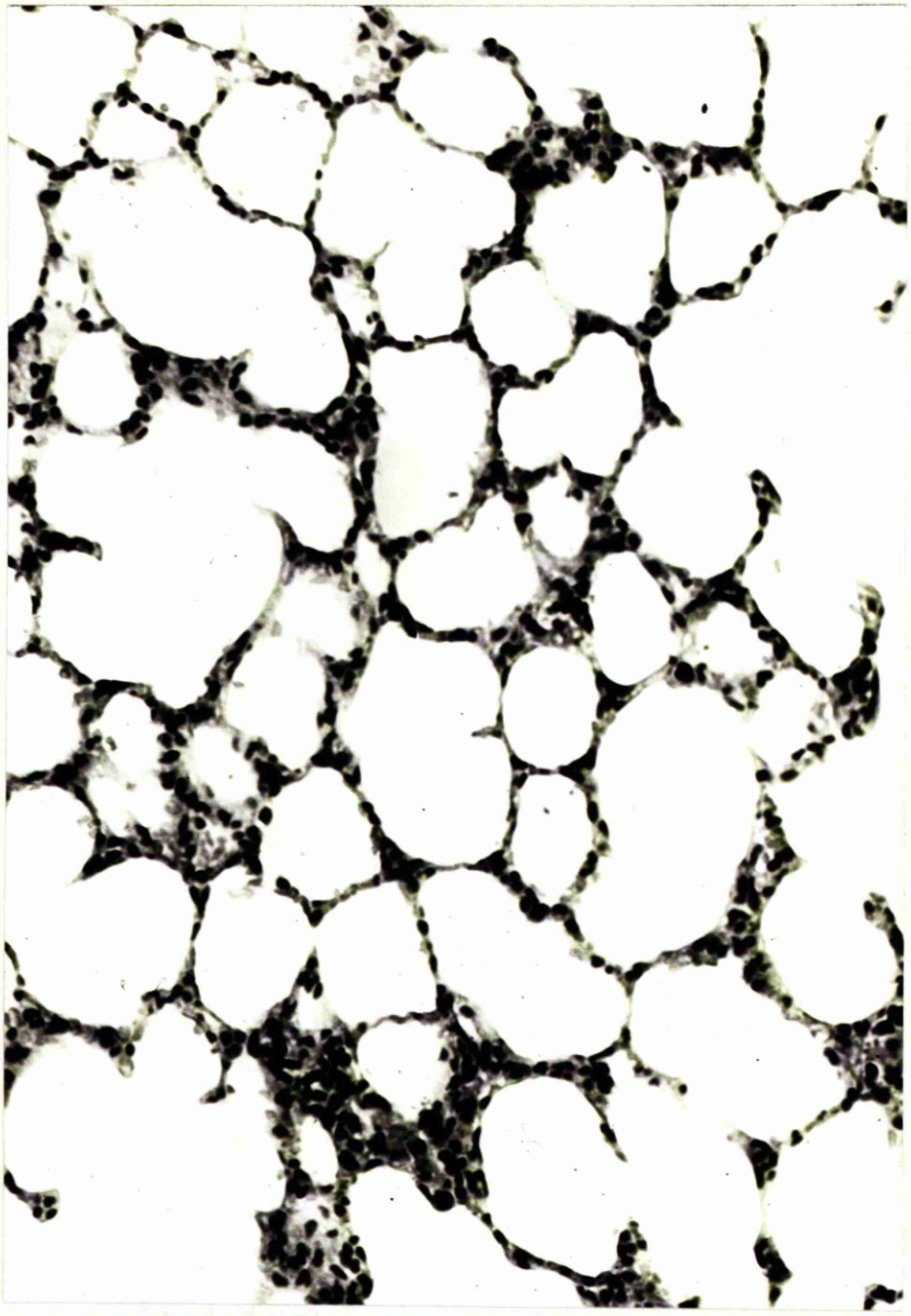


Figure 25

Grade 0 lung changes. Normal rat lung.

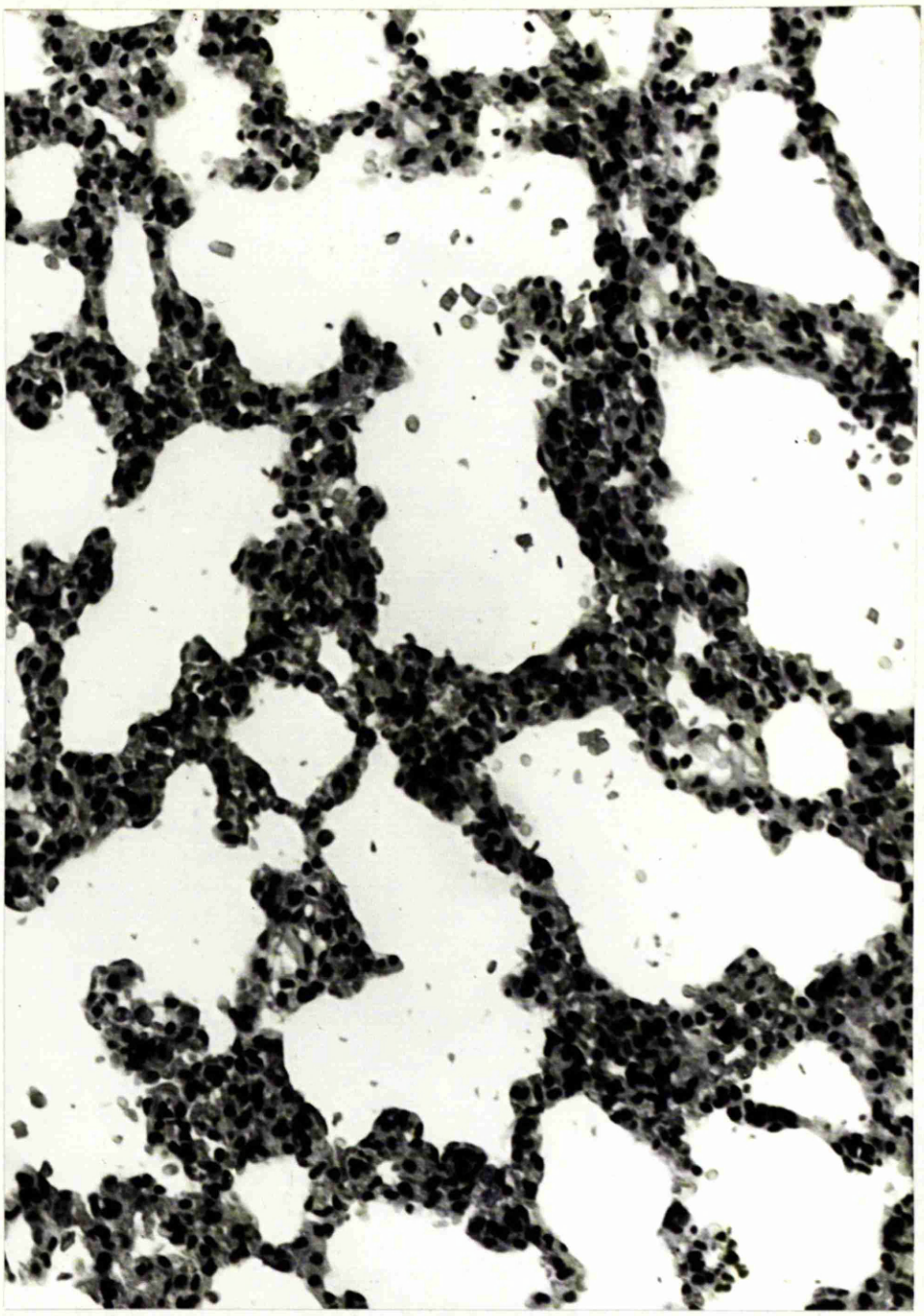


Figure 26

Grade 1 lung changes. Thickening of alveolar septa but no collapse.

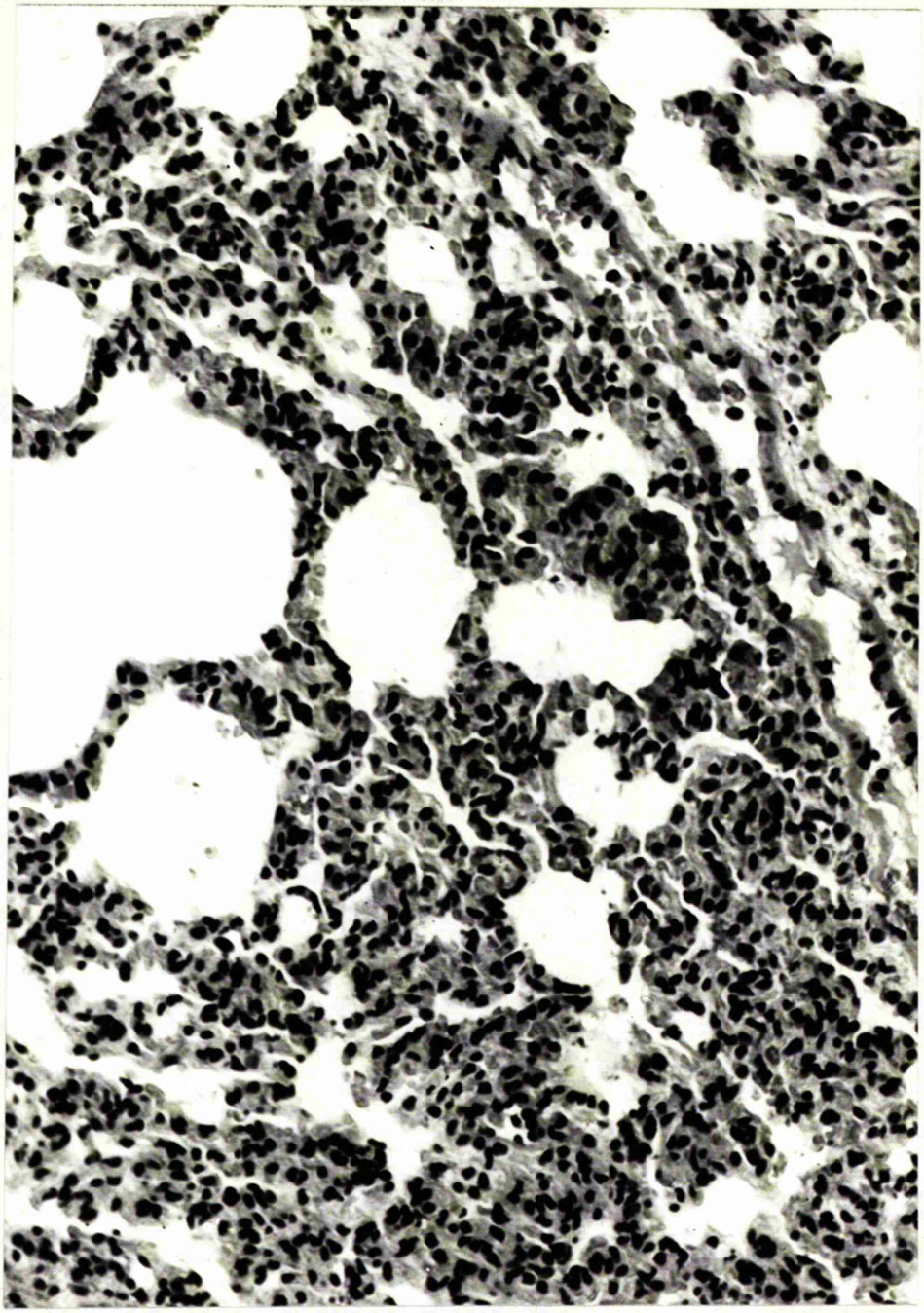


Figure 27.

Grade 2 lung changes. Patchy areas of collapse with areas of focal emphysema.

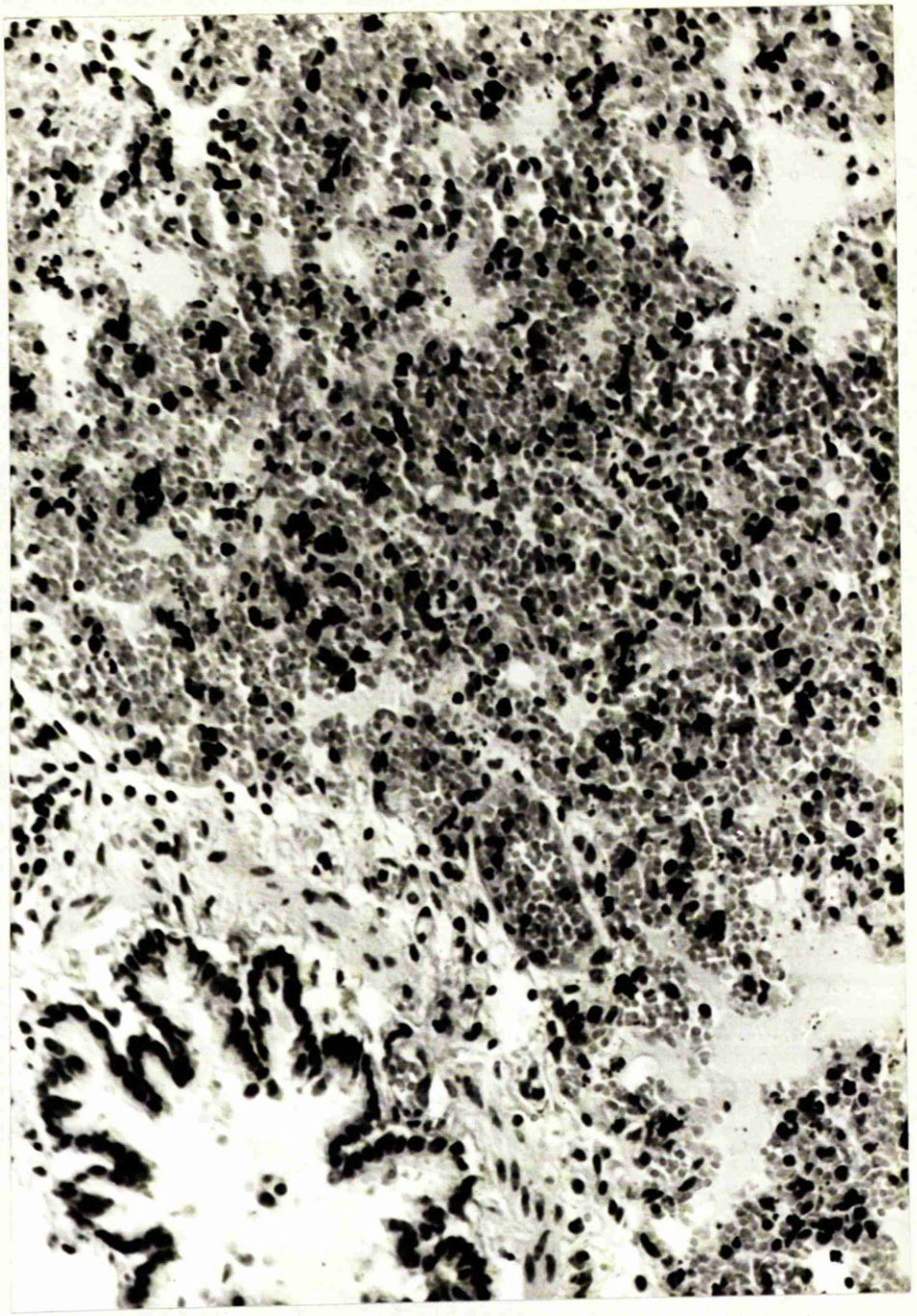


Figure 28.

Grade 3 lung changes. Extensive areas of collapse, severe capillary congestion, acute pulmonary oedema and perivascular oedema.

GRADE 3 Extensive areas of collapse, severe capillary congestion, acute pulmonary oedema and peri-vascular oedema. This implies severe lung damage. (See Figure 28).

In one animal polymorphonuclear leukocytes were present in a main bronchus but these cells were found in no other animal. There was a marked infiltration of the tissues of the animals showing grade 2 and 3 lung changes with macrophages but there was no polymorphonuclear leukocyte infiltration.

Table 17 shows the distribution of lung changes in the animals which survived exposure to hyperbaric oxygen while table 18 shows the distribution of lung changes in the animals which died following exposure to oxygen at increased pressure.

The main findings in the examination of brain, heart, kidney, spleen, liver and adrenal was acute venous congestion in the animals dying within two days of pressurisation. No cardiac lesions were demonstrated histologically and no abnormal features were detected in the brain sections of the animals with neurological signs.

Distribution of Lung Changes

Duration of each exposure	No. of Exposures	No. of Survivors	Grade 0	Grade 1	Grade 2	Grade 3
18	1	0	-	-	-	-
6	3	6	-	-	6	-
12	1	7	-	-	7	-
4	3	8	-	2	6	-
6	1	10	1	8	-	-
2	3	10	5	2	3	-

TABLE 17.

Distribution of lung changes found in rats which survived exposure to hyperbaric oxygen.

Distribution of Lung Changes

Duration of each exposure Hr.	No. of Exposures	No. of Deaths	Grade 0	Grade 1	Grade 2	Grade 3
18	1	10	-	-	2	8
6	3	5	-	-	-	5
12	1	3	-	-	2	1
4	3	2	-	-	2	-
6	1	0	-	-	-	-
2	3	0	-	-	-	-

TABLE 18.

Distribution of lung changes found in rats which died following exposure to hyperbaric oxygen.

DISCUSSION.

In this series of experiments continuous exposure of rats to oxygen at 2 atmospheres pressure for 18 hours has resulted in death of all the animals and it has been necessary to reduce the duration of the exposure to 6 hours to abolish clinical signs of respiratory or neurological involvement. Repeated exposures, at daily intervals, is cummulative and it does not abolish mortality. Repeated exposures over three days, has however, reduced the mortality rate by 50%, in this series, compared to that found if the total exposure is administered continuously.

The lung changes tended to be of grades 2 and 3 in those animals dying as a result of the exposure to hyperbaric oxygen and there was little change in the lung condition resulting from intermittent rather than continuous exposure to oxygen. The rats of Groups A - D (12 and 18 hours exposure) which survived the exposure all showed some degree of lung damage. This was of grade 2 in all except 2 cases, although 20 rats in these groups made complete clinical recoveries. The lung changes did not vary greatly according to whether the exposure had been intermittent or continuous.

Only six of the twenty rats exposed to two atmospheres of oxygen for six hours showed completely normal lungs and in three cases the changes had advanced to grade 2, in spite of the fact that all of these animals had remained clinically normal throughout the procedure. These figures are not at variance with existing date, though Burnett, Sandison and Smith (1960) found it necessary to expose their rats to oxygen at two atmospheres pressure for 24 hours to achieve 100% mortality.

It is generally considered that the neurological component of oxygen toxicity is not seen at pressures below three atmospheres (Bean, 1945; Donald 1947 a, b,) but in this series it has been usual to find neurological signs in association with the pulmonary signs, or even alone. Neurological lesions, which consisted of lower limb paraplegia, have all eventually disappeared in the rats which recovered. Skene (1964) has also observed neurological lesions of a similar nature in mice exposed to oxygen at two atmospheres pressure.

Lorrain Smith (1899) and Burrows (1917) considered the pulmonary changes to be in the nature of a physiological, protective reaction to prevent

exposure of the brain to the damaging properties of an excess of oxygen and the exaggeration of these changes to cause irreversible pathological changes in the lungs, which eventually lead to death.

There is little doubt of the truth of Bert's statement that oxygen at elevated pressures is 'toxic to every living thing'. While oxygen toxicity presents a barrier to progress in the therapeutic application of hyperbaric oxygen in many fields, it seemed worth while investigating the ability of hyperbaric oxygen to suppress the growth of pathogenic bacteria. If bacterial growth could be arrested at lesser pressures of oxygen than cause irreversible damage to host cells then it may be possible to direct oxygen toxicity into useful channels.

Inhibitory Effects of Hyperbaric Oxygen on Micro-organisms.

The toxic nature of oxygen at elevated pressures has been known since the time of Bert (1878) and in more modern times this has imposed a limitation on the use of hyperbaric oxygen in clinical practice. Oxygen toxicity might, however, be turned to advantage if it were possible to influence the growth or viability of pathogenic bacteria by exposing them to pressures of oxygen lower than that which would cause severe toxic reactions in mammalian host cells (McAllister, Stark, Norman and Ross, 1963).

The effects of oxygen at increased pressure in the treatment of anaerobic infections has been reported (de Almedia and Pacheco, 1961; Brummelkamp, Hoogendyk and Boerema, 1961; Brummelkamp, Boerema, Hoogendyk 1963; Smith, Sillar, Norman, Ledingham, Bates, Scott, 1962; Wallyn and Gumbiner, 1964). The effect of high pressures of oxygen on aerobic bacteria have also been studied in the past (Thayser, 1934; Bean, 1945), but in most instances, the pressure of oxygen used was in the region of 8 - 10 atmospheres and thus outside the therapeutic range.

In view of the increasing use of hyperbaric oxygen it seemed desirable to study the reactions of some common human pathogens to different oxygen tensions and the following experiment deals with this.

METHODS.

The micro-organisms listed in Table 19 were cultured on horse-blood agar plates and placed in a small pressure chamber fitted with a 'Perspex' lid through which temperature could easily be recorded. The chamber was placed in a 'hot-room' thermostatically controlled at 37° C. and the control plates were also incubated in this room. Cylinders of compressed air or oxygen were used to expose the plates in the chamber to four different oxygen tensions, namely, air at one atmosphere pressure (pO_2 150 mm. Hg.), air at two atmospheres pressure (pO_2 300 mm. Hg.), oxygen at one atmosphere pressure (pO_2 760 mm. Hg.) and oxygen at two atmospheres pressure (pO_2 1520 mm. Hg.). The control plates were exposed to one atmosphere of air. All plates were incubated for 18 hours. It was necessary to allow a small, continuous flow of gas to pass through the chamber to maintain a constant pressure but the flow rate for each experiment was kept constant. The temperatures of the 'hot-room' and the chamber were kept under continuous surveillance; and, apart from an initial slight rise in the temperature (1 - 2° C.) within the chamber during pressurisation, and a similar fall during decompression

the chamber and the 'hot-room' remained in thermal equilibrium.

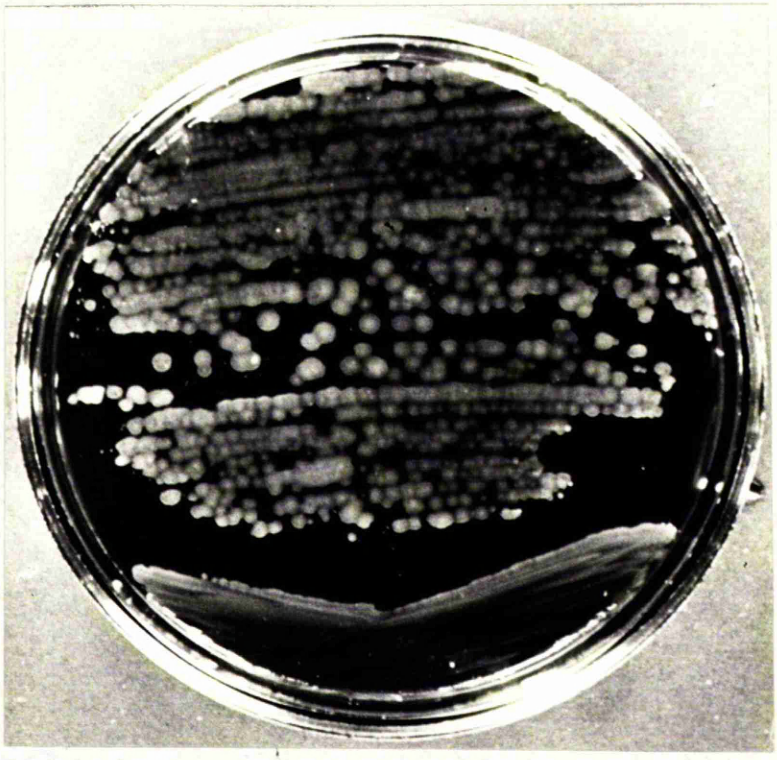
RESULTS.

The results are summarised in table 19 and figures 29 - 32. It can be seen that the micro-organisms studied varied in their susceptibility to increased oxygen tension. Pseudomonas pyocyanea and Aspergillus fumigatus were most affected and showed no growth after 18 hours incubation. Staphylococcus aureus continued to grow as infrequent, small, stunted, depigmented colonies: it was markedly affected but not completely inhibited. Escheriohia coli was only slightly affected and produced stunted colonies but of equal number to the control. There was little change in the plates exposed to pressures of oxygen less than two atmospheres.

Micro-organisms	Oxygen at two Atmospheres	Oxygen at One Atmosphere	Air at two Atmospheres	Air at One Atmosphere
Pseudomonas pyocyanea	complete inhilation	Reduced number of colonies. No proteolysis	No change	No change
Staphylococcus aureus (289)	Equal numbers of colonies but all reduced in size and non-pigmented	Colonies smaller and non-pigmented	No change	No change
Aspergillus fumigatus	No growth	-	-	No change
Escherichia coli	Equal numbers of colonies but all stunted	No Proteolysis otherwise no change.	No change	No change
Proteus vulgaris	Inhibition of spreading; colonies discrete. No proteolysis	No change	No change	No change

TABLE I.

Effect of various tensions of oxygen on bacteria as compared to controls maintained in air at one atmosphere.



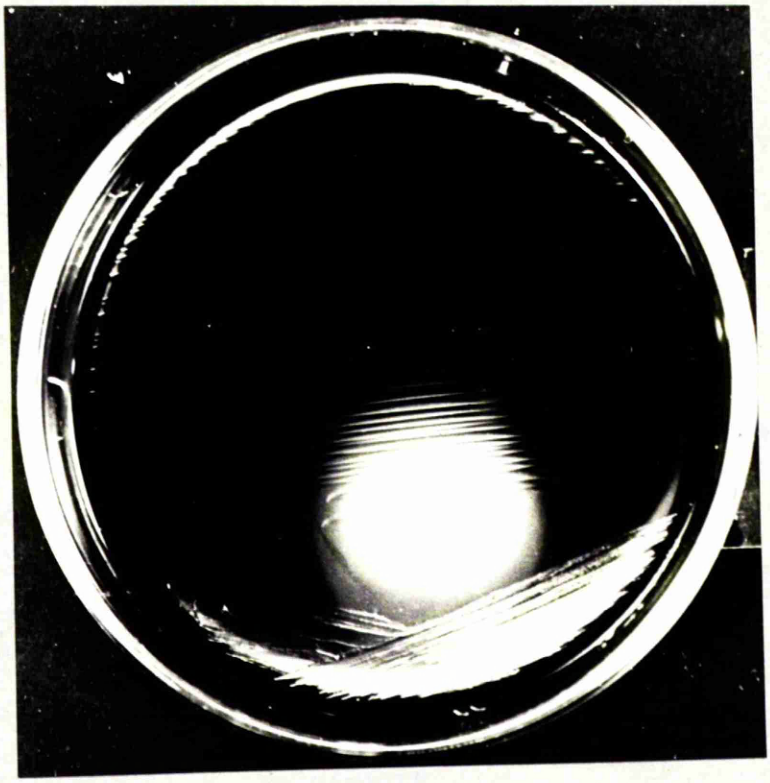
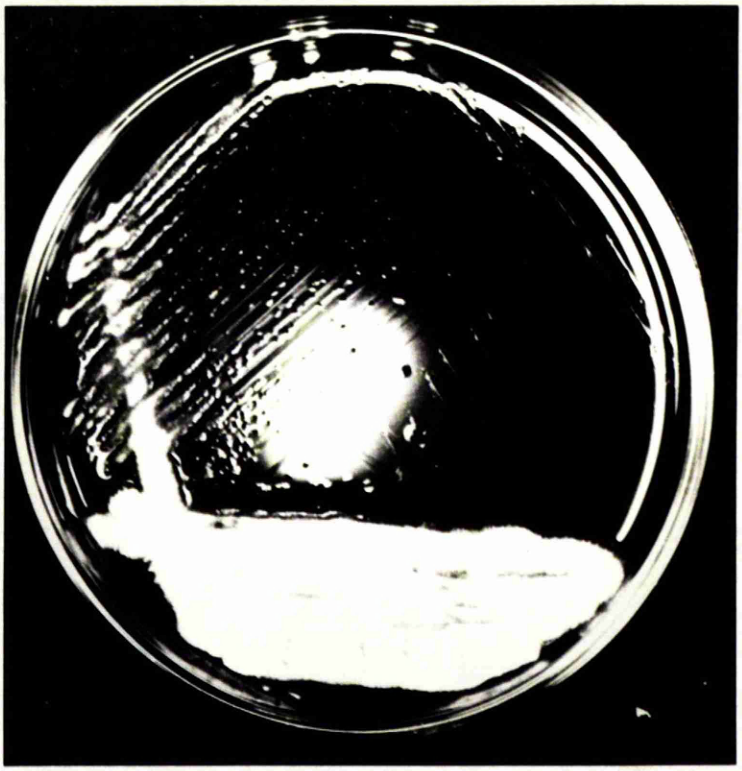


Figure 29.

Pseudomonas pyocyanea exposed to air at one atmosphere pressure (above) and to oxygen at two atmospheres pressure (below).



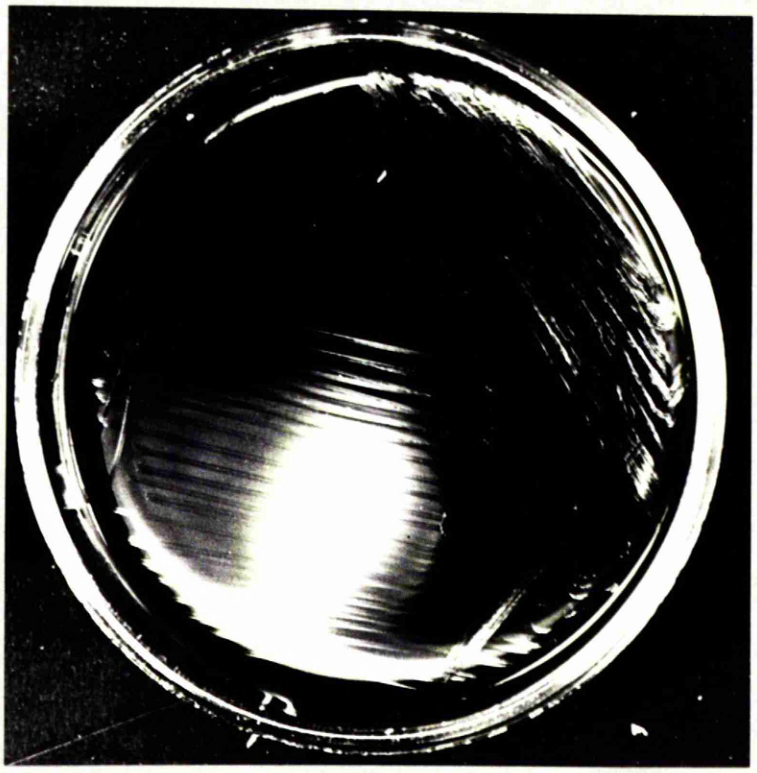


Figure 30.

Aspergillus fumigatus exposed to air at one atmosphere pressure (above) and oxygen at two atmospheres pressure (below).

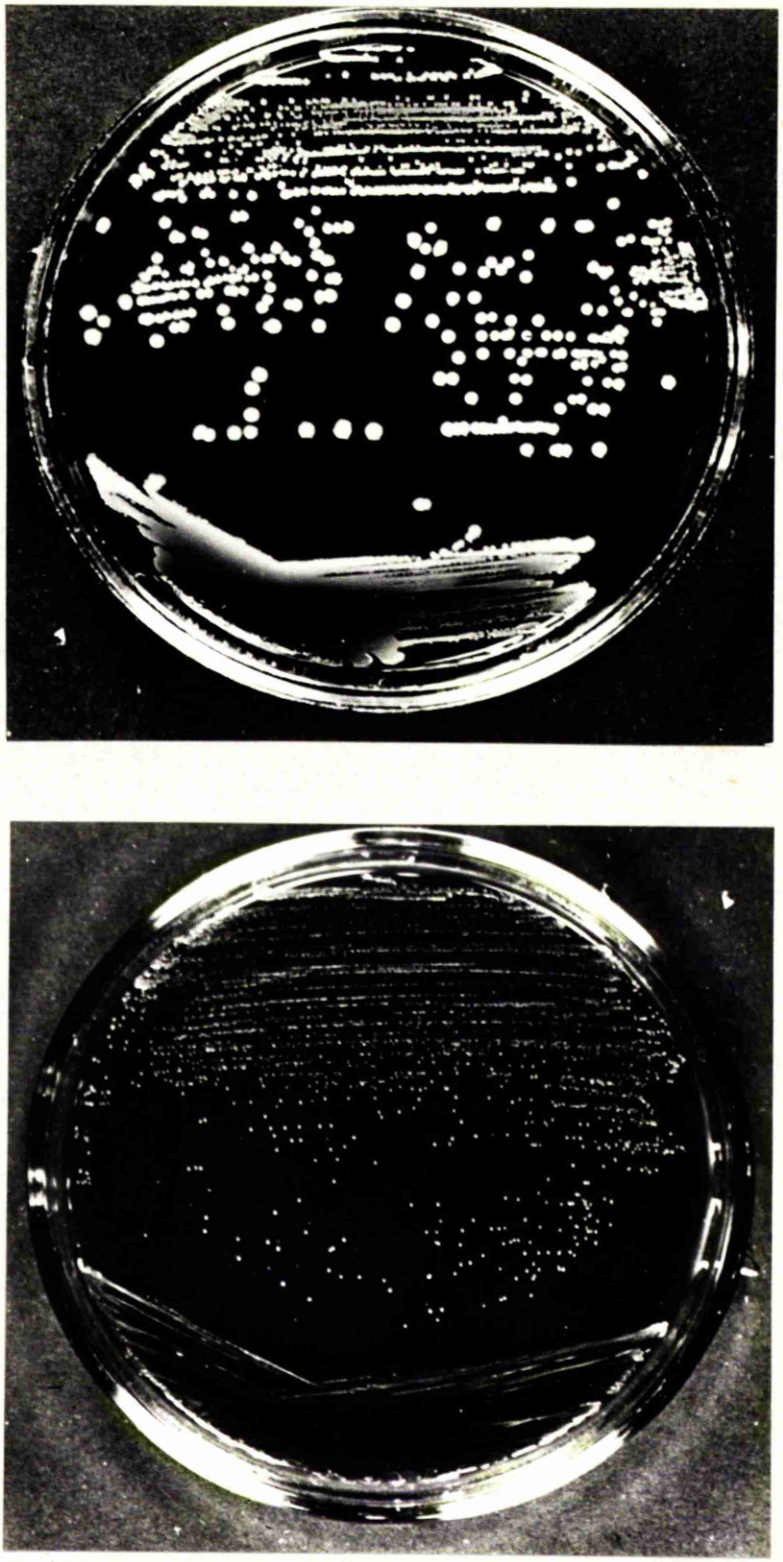
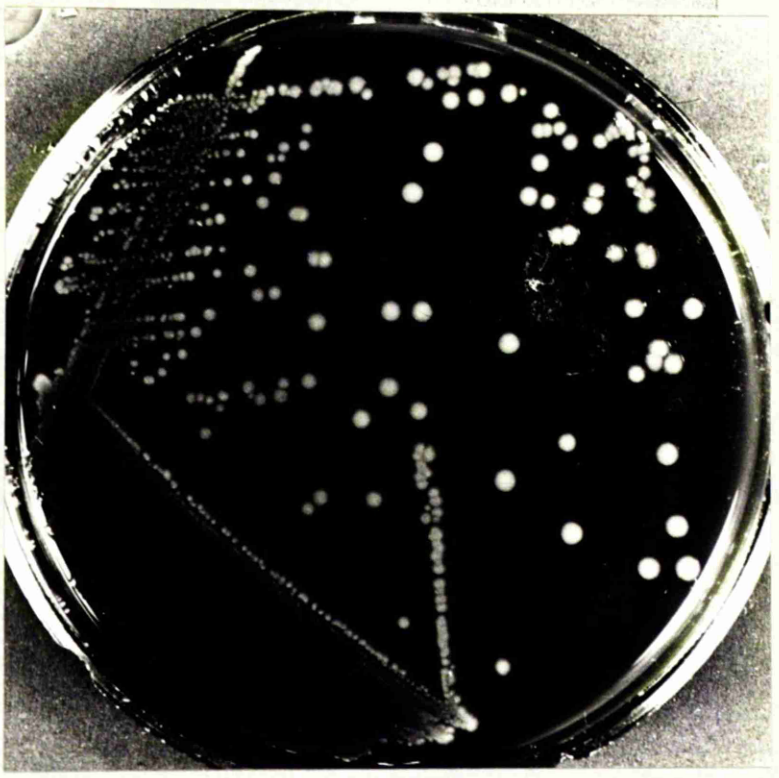


Figure 31.

Staphylococcus aureus exposed to air at one atmosphere pressure (above) and oxygen at two atmospheres pressure (below).



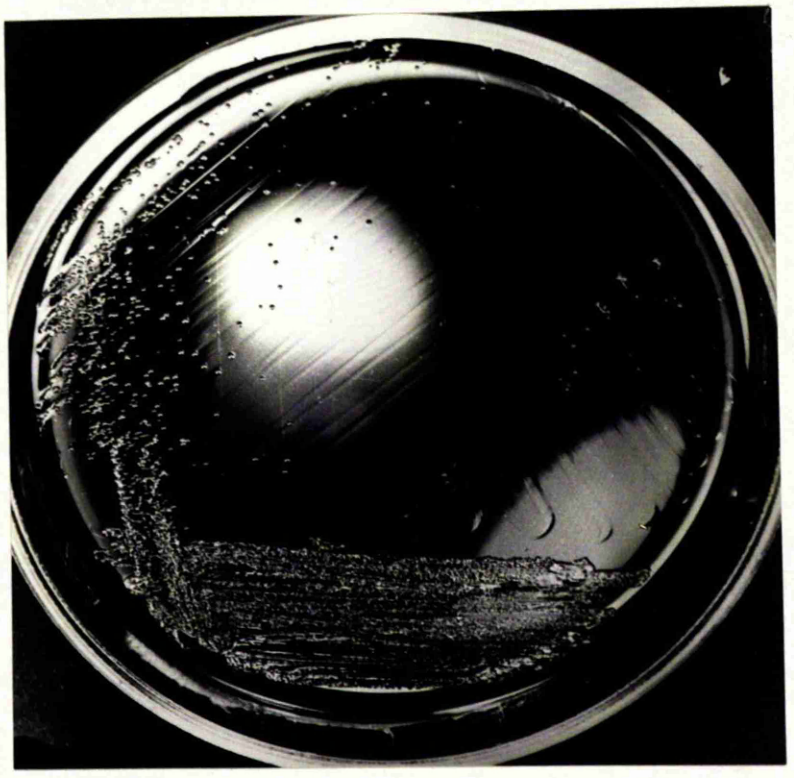


Figure 32.

Escherichia coli exposed to air at one atmosphere pressure (above) and oxygen at two atmospheres pressure (below).

DISCUSSION.

Oxygen at a pressure of two atmospheres absolute is bacteriostatic for anaerobes and for certain aerobes. That the inhibitory powers of hyperbaric oxygen are mediated by the raised oxygen tensions and not by increased pressure per se or by toxic substances or conditions in the apparatus is indicated by the absence of noticeable effects in columns 3 and 4 of table 1.

The conventional definition of aerobes and anaerobes implies air at one atmosphere pressure as the standard. It seems likely that each micro-organism will be inhibited at a certain level of oxygen pressure. A more accurate description of a particular micro-organism would include the tension of oxygen by which it is inhibited. Since patients can now be treated at greatly increased oxygen tensions a knowledge of the behaviour of pathogens and commensals over a wide range of oxygen tensions from very low to those now therapeutically attainable is of considerable practical importance.

The temptation to extrapolate the inhibitory effects of oxygen on micro-organisms must be tempered by the

knowledge that hyperbaric oxygen will be of value in infections only if it is selectively toxic. Since the basic lesion in oxygen poisoning is presumably the inactivation of thiol containing enzymes it is reasonable to suppose that the susceptibility of living cells to damage by high oxygen tensions is dependent upon their enzyme pattern. The susceptibility of each micro-organism to hyperbaric oxygen is thus likely to be related to its particular enzyme pattern. Since the various organisms studied react differently to hyperbaric oxygen it is possible that certain of them will be more susceptible to the damaging effects of oxygen than mammalian cells.

The practical application of hyperbaric oxygen in the treatment of infection may, nevertheless, be limited by oxygen poisoning in the host which is related both to the pressure at which oxygen is administered and the duration of exposure to it. Patients with traumatic ischaemia have been exposed, intermittently, to two atmospheres of oxygen for as long as 48 hours without apparent ill effect (Illingworth, 1962). Since oxygen

was administered to these patients by the B.L.B. mask, it is likely, however, that the arterial pO_2 levels were considerably less than two atmospheres, and it may be that the maximum safe exposure, even at this pressure, is very much less. Subsequently work by Jacobson, Ledingham, Norman and McDowall (1964) has shown that oxygen administered in this way is unlikely to raise the arterial pO_2 to higher levels than 1000 mm. Hg. In Amsterdam, administration of oxygen by the B.L.B. mask at a pressure of three atmospheres absolute raises the arterial pO_2 to about 1500 mm. Hg. only (Schoemaker, 1964) and, under these circumstances, oxygen poisoning has been observed in patients suffering from carbon monoxide poisoning or carbon dioxide retention, following about 4 hours exposure to hyperbaric oxygen.

A further limiting factor is imposed by the level to which it is possible to raise tissue pO_2 and this will be much less than arterial pO_2. Indeed, Jacobson et. al. (1963) have shown only small increases in the saggital sinus venous pO_2 of dogs exposed to hyperbaric oxygen, despite the finding of an arterial pO_2 of the

expected order.

While hyperbaric oxygen is less likely to be of value in infections of solid organs it is possible that it may prove a valuable adjunct to the treatment of blood stream infections or those affecting the valves of the heart. It is also possible that it may be used in surface infections such as burns or persistent fungal infections of skin where the hyperbaric oxygen could be applied directly to the skin, while the patient breathed only air at increased pressure.

It is also possible that a moderate rise in tissue oxygen tension may place the micro-organisms at such a disadvantage that host defence mechanisms are rendered more active in bringing the infection under control.
It is interesting to note in conclusion that the first application of hyperbaric oxygen was in 1887, when Valenzuela, a young Spanish physician, successfully treated a case of pneumonia with oxygen at a pressure of 1520 mm. Hg., administered intermittently.

INHIBITORY EFFECTS OF HYPERBARIC OXYGEN ON BACTERIA AND FUNGI

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Preliminary Communication

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INHIBITORY EFFECTS OF HYPERBARIC OXYGEN ON BACTERIA AND FUNGI

THE effects of oxygen at increased pressures in the treatment of anaerobic infections have been reported,[1–5] but little attention has been directed to the effects of hyperbaric oxygen on aerobic microorganisms. Bert [6] noted that high tensions of oxygen were toxic to most living things, including bacteria and yeasts, and Bean [7] in his review on oxygen at increased pressure, cites several reports of its toxicity for microorganisms.

With the increasing clinical use of hyperbaric oxygen it seemed important to assess the behaviour of some common human pathogens at different oxygen tensions, and the initial studies are reported below.

METHODS AND MATERIALS

The microorganisms listed in the table were cultured on horse-blood-agar plates placed in a specially constructed portable metal chamber, fitted with a pressure gauge and a transparent 'Perspex' lid through which the temperature could easily be recorded. All experiments were conducted in a "hot room", thermostatically controlled at 37°C, and the control plates were also incubated in this room. Cylinders of compressed air or oxygen were used to expose the plates in the chamber to four different oxygen tensions—namely, air at 1 atmosphere (Po_2 150 mm. Hg), air at 2 atmospheres (Po_2 300 mm. Hg), oxygen at 1 atmosphere (Po_2 760 mm. Hg), and oxygen at 2 atmospheres (Po_2 1520 mm. Hg). The controls were all exposed to 1 atmosphere of air. All plates were incubated for 18 hours. Those exposed to oxygen at 2 atmospheres for 18 hours, together with a further series exposed for 42 hours, were reincubated in the "hot room" (air at 1 atmosphere) for periods of 24 and 30 hours respectively, and compared with their controls which had been incubated for the same total time.

1. de Almeida, A. O., Pacheco, G. *Rev. bras. Biol.* 1941, **1**, 1.
2. Klopper, P. J., Brummelkamp, H., Hoogendijk, J. L. *Pr. méd.* 1962, **41**, 1874.
3. Brummelkamp, W. H., Hogendijk, J., Boerema, I. *Surgery*, 1961, **49**, 299.
4. Brummelkamp, W. H., Boerema, I., Hogendyk, L. *Lancet*, 1963, i, 235.
5. Wallyn, R. J., Gumbiner, S. Proceedings of 1st International Congress on Clinical Application of Hyperbaric Oxygen. 1963 (in preparation).
6. Bert, P. La pression barometrique. Paris, 1878.
7. Bean, J. W. *Physiol. Rev.* 1945, **25**. 1.

EXPOSURE OF MICROORGANISMS FOR 18 HOURS AT 37°C TO FOUR DIFFERENT TENSIONS OF OXYGEN

(Each group is compared with its control)

Microorganism	Oxygen at 2 atmospheres	Oxygen at 1 atmosphere	Air at 2 atmospheres	Air at 1 atmosphere
Pseudomonas pyocyanea ..	Much inhibition of growth; scanty atypical pearly colonies on butt; no pigment; no proteolysis	Reduction in number of colonies, with variation in size; no proteolysis	Identical*	Identical
Staphylococcus aureus (289)	Equal numbers of colonies but all reduced in size and non-pigmented; no hæmolysis	Colonies all smaller and non-pigmented	Identical	Identical
Streptococcus viridans (Horne)	Very scanty growth; colonies smaller; no hæmolysis	Identical	Identical	Identical
Streptococcus pyogenes (755)	Colonies reduced in size; alpha-hæmolysis only	No growth	Reduction in number of colonies; alpha-hæmolysis	Identical
Streptococcus fæcalis ..	Comparable; doubtful increase in hæmolysis	Identical	Identical	Identical
Escherichia coli	Equal numbers of colonies but all stunted; no proteolysis	All colonies slightly reduced in size	Identical	Identical
Proteus	Inhibition of spreading; colonies discrete; no proteolysis	No proteolysis; otherwise identical	Identical	Identical
Clostridium welchii	No growth (anaerobic control)	..	..	No growth
Candida albicans	No growth	..	..	Identical
Aspergillus fumigatus ..	No growth	..	..	Identical

* " Identical " means that the test organism and its control grew with the production of equal numbers of colonies of the same size and appearance.

For each experiment the pressure in the chamber was raised over 15 minutes and lowered over the same period. It was necessary to allow a small continuous flow of gas to pass through the chamber to maintain a constant pressure. The flow-rate for each experiment was constant. The temperatures of the " hot room " and the chamber were kept under continuous surveillance; and, apart from an initial slight rise (1–2°C) in the chamber during pressurisation and a similar fall during decompressure, the chamber and the " hot room " remained in thermal equilibrium.

RESULTS

The results are summarised in the table and in figs. 1–3. It will be seen that different microorganisms vary in their susceptibility to increased oxygen tension, with *Pseudomonas pyocyanea*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Aspergillus fumigatus* being most affected. None of the microorganisms was killed by exposure to oxygen at 2 atmospheres for 18 or 42 hours, and when incubated thereafter under normal control conditions all (including *Clostridium welchii*) continued to grow, although to varying degrees. The basic effect of hyperbaric oxygen appears to be inhibitory rather than cidal.

Ps. pyocyanea, *Staph. aureus*, and *Esch. coli* appeared to be permanently altered by their exposure to hyperbaric oxygen, and they failed to attain the appearances of the controls. *Staph. aureus*, for example, after exposure for 42 hours continued to grow as stunted non-pigmented colonies, though these remained slide-coagulase positive. A few colonies, however, and especially those at the ends of rows or well separated from their fellows, were larger, atypical, and hyperpigmented. We have, for convenience, termed these " hyperbars ". A similar effect was found with *Ps. pyocyanea* and *Esch. coli*, their " hyperbars " being opaque and pearly. After 18 hours' exposure, *Esch. coli* and *Staph. aureus* grew normally but *Ps. pyocyanea* remained stunted and opaque, resembling normal aerobic staphylococcal colonies.

Using simple disc-diffusion methods there seemed to be no dramatic alteration in antibiotic sensitivity of the bacteria grown in hyperbaric oxygen, although on two occasions *Ps. pyocyanea* appeared more resistant to streptomycin and showed hormesis with tetracycline.

DISCUSSION

Hyperbaric oxygen at 2 atmospheres is bacteriostatic for aerobes and anaerobes. That its inhibitory powers are mediated by the raised oxygen tensions and not by increased pressure per se or by toxic substances or conditions in the apparatus is indicated by the absence of noticeable effects in columns 4 and 5 of the table. In microbiology hyperbaric oxygen is a relatively unexplored parameter and its effects on bacterial, fungal, and viral metabolism and pathogenicity are worthy of further investigation. With regard to bacteria, for example, the

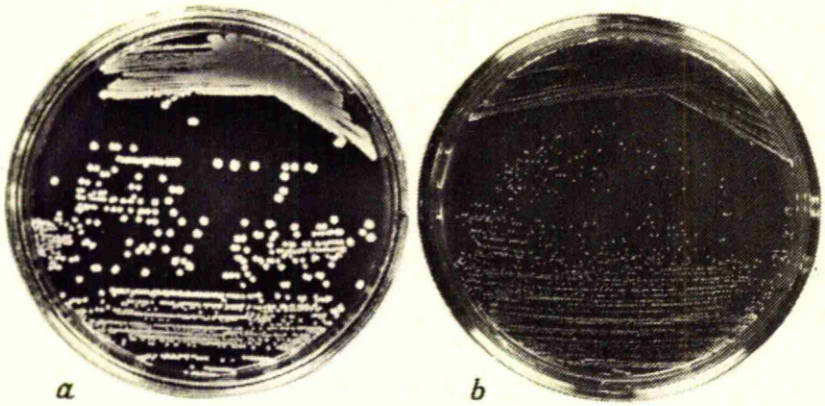

Fig. 1—*Staph. aureus* (289) grown for 18 hours (a) in air at 1 atmosphere (control), and (b) in oxygen at 2 atmospheres.

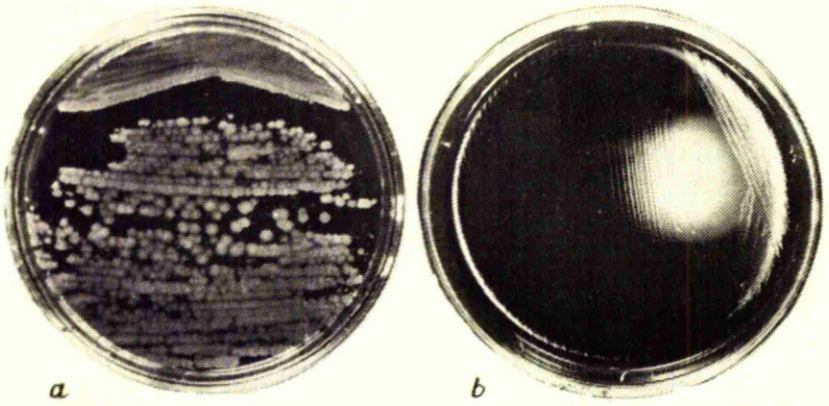

Fig. 2—*Ps. pyocyanea* grown for 18 hours (a) in air at 1 atmosphere control), and (b) in oxygen at 2 atmospheres.

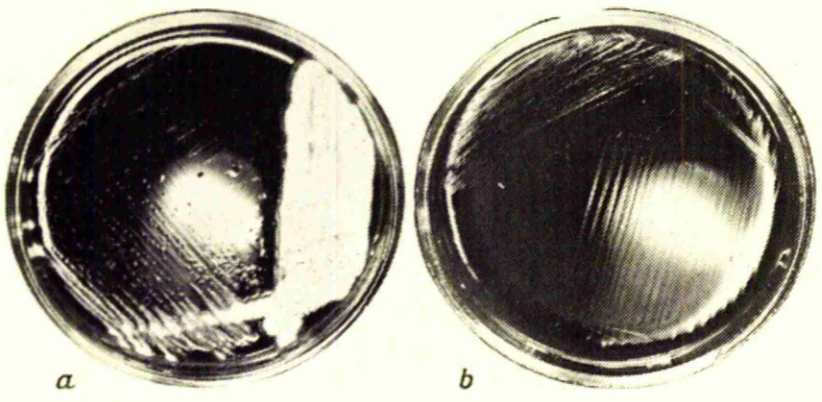

Fig. 3—*Asp. fumigatus* grown for 18 hours (a) in air at 1 atmosphere (control), and (b) in oxygen at 2 atmospheres.

alterations in morphology and production of hæmolysins, which are of considerable academic interest, are being studied further.

The conventional definition of aerobes and anaerobes implies air at 1 atmosphere as the standard. Since patients

can now be treated at greatly increased oxygen tensions [8–10] this base line has become outmoded, and a knowledge of the behaviour of pathogens and commensals over a wide range of oxygen tensions from very low to those now therapeutically attainable is of considerable practical importance.

It is essential to know the oxygen tensions at which individual bacterial species might be stimulated or inhibited, and growth/oxygen-pressure curves for each should be drawn to avoid alteration of normal body flora or the differential stimulation of pathogens in infection. It may, indeed, be necessary to avoid certain ranges of oxygen tension in treatment.

The temptation to extrapolate the inhibitory effects of microorganisms to clinical practice must be tempered by the knowledge that, like the antibiotics, hyperbaric oxygen will be of value in infections only if it is selectively toxic. On the other hand, the first clinical application of hyperbaric oxygen was in 1887, when a Spanish physician, Valenzuela,[11] reported the use of oxygen at a pressure of 2 atmospheres absolute in successfully treating a young man with pneumonia. He had already observed that oxygen at increased pressure reduced the temperature of mice with septicæmia, compared to controls, and he used this agent because of its antipyretic properties. Earlier workers had already observed that increased pressures of oxygen caused a fall in body temperature.[6 12] This was probably owing to the decreased oxidations which were later recognised as part of the syndrome of oxygen poisoning.[13–15] Since the basic lesion of this toxicity is the inactivation of certain enzymes, particularly those containing a thiol group,[16 17] it is reasonable to suppose that the susceptibility of living cells to damage by high oxygen tensions is dependent upon their enzyme pattern.

The practical application of hyperbaric oxygen in the treatment of infection may be limited by oxygen poisoning, which is related both to the oxygen pressure and the period of exposure. Patients with traumatic ischæmia have been exposed, intermittently, to 2 atmospheres of oxygen for as

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long as 48 hours without apparent ill effect.[18] Since oxygen was administered to these patients by the B.L.B. mask, it is likely that the arterial Po_2 levels were less than 2 atmospheres, and it may be that the maximum safe exposure period at a tissue Po_2 of 2 atmospheres is much shorter. The results suggest that there is a considerable inhibitory effect on exposure of certain microorganisms to oxygen at 2 atmospheres for 18 hours, but it may be possible to produce the same effect by varying the pressure/time relationships, for example, by using repeated exposure to high oxygen pressure for short periods.

Before hyperbaric oxygen can be used in infected patients as an adjunct to therapy, its effect on host defence mechanisms, for example phagocytosis and antibody production, must be studied by using tissue-culture techniques and laboratory animals. In this respect the reaction of virus-induced tumours will be of interest. The activity of antibiotics at different oxygen tensions must also be explored.

SUMMARY

Hyperbaric oxygen is toxic for aerobic and anaerobic bacteria and for fungi; its effect is static rather than cidal, and it permanently alters the cultural appearance of some bacteria. These pilot observations lead to speculation about its application in other fields of microbiology. Whether the toxicity is selective enough to be of value in infection remains to be seen; but with the increasing clinical use of hyperbaric oxygen it is, nevertheless, essential to chart the behaviour of microorganisms and antibiotics at different oxygen tensions. It is suggested that the conventional concept of aerobiosis, with air at 1 atmosphere as the reference point, is outmoded.

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INHALATION OF OXYGEN AT 2 ATMOSPHERES FOR *Clostridium welchii* INFECTIONS

A CENTURY ago Pasteur noted that oxygen inhibited the growth of certain microorganisms concerned with butyric fermentation. By 1863 he showed that several organisms concerned with putrefaction were not only unable to grow but were killed by the presence of oxygen.[1] Since then many varieties of anaerobes have been found to be pathogenic for man. Of these the organisms of gas gangrene are strict anaerobes, requiring a low oxidation-reduction potential in their environment for continued growth.

One of the main determinants of this potential is the amount of oxygen present, and it follows that a high environmental oxygen content will be inimicable to such bacteria. Such a high oxygen content might be achieved by allowing a patient with a gas-gangrene infection to breathe oxygen while in a compression chamber. Preliminary reports by Boerema et al.,[2 3] first of guineapigs injected intramuscularly with cultures of *Clostridium welchii*, and later of two cases of severe clostridial myositis in man, suggest that inhalation of oxygen at pressures greater than atmospheric may have a significant therapeutic effect on the course of such infections.

This report is concerned with the application of this therapy to three cases of *Cl. welchii* infection of a limb in man.

THE FIRST CASE

A young agricultural student, aged 19, was involved in a motor accident on Oct. 10, 1961. He was admitted to the Southern General Hospital the same day, with irregular laceration of the right knee and with an avulsion of the skin and soft tissues from the heel of the same side. The flap was attached anteriorly about half way along the sole of the foot. The blood-supply appeared adequate, and after excision of the contused edges the wounds were sutured, using local anæsthesia. He was given antitetanus serum 1500 units, and no antibiotics were given.

The wound was inspected on the 5th day, there having been no untoward signs or symptoms in the intervening 5 days. It was noted that an area of skin some 3×1 cm. at the posterior end of the heel flap was black, with a slight ooze of serous material. The rest of the wound seemed to be healing in a satisfactory fashion. It was decided to examine the wound

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2. Boerema, I., Brummelkamp, W. H. *Ned. Tijdschr. Geneesk.* 1960, **104**, 2549.
3. Brummelkamp, W. H., Hogendijk, J., Boerema, I. *Surgery*, 1961, **49**, 299.

next day in the operating-theatre, and a striking change was found in the appearances. The ankle and the dorsum of the foot were swollen, and when the wound edges were separated there escaped foul-smelling pus and gas bubbles. The blackened area had doubled in size, and at the advancing line there was a white vesicular area with small isolated vesicles in front of this. The patient was anæsthetised, the wound was laid open, and the blackened skin was excised, but there was no bleeding from the cut edges of the skin of the foot. The laceration had extended into the deep plantar compartment of the foot, and pus was present there.

During the span of 2 hours, while the position was reviewed by *three surgeons*, two of whom had served as field medical officers throughout the second world war, the œdema spread to the level of the knee. A bacteriological examination of the fluid showed the presence of gram-positive bacilli morphologically resembling *Cl. welchii* and subsequently proven so on culture. Blood-transfusion was started and a below-knee amputation was performed through the œdematous yellow subcutaneous tissue. The muscles appeared normal and there was no gas at the line of section. He was given 30 ml. of mixed gas-gangrene antitoxin *B.P.* intravenously, and 2 mega-units of crystalline penicillin intramuscularly. The skin flaps were loosely approximated, and he was transferred to the Western Infirmary to be nursed in the pressure chamber there at 2 atmospheres absolute pressure, breathing oxygen.

The serosanguinous fluid from the amputation stump was cultured every 12 hours. The second examination showed degenerate gram-positive rods in small numbers on direct smear. Subsequent smears and cultures on aerobic and anaerobic media were negative. The original material from the foot on culture produced a heavy growth of *Cl. welchii* and coliform bacilli, together with a light growth of *Bacillus cereus*. He was given crystalline penicillin 1 mega-unit intramuscularly and ampicillin 250 mg. by mouth in 6-hourly doses, and after the first 24 hours 30,000 units of polyvalent anti-gas-gangrene serum and 8000 units of antiperfringens serum were added.

By the end of 36 hours the serous fluid from the wound was much less and the wound edges were less swollen. A further three examinations of the fluid showed no organisms, and on subsequent culture none grew. He was therefore returned to the wards. Convalescence was uneventful, and he was discharged from hospital 3 weeks later with the amputation stump healed.

THE SECOND CASE

This man, aged 20, who was semiconscious and severely shocked on admission to hospital, had been run over by a bus and had sustained a compound comminuted fracture of the left thigh, with degloving of the skin from more than two-thirds of the thigh and extending up into the perineum. The inferior pubic ramus was fractured. The scrotum was torn and the testes were exposed. After treatment of shock the wound was explored by Mr. T. W. Howat. The fracture was reduced and

the lacerated muscle was excised. This included most of the hamstring and adductor groups; the vasti were preserved. The femoral artery was intact though the vein, being torn, was ligated. After defatting, fairly complete skin closure was effected. A pressure dressing and a toe-to-groin plaster were applied. He was given penicillin 0·5 mega-units at 4-hourly intervals and chlortetracycline 250 mg. every 6 hours by the intramuscular route. Antitetanus serum 1500 units was also administered by injection.

By the following day the main anxiety was for the blood-supply to the lower limb; and 18 hours after admission he was nursed in the pressure chamber, breathing oxygen at 2 atmospheres absolute. Some 3 hours later it was obvious that his condition was deteriorating. He looked toxic, his temperature was 101·6°F, and his pulse was rapid and thready at 140 per minute. Gas was felt in the subcutaneous tissues above the left groin, and he was accordingly taken to the operating-theatre, where the wound was reopened. Gas bubbled out, and from the fluid around the vasti *Cl. welchii* was subsequently cultured. These muscles showed the typical brick-red colour change associated with infection by this organism. A high thigh amputation was performed. He was given a total of 277·5 ml. of mixed gas-gangrene antitoxin *B.P.* intravenously, and penicillin 2 mega-units 4-hourly over the next 3 days. By this time it was obvious that the infection had been overcome.

Healing of the stump was somewhat tardy owing to the degloving injury, and he was discharged from hospital some 6 weeks after injury.

THE THIRD CASE

A man of 62 was admitted to hospital with gangrene of the toes of the right foot. Below-knee amputation was carried out, with primary closure. The patient was given tetracycline 250 mg. 6-hourly by mouth. 4 days later he complained of pain in the stump, which was then examined. It was found to be much swollen, and the flaps were showing greenish discoloration. There was crepitus owing to gas in the subcutaneous tissues of the anterior aspect of the thigh and the lower abdominal wall. A mid-thigh amputation was performed through the muscle, which appeared healthy and which bled. The flaps were left open. Penicillin 1 mega-unit was given every 4 hours intramuscularly for 5 days, and mixed gas-gangrene antitoxin *B.P.* 67·5 ml. was given intravenously during the first 24 hours. After the second amputation he was nursed in the pressure chamber, breathing oxygen at 2 atmospheres for the next 24 hours continuously. *Cl. welchii* was cultured from the below-knee amputation stump. At the end of this period the wound seemed healthy, and 2 days later secondary suture was performed. Convalescence thereafter was uneventful.

DISCUSSION

Whereas the Dutch group have used oxygen at 3 atmospheres absolute pressure, and given three treatments of some 2–3 hours duration, we have elected to use

2 atmospheres absolute pressure and to employ this more continuously. Thus, the first patient was decompressed for 30 minutes every 12 hours, while the third patient was exposed for 24 hours. All were nursed in bed, just as they would have been in an ordinary ward. There has been no evidence of any untoward effects on these patients from this form of treatment.

In the second case a considerable time elapsed before the patient was given this form of treatment, and in spite of it his condition deteriorated. It seems that while breathing oxygen at increased pressure is likely to prove a valuable ancillary aid in severe anaerobic infection, it does not in any way replace adequate surgical excision of all dead and devitalised tissue (and particularly muscle) at the time of primary debridement. Further, all measures to reduce tension in the wound must be retained. These fundamental precautions are obvious since the increased oxygen content of the part at risk can be achieved only if there is some circulation still present. The increased plasma-oxygen which results from breathing oxygen at pressures above atmospheric levels is of little avail in clostridial infection unless it can be brought into the environment in which the anaerobes are present.

The technique represents an extension of methods tried in the past for treating anaerobic infections. These have consisted of oxygen inhalations, injection of oxygen or hydrogen peroxide into the tissues, and the application of hydrogen or zinc peroxide to wounds. In common with these the present method is an aid to, but does not replace, adequate primary surgery.

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CONCLUSIONS

1. During the course of carbon monoxide poisoning hyperventilation occurs which causes respiratory alkalosis. At the stage of respiratory depression the blood pCO_2 rises to the normal range only.

2. The use of carbon dioxide containing mixtures is not contraindicated in the treatment of carbon monoxide poisoning.

3. There is no difference in the speed with which 5% and 7% carbogen remove carbon monoxide from the haemoglobin.

4. Oxygen at two atmospheres pressure remove carbon monoxide from the blood twice as fast as carbogen mixtures.

5. Oxygen at two atmospheres pressure has been used with considerable success in the treatment of carbon monoxide poisoning in man.

6. The oxygen consumption of rat liver homogenates, at 37° C., decreases at the tension of oxygen to which it is exposed is increases from 150 mm. Hg. to 1520 mm. Hg.

7. There is an initial rise in the oxygen consumption of rat liver homogenates at 28° C. and 15° C., as the tension of oxygen to which it is exposed rises, followed by a fall in oxygen consumption when the pO_2 rises beyond about 500 mm. Hg. at 28° C. and about 1000 mm. Hg. at 15° C.

8. Hypothermic tissues may not be adequately oxygenated unless oxygen is supplied to them at a sufficiently high pressure.

9. The rate of metabolism of succinate by tissue exposed to various temperatures and oxygen pressures is similar to the rate of endogenous oxygen consumption of the tissue under the same conditions.

10. The safe duration of total circulatory arrest, in dogs, can be increased from 5 minutes to 8 minutes at 37° C. if the animal breathes oxygen at two atmospheres pressure instead of one atmosphere pressure.

11. At 28° C. the safe duration of total circulatory arrest in dogs is increased from 20 minutes to 30 minutes if the dog breathes oxygen at two

atmospheres pressure instead of one, but at 20° C. the circulation can be arrested for only 40 minutes whether the animal breathes oxygen at one or two atmospheres pressure.

12. Rats exposed to oxygen at two atmospheres pressure for 18 hours die, while those exposed for 6 hours survive. 20% die when exposed for 12 hours.

13. Mortality still occurs when rats are exposed to two atmospheres of oxygen intermittently but it is reduced to 50% of that found following continuous exposure for 12 or 18 hours.

14. Clinically, neurological signs occur in association with pulmonary signs when rats are exposed to oxygen at two atmospheres pressure.

15. The histological changes in the lungs of rats exposed to oxygen at two atmospheres pressure for prolonged periods of time consist of patchy atelectasis with focal emphysema progressing to massive collapse, acute pulmonary oedema and peri-vascular oedema.

16. Oxygen at two atmospheres pressure is bacterio-static for certain pathogenic bacteria and there

seems to be a spectrum of sensitivity which indicates that it may be selectively toxic to certain bacteria in doses which do not effect host cells.

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APPENDIX 1.

The measurements of oxygen consumption of rat liver homogenates when exposed to various temperatures and tensions of oxygen are given below together with the time taken by each preparation to metabolise a standard quantity of succinate. Measurements of oxygen consumption were made at ten minute intervals and the figure quoted at each point is the mean value obtained from all the respirometer flasks used for that experiment. The results are expressed in terms of micro-litres of oxygen per mg. Nitrogen in the homogenate.

Oxygen Consumption of Rat Liver Homogenates ($\mu l.O_2/mg.\ N_2$).

37° C. with pO_2 150 mm. Hg. VERSUS 37° C. with pO_2 300 mm.Hg.

1. CONTROLS 37° C. with pO_2: 150 mm.Hg.

Expt.	Time (Min.) 10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min
12A	6.6	12.5	17.1	19.1	21.3	22.0	23.4	24.9	25.8	26.8	27.7	28.5	14.0
12B	6.7	11.7	15.5	18.3	19.6	21.3	22.6	23.9	24.9	25.8	26.9	27.7	8.5
12C	7.3	13.8	17.5	19.7	20.8	21.8	22.8	23.4	24.8	25.4	26.4	27.4	12.0
12E	7.2	14.3	17.8	20.0	21.5	23.2	24.4	25.4	26.4	27.5	28.4	29.4	12.5
12F	4.6	8.9	13.3	15.8	17.6	18.6	20.5	21.4	22.5	23.4	24.1	25.1	11.5
12G	7.8	11.6	13.7	15.8	17.5	18.9	20.3	21.5	22.5	23.4	24.2	24.9	12.0
MEAN	6.7	12.1	15.8	18.1	19.7	20.9	22.3	23.4	24.5	25.4	26.3	27.2	11.7

2. TEST 37° C. with pO_2:300 mm. Hg.

12A	7.1	13.7	15.8	17.6	19.7	21.3	22.5	23.8	24.6	25.7	26.3	27.2	14.0
12B	7.9	12.0	14.7	16.4	18.4	20.3	21.8	23.1	24.2	25.3	26.3	27.1	12.0
12C	6.7	12.8	16.6	17.8	18.4	19.4	20.3	21.9	22.0	23.1	24.5	25.3	13.5
12E	6.9	11.6	15.0	17.5	20.7	22.3	23.7	25.0	25.9	26.9	27.5	28.2	7.5
12F	5.0	9.7	13.2	14.5	16.5	17.9	19.0	19.9	20.7	21.7	22.7	23.5	12.0
12G	7.1	10.5	12.9	14.1	15.3	16.4	17.5	18.6	19.4	20.1	21.9	22.6	11.5
MEAN	6.8	11.7	14.7	16.3	18.1	19.6	20.8	22.0	22.8	23.8	24.9	25.6	11.7

Oxygen Consumption of Rat Liver Homogenates ($\mu l. O_2/mg. N_2$).

37^0 C. with pO_2 760 mm. Hg. VERSUS 37^0 C. with pO_2 1520 mm. Hg.

2. CONTROLS 37^0 C. with pO_2: 760 mm. Hg.

	Time (Min)												Succinate
Expt.	10	20	30	40	50	60	70	80	90	100	110	120	Time (Min)
13A	6.1	11.3	14.5	17.2	19.0	20.0	21.3	22.4	23.5	24.7	25.7	26.6	8.5
13B	6.1	11.2	14.7	16.7	18.2	19.5	21.3	22.6	23.8	25.0	26.1	27.1	7.5
13C	6.5	8.9	12.1	13.9	16.3	17.5	18.8	20.2	21.7	23.1	24.5	25.3	12.0
13D	6.2	10.1	12.6	14.7	16.5	17.8	19.2	20.4	21.7	22.4	23.3	24.0	11.5
13E	5.6	9.9	12.3	14.0	15.6	17.0	18.2	19.6	20.3	21.5	22.4	23.0	11.5
13F	2.0	3.7	4.2	5.2	6.0	6.5	7.1	7.7	8.1	8.5	8.9	9.3	11.0
MEAN	5.4	9.2	11.7	13.6	15.3	16.4	17.6	18.8	19.8	20.9	21.8	22.6	10.3

2. TEST 37^0 C. with pO_2 1520 mm. Hg.

13A	5.0	9.4	11.9	13.5	14.9	15.7	17.8	18.8	20.0	21.0	22.0	23.0	11.5
13B	5.6	9.3	11.2	12.9	13.9	15.1	16.3	17.2	18.3	19.2	20.0	21.0	13.0
13C	5.7	8.3	11.7	12.5	14.7	16.4	17.2	19.0	20.1	20.8	21.5	22.4	13.0
13D	6.0	9.6	11.9	13.2	14.7	16.4	17.4	18.4	19.6	20.3	20.8	21.5	14.5
13E	4.4	8.3	10.6	11.7	12.2	12.5	13.8	14.7	15.7	16.1	16.6	17.4	13.5
13F	1.8	2.9	3.3	4.0	4.5	4.8	5.2	5.4	6.2	6.7	7.2	7.7	12.5
MEAN	4.8	8.0	10.1	11.3	12.5	13.6	14.6	15.6	16.6	17.4	18.0	18.8	13.0

Oxygen Consumption of Rat Liver Homogenates ($\mu l. O_2/mg. N_2$).

37° C. with pO_2 150 mm. Hg. VERSUS 28° C. with pO_2 150 mm. Hg.

1. CONTROLS. 37° C. with pO_2: 150 mm. Hg.

Expt.	Time (Min.) 10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min.
4A	5.3	8.9	13.0	16.8	17.8	18.8	19.4	20.3	21.0	21.6	22.3	23.9	15.0
4B	7.7	10.5	12.6	15.3	19.9	21.1	22.4	23.4	24.4	25.5	26.3	27.2	11.0
4C	5.9	9.9	14.0	17.1	19.3	20.8	22.1	23.4	24.5	25.4	26.4	27.0	14.5
4D	5.5	12.1	16.1	18.8	19.6	20.0	20.4	21.1	21.8	22.4	23.1	23.8	13.0
4E	9.0	12.3	14.9	16.6	18.6	20.1	21.8	23.3	24.7	26.2	27.5	28.9	9.5
4F	6.3	10.3	12.5	15.9	18.2	20.4	21.4	22.7	23.6	24.7	25.2	26.3	11.0
MEAN	6.6	10.7	13.8	16.7	18.9	20.2	21.2	22.4	23.3	24.3	25.1	26.2	12.3

2. TEST 28° C. with pO_2: 150 mm. Hg.

4A	4.1	6.9	9.9	15.4	16.8	17.5	18.1	18.7	19.2	19.7	20.1	20.5	15.0
4B	4.2	7.1	9.8	13.0	15.2	16.1	17.1	18.9	20.7	21.5	22.2	23.0	13.5
4C	3.3	5.1	7.9	9.3	10.2	11.8	13.5	15.2	16.9	18.0	19.7	20.3	17.5
4D	3.8	6.1	8.2	9.7	10.5	12.1	13.2	15.8	16.4	17.8	18.4	19.0	20.0
4E	5.0	9.9	13.1	14.8	16.1	17.2	18.2	19.5	20.5	21.6	22.3	23.3	15.5
4F	4.0	6.9	9.1	11.7	12.0	13.2	14.4	15.4	15.3	17.9	18.7	19.3	18.5
MEAN	4.1	7.0	9.7	12.3	13.5	14.6	15.7	17.2	18.2	19.4	20.2	20.9	16.7

Oxygen Consumption of Rat Liver Homogenates (Ul. O_2/mg. N_2).

37° C. with pO_2 150 mm. Hg. VERSUS 28° C. with pO_2 300 mm. Hg.

1. CONTROLS 37° C. with pO_2: 150 mm. Hg.

	Time (Min.)												
Rat	10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min.
8A	7.2	12.4	15.8	17.6	20.0	21.8	23.7	24.8	25.7	26.7	27.8	28.6	16.0
8B	6.0	10.5	15.3	17.7	18.5	20.3	21.4	22.8	23.9	25.2	25.9	26.4	11.5
8C	5.2	9.6	14.5	16.6	19.1	20.4	22.4	23.2	24.1	24.8	25.4	26.3	11.0
8D	7.0	10.1	12.4	14.8	16.7	18.2	19.2	20.3	21.4	22.8	23.6	24.6	11.5
8E	6.4	10.3	12.6	16.0	19.6	21.9	23.2	24.0	24.9	25.9	26.8	27.6	12.0
8F	6.4	10.9	12.7	15.9	19.2	21.2	22.5	23.0	24.1	25.5	26.1	27.5	15.0
MEAN	6.4	10.6	13.9	16.4	18.8	20.6	22.1	23.0	24.0	25.1	25.9	26.8	12.8

2. TEST 28° C. with pO_2: 300 mm. Hg.

8A	4.9	8.1	11.5	14.5	16.0	17.3	18.3	19.2	20.2	20.9	21.6	22.9	13.0
8B	3.3	6.6	8.8	11.3	14.1	14.9	17.0	18.0	19.1	20.0	20.9	21.5	14.0
8C	6.2	9.6	11.7	13.8	15.8	17.1	18.1	19.1	20.0	20.7	21.5	22.1	15.0
8D	5.1	8.8	11.6	15.2	16.7	17.7	18.8	19.8	20.6	21.6	22.5	23.0	16.5
8E	3.9	6.5	9.5	12.4	15.2	17.6	18.4	19.4	19.9	20.9	21.4	21.9	12.0
8F	4.0	6.6	8.4	12.2	15.2	16.3	17.1	18.2	19.8	21.7	22.5	23.1	18.0
MEAN	4.6	7.7	10.2	13.2	15.5	16.8	17.9	19.0	19.9	21.0	21.7	22.4	14.8

Oxygen Consumption of Rat Liver Homogenates (Cl. O_2/mg. N_2).

37° C. with pO_2 760 mm. Hg. VERSUS 28° C. with pO_2 760 mm. Hg.

1. CONTROLS 37° C. with pO_2: 760 mm. Hg.

Time (Min).

Expt.	10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min.
14C	7.2	10.1	13.0	14.4	15.6	17.0	18.0	19.4	20.5	21.6	22.5	23.3	8.5
14D	6.8	10.1	12.8	13.8	15.5	16.6	17.7	18.8	19.9	21.5	22.1	22.8	12.0
14E	9.3	13.5	16.7	17.9	19.6	21.2	22.4	23.6	24.7	25.0	25.2	27.4	11.5
14F	6.8	11.0	13.0	14.4	18.5	20.5	21.3	22.3	23.6	24.0	25.2	26.0	11.5
14G	6.6	9.8	13.8	14.1	15.5	16.1	17.1	18.9	19.2	20.2	21.4	22.2	12.0
14H	6.3	7.9	10.9	11.3	12.7	13.7	15.4	16.2	17.1	18.0	19.5	20.3	10.5
MEAN	7.2	10.4	13.4	14.3	16.2	17.5	18.6	19.9	20.8	21.7	22.8	23.7	11.0

2. TEST 28° C. with pO_2: 760mm. Hg.

14C	4.4	8.9	12.4	14.3	16.7	18.0	19.1	20.4	21.1	22.2	23.3	24.1	6.0
14D	3.5	9.6	12.6	14.9	16.9	17.4	18.4	19.8	20.3	21.5	22.4	23.3	16.0
14E	4.9	8.3	12.1	15.6	17.1	19.5	20.9	22.1	23.1	24.4	25.3	26.2	14.0
14F	3.0	5.7	10.8	12.6	15.5	17.8	18.4	19.5	20.8	21.5	22.1	23.6	16.5
14G	3.3	7.1	10.1	12.5	14.5	15.3	16.0	17.8	18.9	19.8	22.6	24.3	21.5
14H	5.1	7.5	9.4	12.7	12.2	13.2	14.8	15.8	16.3	17.6	18.4	19.1	22.5
MEAN	4.0	7.8	11.2	13.8	15.5	16.9	17.9	19.2	20.1	21.2	22.3	23.4	16.1

Oxygen Consumption of Rat Liver Homogenates (Ul. O_2/mg. N_2).

37° C. with pO_2 760 mm. Hg. VERSUS 28° C. with pO_2 1520 mm. Hg.

1. CONTROL 37° C. with pO_2: 760 mm. Hg.

	Time (Min.)												Succinate
Expt.	10	20	30	40	50	60	70	80	90	100	110	120	Time (Min.
XA	4.2	9.6	11.9	14.2	15.9	16.9	18.3	19.2	20.1	21.0	21.5	22.3	7.5
XB	4.8	9.8	12.8	15.1	16.7	17.9	19.0	20.1	20.6	21.5	21.9	22.8	11.0
XC	4.8	8.9	11.3	13.9	15.4	16.5	17.6	18.6	19.5	20.5	21.7	22.1	12.0
XD	4.8	8.5	11.8	14.3	15.9	17.7	18.2	19.6	19.4	20.3	21.2	22.4	13.0
XE	4.3	9.9	12.5	14.9	16.6	18.0	18.9	19.8	19.7	20.4	21.3	22.4	12.0
XF	4.6	9.6	13.2	14.7	15.3	16.3	17.4	18.5	19.7	20.3	21.4	22.9	11.5
MEAN	4.6	9.4	12.2	14.5	16.0	17.2	18.2	19.3	19.8	20.7	21.5	22.5	11.2

2. TEST 28° C. with pO_2: 1520 mm. Hg.

XA	3.1	7.1	9.5	11.5	12.1	13.6	14.2	14.5	15.2	16.2	17.4	18.6	14.0
XB	3.3	7.5	9.7	11.7	12.6	13.8	14.3	14.7	15.3	16.2	17.8	18.8	18.0
XC	3.6	6.5	8.8	10.7	11.5	13.0	13.9	14.9	15.6	16.5	17.1	18.3	16.5
XD	2.5	5.9	7.8	10.4	12.8	14.6	15.9	17.1	17.4	18.2	19.6	20.9	19.0
XE	3.0	6.0	8.0	10.5	12.7	14.3	15.6	16.8	17.2	18.0	19.2	20.8	15.0
XF	3.0	5.7	7.4	10.3	11.8	13.3	14.7	15.7	16.5	17.3	18.3	19.8	19.5
MEAN	3.1	6.4	8.5	10.9	12.2	13.8	14.8	15.6	16.2	17.1	18.2	19.5	17.0

Oxygen Consumption of Rat liver Homogenates (Ul. O_2/mg. N_2).

37° C. with pO_2 150 mm. Hg. VERSUS 15° C. with pO_2 150 mm. Hg.

1. CONTROLS 37° C. with pO_2: 150 mm. Hg.

Expt.	Time (Min.) 10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min)
6A	6.6	12.3	15.6	17.9	18.8	19.9	21.8	23.6	24.3	25.1	25.9	26.6	11.0
6C	7.4	12.0	14.1	15.6	17.8	19.2	20.4	21.5	22.6	23.4	24.7	25.4	12.0
6D	8.1	13.0	15.3	17.1	18.9	20.3	21.5	22.7	23.6	24.4	25.2	25.9	12.0
6E	8.1	13.1	15.2	16.1	17.8	19.2	20.6	21.5	22.3	23.0	23.9	24.6	12.0
6F	5.7	11.4	15.7	17.9	19.9	21.8	23.7	24.8	26.0	27.3	28.2	29.1	10.5
6G	5.8	11.3	15.6	17.3	19.1	20.7	22.2	23.4	24.5	25.9	27.0	27.8	15.0
MEAN	6.9	12.2	15.2	17.0	18.7	20.2	21.7	22.9	23.9	24.8	25.8	26.6	12.1

2. TEST 15° C. with pO_2: 150 mm. Hg.

6A	1.0	1.9	2.8	3.0	3.9	4.9	5.6	6.5	7.3	8.4	8.9	9.7	30.0
6C	1.4	2.3	3.2	3.9	4.9	5.7	6.4	7.3	8.1	8.8	9.7	10.4	21.0
6D	1.6	2.4	3.0	3.3	3.9	4.2	5.5	6.1	7.0	7.7	8.6	9.4	23.5
6E	0.9	1.7	2.4	2.8	3.5	4.3	5.2	5.9	6.7	7.5	8.6	9.4	24.5
6F	1.6	2.6	3.5	4.4	5.0	5.8	6.8	7.5	8.5	9.4	10.5	11.6	25.0
6G	1.7	2.5	3.3	3.9	4.7	5.5	6.3	7.0	7.7	8.6	9.4	10.2	20.5
MEAN	1.4	2.2	3.0	3.5	4.3	5.1	6.0	6.7	7.6	8.4	9.3	10.1	24.0

Oxygen Consumption of Rat Liver Homogenates (Ul. O_2/mg. N_2).

37° C. with pO_2 150 mm. Hg. VERSUS 15° C. with pO_2 300 mm. Hg.

1. CONTROLS 37° C. with pO_2: 150 mm. Hg.

	Time (Min.)												
Expt.	10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min.
10A	8.2	12.7	15.0	16.3	18.0	19.2	20.3	21.3	20.4	23.2	24.0	25.7	10.5
10B	6.2	10.3	13.8	15.5	17.4	18.7	19.9	20.8	21.9	23.4	24.8	25.8	13.0
10C	7.3	12.2	16.8	18.6	20.6	22.8	24.2	25.4	26.4	27.4	28.5	29.4	11.0
10D	8.2	13.7	16.0	17.8	18.6	20.0	21.4	22.3	23.2	24.2	25.0	25.9	10.0
10G	6.6	12.7	15.6	16.6	18.3	19.5	20.9	22.0	23.0	23.9	24.7	25.8	11.5
10H	8.1	13.0	15.7	17.3	19.4	21.2	24.5	23.7	24.2	25.1	26.2	27.2	12.5
MEAN	7.4	12.4	15.5	17.0	18.7	20.2	21.9	22.6	23.5	24.5	25.5	26.6	11.4

2. TEST 15° C. with pO_2: 300 mm. Hg.

10A	1.3	2.4	3.3	4.8	5.9	6.6	7.1	8.3	9.5	10.7	11.1	12.2	24.5
10B	1.6	1.8	2.6	4.4	4.8	5.5	6.9	7.3	8.5	9.7	10.4	12.3	20.5
10C	1.8	2.0	3.4	4.6	5.2	8.6	9.6	10.6	11.6	12.3	13.9	14.3	25.0
10D	1.3	2.1	2.5	2.9	3.6	4.2	5.0	5.8	6.9	7.8	8.9	10.0	25.5
10G	1.5	2.3	3.2	3.6	4.2	4.8	5.9	6.8	7.7	8.4	9.0	9.9	26.0
10H	1.6	2.5	3.3	4.5	5.0	5.8	7.4	8.3	9.1	10.0	10.6	11.8	20.5
MEAN	1.5	2.2	3.0	4.1	4.8	5.9	7.0	7.8	8.9	9.8	10.6	11.7	23.7

Oxygen Consumption of Rat Liver Homogenates (μl. O_2/mg. N_2).

37° C. with pO_2 760 mm. Hg. VERSUS 15° C. with pO_2 760 mm. Hg.

1. CONTROL 37° C. with pO_2: 760 mm. Hg.

Expt.	Time (Min.) 10	20	30	40	50	60	70	80	90	100	110	120	Succinate Time (Min.)
16A	6.0	8.2	11.2	13.0	15.0	16.6	18.1	18.9	20.1	21.0	21.5	22.4	12.0
16B	6.6	8.7	10.9	11.3	13.0	15.0	18.7	18.7	20.6	22.3	23.4	24.4	11.5
16C	4.7	7.7	9.6	10.8	12.3	13.4	15.4	15.4	16.4	17.4	18.3	18.9	10.5
16D	5.5	9.3	12.2	13.7	15.6	16.8	19.3	19.3	20.5	21.3	22.0	22.9	12.5
16E	5.9	8.2	11.2	12.8	15.1	16.3	18.8	18.8	20.0	21.0	21.7	22.2	13.0
16F	4.6	7.5	9.1	12.6	14.8	16.7	19.2	19.2	20.1	21.7	22.2	23.8	12.0
MEAN	5.5	8.3	10.7	12.4	14.3	15.8	18.3	18.4	19.6	20.8	21.5	22.4	11.9

2. TEST 15° C. with pO_2: 760 mm. Hg.

16A	1.4	2.6	3.9	4.8	5.8	7.1	7.9	9.1	10.8	11.8	12 .6	13.9	20.5
16B	1.7	2.3	4.1	4.8	6.1	7.7	9.2	10.3	11.5	13.3	14.8	15.6	21.0
16C	1.1	2.0	3.0	3.4	4.8	5.9	6.9	8.2	9.4	10.4	11.5	12.4	25.0
16D	1.5	2.2	3.3	4.0	5.3	6.4	7.3	9.1	10.4	11.7	12.9	14.1	22.0
16E	1.7	2.6	3.0	4.1	5.0	5.7	9.5	9.3	10.4	11.8	12.5	13.6	24.0
16F	1.3	1.8	2.8	3.8	5.0	6.7	7.4	9.1	10.7	11.8	13.5	14.8	20.5
MEAN	1.4	2.2	3.3	4.1	5.3	6.6	8.0	9.2	10.5	11.8	13.0	14.1	22.2

Oxygen Consumption of Rat Liver Homogenates (Ul. O_2/mg. N_2).

37° C. with pO_2 760 mm. Hg. VERSUS 15° C. with pO_2 1520 mm. Hg.

1. CONTROL 37° C. with pO_2:760 mm. Hg.

	Time (Min.)												Succinate
Expt.	10	20	30	40	50	60	70	80	90	100	110	120	Time (Min.)
7A	6.0	8.4	12.8	14.9	15.2	16.6	17.8	18.4	19.9	21.6	22.2	23.2	10.0
7B	5.6	7.0	11.7	13.0	13.5	14.2	15.2	15.8	18.3	18.6	18.3	19.2	11.5
7C	5.7	8.2	12.2	14.3	14.9	15.8	16.9	18.2	19.4	20.3	21.9	22.9	13.0
7D	5.5	7.5	10.0	14.8	15.5	16.4	17.5	19.1	19.9	20.7	21.0	21.9	10.5
7E	5.6	7.4	10.0	14.6	15.2	16.1	17.2	18.6	19.6	19.8	21.5	22.4	8.5
7F	5.8	7.7	10.6	14.7	15.2	16.3	17.5	18.5	19.7	20.8	21.3	22.8	11.5
MEAN	5.7	7.7	11.2	14.4	14.9	15.9	17.0	18.1	19.5	20.3	21.2	22.1	11.2

2. ANOX 15° C. with pO_2: 1520 mm. Hg.

7A	1.6	2.5	3.0	3.5	4.0	5.0	6.2	7.9	8.3	9.6	10.0	11.1	29.0
7B	1.8	2.3	3.2	3.7	4.2	5.2	6.1	6.4	7.4	8.4	8.5	9.1	27.0
7C	1.4	2.4	3.0	3.8	4.0	5.5	6.2	7.0	8.3	9.9	10.2	11.6	25.0
7D	1.3	1.5	2.4	3.6	4.0	5.0	6.5	5.8	8.2	9.9	10.1	11.1	24.5
7E	1.7	2.5	3.5	4.4	5.0	5.9	6.6	7.5	8.8	9.4	10.4	11.2	25.0
7F	1.4	2.0	2.9	3.8	4.2	5.4	6.5	7.0	8.2	9.6	10.6	11.5	27.0
MEAN	1.5	2.2	3.0	3.8	4.2	5.3	6.3	7.1	8.2	9.5	10.0	10.9	26.3

PROLONGATION OF THE TIME OF "SAFE" CIRCULATORY ARREST BY PRELIMINARY HYPERBARIC OXYGENATION AND BODY COOLING

GEORGE SMITH, M.D., F.R.C.S., F.A.C.S., I. McA. LEDINGHAM, M.B., J. N. NORMAN, M.D., T.A. DOUGLAS, B.Sc., Ph.D., M.R.C.V.S., E. H. BATES, M.B., F.R.C.S., and F. D. LEE, M.B., Glasgow, Scotland

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PROLONGATION OF THE TIME OF "SAFE" CIRCULATORY ARREST BY PRELIMINARY HYPERBARIC OXYGENATION AND BODY COOLING

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THE PRINCIPAL DETERMINANT of the length of time for which the circulation can be stopped is the degree of anoxia which cells, particularly those of the nervous system, are able to sustain and yet recover normal function. It follows that prolongation of this safe period could be effected either by reducing the oxygen requirements of the cells or by ensuring that more oxygen than normal is present in and around the cells at the moment of circulatory arrest. The former requirement is met by cooling, the latter by allowing the organism to breath oxygen at tensions greater than normal.

By a combination of these 2 techniques, further advantages would be gained. The effect would not simply be additive, for as the body temperature is lowered the coefficient of solubility of oxygen in the body fluids increases. This is a simple solubility effect, so that the oxygen is readily available to the cells as opposed to the increasing difficulty encountered in the dissociation of oxyhemoglobin when the body temperature is lowered.

This article consists, therefore, of 2 sets of experiments performed on dogs. An attempt was made in group 1 to demonstrate that, in normothermic animals, prolongation of the safe time of circulatory arrest could be effected by increase of the tension of oxygen in the body. In group 2, an attempt was made to demonstrate that further extension of the safe period of circulatory arrest could be attained by use of hypothermia in conjunction with hyperbaric oxygenation.

METHODS

Healthy mongrel dogs were anesthetized with pentobarbital sodium injected intravenously in doses of 30 milligrams per kilogram of body weight. Endotracheal intubation was accomplished with a cuffed Magill tube which was connected through a Reuben valve to a soda lime canister and then to a 2 liter bag into which air or oxygen passed continuously. Through a fourth interspace thoracotomy on the right side, snares were placed around the venae cavae, centrally to the azygos vein. Before these snares were tightened, hyperventilation was produced with various tensions of oxygen for 10 minutes. After the venous inflow was shut off, the roots of the aorta and pulmonary artery were cross clamped. At the end of the period of circulatory arrest, the vessels were rendered patent in the reverse order.

In group 1 dogs, 3 subgroups existed, depending upon the oxygen tension of the gas with which the animals were hyperventilated prior to circulatory arrest. These were: (1) atmospheric air; (2) oxygen at 1 atmosphere of pressure; (3) oxygen at 2 atmospheres of pressure.

Since the safe arrest period of these normothermic animals would be measured in minutes, to detect any real differences between the subgroups it was essential that the hearts in all dogs should take up an adequate output quickly when the circulation was restored.

To this end, arterial p_H, carbon dioxide

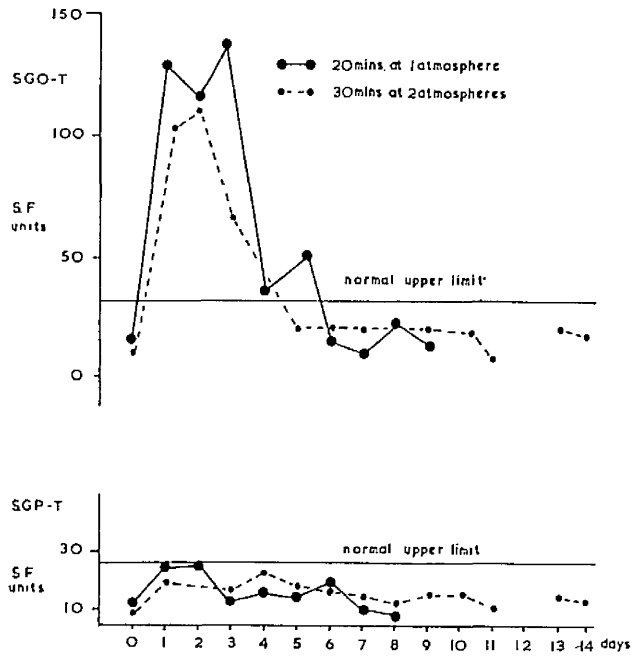

FIG. 1. Group 2. Levels of serum glutamate oxalacetate transaminase and serum glutamate pyruvic transaminase attained postoperatively in 4 dogs with circulatory arrest for 20 minutes after ventilation with oxygen at 1 atmosphere and in 4 dogs for 30 minutes after oxygen at 2 atmospheres of pressure.

tension, standard bicarbonate, and base excess were determined just prior to circulatory arrest by the micro-Astrup technique as reported by Anderson and his associates. In previous experiments of this type, a much more uniform success rate was obtained in establishing good cardiac action when the inflow-outflow arrest was discontinued if the animals were given 1 milliequivalent per milliliter of sodium bicarbonate solution intravenously before the clamps were applied. The dose administered was that which would afford a normal *p*H and no base deficit in the arterial blood at the end of the arrest period. In our experience, the formula which has proved satisfactory in calculating the dose of sodium bicarbonate for infusion is:

Animal weight (kgm.) × 0.43 [recorded base excess just prior to arrest (mEq./L.) + (1 mEq. $NaHCO_3$ × time of arrest mins.)].

The factor 0.43 has been empirically derived and falls between that given by Astrup and his associates for the extracellular body space and that given by Palmer and Van Slyke for the whole body in corrections for nonrespiratory disturbances of acid-base balance.

In group 2 dogs, this correction was not carried out. In these animals, cooling was effected by immersion in an ice water bath so that the nasopharyngeal and midesophageal temperatures at the inception of circulatory arrest was 27 ± 1 degree C. The 2 subgroups of the group 2 dogs were those ventilated for 10 minutes prior to circulatory arrest (1) with oxygen at 1 atmosphere of pressure and (2) with oxygen at 2 atmospheres of pressure. After restoration of circulation, adequate heart action was ensured by massage after electrical defibrillation, if necessary.

Thereafter, the chest was closed and the dog allowed to recover. In the ensuing days and weeks, the clinical condition of the dogs was carefully observed, particularly with respect to evidence of damage to the central nervous system.

Serum electrolytes, nonprotein nitrogen, serum glutamate oxalacetate transaminase, and serum glutamate pyruvic transaminase in venous blood were estimated before induction of anesthesia and daily, thereafter, for from 8 to 10 days. At various times after arrest, the dogs were sacrificed, and histologic examination of the organs was carried out, particular attention being paid to the brain, myocardium, and kidneys of those animals which had undergone the longer periods of arrest.

In the group 1 dogs, the initial period of circulatory arrest was 3 minutes and 2 dogs in each of the 3 subgroups were so subjected. With subsequent pairs the time of arrest was increased by 1 minute.

In the group 2 dogs, the initial period of circulatory arrest was 10 minutes, and 4 dogs in each of the 2 subgroups were so subjected.

For the subsequent group of 4 dogs, the arrest period was increased by 5 minutes.

The safe circulatory arrest period in the various groups was considered as that from

which all the dogs in any one group showed no permanent neurologic damage. The earliest evidence of damage appeared to be minor degrees of ataxia and head "weaving" which frequently disappeared within a few days. More severe damage was permanent ataxia and blindness.

In group 1, the following were considered to be the maximal safe circulatory arrest times: hyperventilation with room air prior to arrest, 4 minutes; with oxygen at 1 atmosphere of pressure, 5 minutes; with oxygen at 2 atmospheres of pressure, 8 minutes.

In group 2, the corresponding times were as follows: hyperventilation with oxygen at 1 atmosphere of pressure, 20 minutes; with oxygen at 2 atmospheres of pressure, 30 minutes.

In these animals, the biochemical changes determined by the electrolytes and urea levels were so slight that discussion will be limited to the changes in the serum transaminase levels of the group 2 dogs subjected to the maximal apparent safe arrest times and of those in which these times exceeded 5 minutes. The results are given in graph form in Figures 1 and 2. It appears that the degree of cell damage as indicated by daily determination of both serum glutamate oxalacetate transaminase, and serum glutamate pyruvic transaminase is about the same in the animals subjected to circulatory arrest for 20 minutes at 1 atmosphere and for 30 minutes at 2 atmospheres of pressure. When these times are exceeded by periods of 5 minutes, the elevations of serum transaminase levels in the 2 groups are again comparable, but at higher levels.

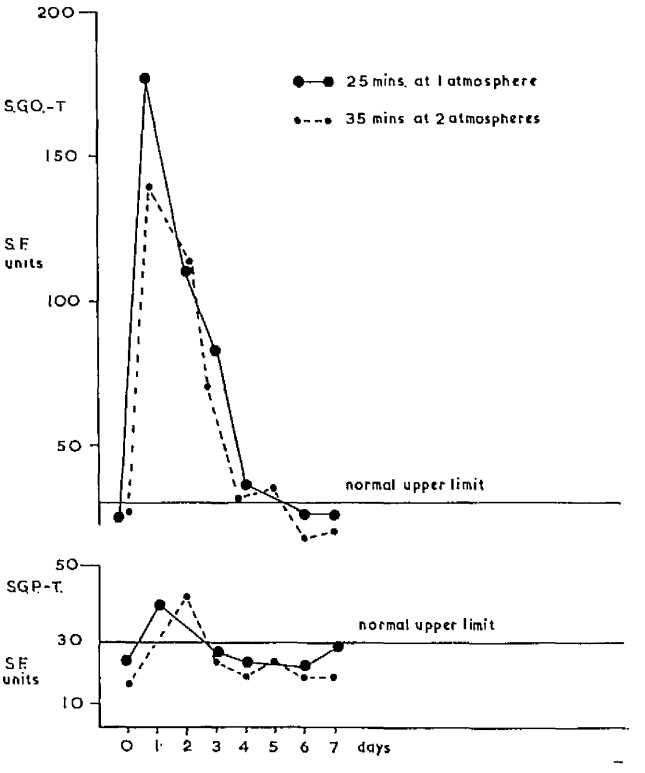

FIG. 2. Group 2. Levels of serum glutamate oxalacetate transaminase and serum glutamate pyruvic transaminase attained postoperatively in 4 dogs with circulatory arrest for 25 minutes after ventilation with oxygen at 1 atmosphere and in 4 dogs for 35 minutes after oxygen at 2 atmospheres of pressure.

PATHOLOGY AND HISTOLOGIC CHANGES

Postmortem examination was carried out on all dogs at the time of sacrifice, up to 134 days after operation. Detailed histologic examination was made of the myocardium, kidneys, lungs, liver, pancreas, and gastrointestinal tract. The brains were removed intact and, after fixation, sections were examined, macroscopically, for damage, while detailed histologic examination was carried out upon sections obtained from the cerebral cortex, the basal ganglia, and the cerebellum. Fixation was effected with 10 per cent formalin saline immediately after death with subsequent postfixation in mercuric chloride-formalin. Paraffin sections were stained with hemalum-eosin and, in addition, hematoxylin-van Gieson, Masson's trichrome, Mallory's phosphotungstic acid hematoxylin, Heidenhain's iron hematoxylin, and the van Kossa technique for calcium deposition were used when necessary, particularly for elucidating the nature of the changes in the heart muscle. A standard block was taken from the apex of the left ventricular muscle in all dogs. Material for histologic examination was taken from the group 2 dogs, from 6 of the dogs subjected to oxygen at 1 atmosphere of pressure and with the circulation arrested for 10 minutes in 2, for 20 minutes in 1, and for 25 minutes

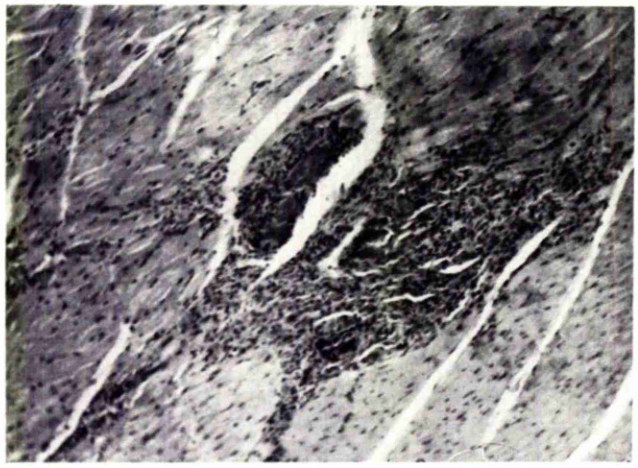

FIG. 3. Aggregations of necrotic cardiac muscle fibers with marked histiocytic infiltration. ×74.

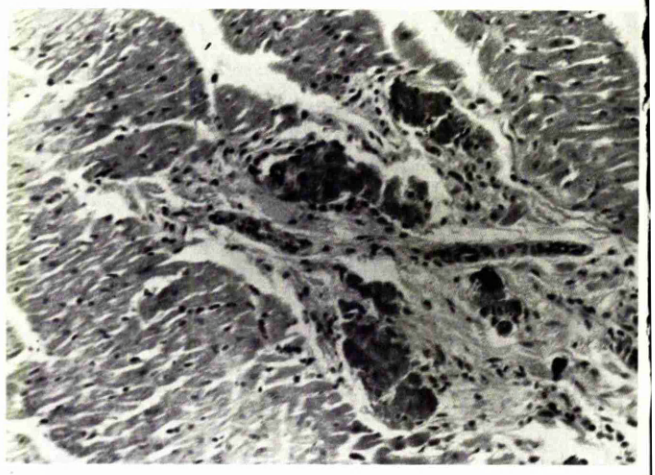

FIG. 4. Remnants of necrotic cardiac muscle fibers with calcium deposition 55 days after operation. ×116.

in 3 dogs, and from 10 dogs hyperventilated with oxygen at 2 atmospheres of pressure. These had undergone circulatory arrest for 30 minutes in 4, for 35 minutes in 4, and for 40 minutes in 2 dogs.

In 2 of the 3 dogs in which arrest had been effected for 25 minutes at 1 atmosphere of oxygen and in 2 of the 4 in which it was continued for 35 minutes at 2 atmospheres of oxygen, numerous focal lesions were scattered irregularly throughout the whole thickness of the myocardium. This was not true with shorter periods of arrest. The lesion consisted of aggregations of necrotic muscle cells associated with marked histiocytic infiltration (Fig. 3). Phagocytosis of necrotic muscle debris by histiocytes was a prominent feature. No polymorphonuclear infiltration was noted, possibly because the earliest stage at which this lesion was observed was at 10 days after operation. At a later stage in the evolution of this lesion, the necrotic foci were replaced by connective tissue. Remnants of necrotic muscle fibers could, however, persist for a considerable period of time and were observed 55 days post-operatively in 1 dog (Fig. 4). The necrotic muscle showed a marked affinity for calcium salts, but their deposition was not constant and did not appear to depend on the age of the lesion. Furthermore, the lesions were not all found at the same stage of evolution in any 1 case. The term microinfarct has been applied to this lesion which closely resembles the one resulting from hypothermia as reported by Sarajas and his associates (10, 11). Duguid and his associates have reported similar lesions in accidental hypothermia in man.

Myocardial damage was evident, however, as well as microinfarction. Muscle fibers, singularly or in groups, which showed evidence of necrosis, were scattered throughout the heart muscle. The affected cells showed markedly eosinophilic protoplasm with partial loss of striation and pyknotic nuclei. There was no histiocytic reaction (Fig. 5). The term necrobiosis has been applied to this change. It was seen not only in 3 of the 4 dogs with micro-infarction but also in the remaining dog in which arrest had been effected for 25 minutes with oxygen at 1 atmosphere and in 4 of the dogs arrested for 30 minutes at 2 atmospheres of pressure. The cause of the necrobiosis is uncertain. It may merely represent a less severe form of microinfarction, but it may indicate progressive muscle damage, since it was seen for as long as 134 days after operation.

No evidence of brain damage was found with an arrest period of 20 minutes at 1 atmosphere of oxygen and 30 minutes at 2 atmospheres.

In 1 dog in which the period of arrest was 35 minutes at 2 atmospheres there was a microscopic focus of necrosis in the cerebral

cortex. It is obvious, however, that a much more detailed examination must be carried out on these brains, and this is being done. Since the dogs arrested for 40 minutes at 2 atmospheres showed clinical neurologic damage, they were sacrificed 1 and 2 days postoperatively. Only in these 2 dogs did significant pathologic lesions develop, in the pancreas in one and in the intestines in both. At autopsy, intestinal hemorrhage was found, while, histologically, necrosis of the tips of the villi and of the superficial parts of the intestinal mucosa was evident without marked leukocytic infiltration. The necrotic process extended into the large intestine, but not into the stomach, in 1 animal. The intestinal lesions were comparable with those reported in man either after an intra-abdominal operation or, rarely, after resection of aortic coarctation or accompanying myocardial infarction associated with peripheral circulatory failure. In 1 of these dogs hemorrhagic pancreatic necrosis was found.

In this latter dog, acute tubular necrosis of the kidneys was also noted which was the only significant lesion detected in the kidneys of any of the dogs examined. Examination revealed that no damage had occurred in the liver and lungs of any of the dogs.

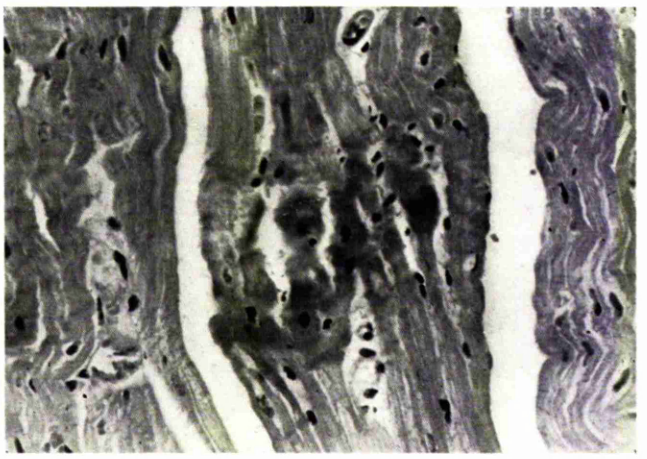

FIG. 5. Necrobiosis of cardiac muscle fibers with deeply eosinophilic cytoplasm, partial loss of striations, and pyknotic nuclei. Note lack of histiocytic infiltration. ×234.

DISCUSSION

From radioactive isotopic studies in which the isotope was placed in the left ventricle and subsequently the brain was assayed, we know that the method of vessel clamping used in this experiment does produce circulatory arrest. The observed prolongation of the safe circulatory arrest time would, therefore, appear to depend upon the increased tension of oxygen breathed prior to arrest, since the observed values of *p*H, carbon dioxide tension, and bicarbonate in whole arterial blood were comparable at that time in all groups of dogs. The relatively little difference in time between the normothermic dogs hyperventilated with air and those with oxygen at 1 atmosphere of pressure is puzzling, but this was noted previously by Smith and Lawson (12, 13) in experiments involving coronary artery occlusion. The difference observed, however, when prior hyperventilation is used with oxygen at 2 atmospheres appears to be significant.

If the times observed in the group 1 dogs are correct, then with a reduction of the body temperature to 27 degrees C. the metabolic requirements of the brain should be reduced to one-third as indicated by Rosomoff and his associates so that the expected safe times would be 15 and 24 minutes in those breathing 1 and 2 atmospheres of oxygen, respectively, prior to arrest. At this temperature, however, the solubility coefficient of oxygen is increased to 0.027. One would, therefore, expect that the safe time of arrest would be prolonged by more than a factor of 3. This expectation was realized. Furthermore, as the temperature of the body is lowered, the benefit accruing from oxygen dissolved in the body fluids and cells will be correspondingly enhanced, since the solubility coefficient of this gas in water increases from 0.027 at 28 degrees C. to 0.049 at 0 degrees C.

If even higher pressures of oxygen are utilized, the arrest times could be correspondingly extended provided that such tensions in themselves can be shown to be nontoxic to cells.

The benefits of an operating room in which the environmental pressure could be increased to 2 or 3 atmospheres absolute would seem to be particularly useful in those branches of surgery in which circulatory arrest or artificial circulation would be beneficial. As Haldane demonstrated in 1895, small mammals remain alive and conscious with very little available hemoglobin when placed in 2 atmospheres of oxygen. Boerema and his associates demonstrated the same phenomenon in pigs, using oxygen at a pressure of 3 atmospheres absolute, while a similar effect at 2 atmospheres absolute of oxygen was achieved in rats and cavies as reported by Lawson and his associates (6, 7). Thus, considerable saving of blood in heart-lung machine techniques might be effected by the substitution of plasma, and lower pump outputs might prove adequate.

The application of the present experiments appears to be more to the field of deep hypothermic arrest without oxygenators according to the method of Drew, or a combination of the 2 methods might possibly prove even more effective.

Again, in the field of intracranial surgery we (14) have already shown evidence of maintenance of cerebral activity under states of much diminished blood flow to the brain when oxygen was breathed at 2 atmospheres of pressure. The present experiments indicate that prolonged periods of total circulatory arrest to both the brain and the entire body might be possible in a pressurized operating room.

SUMMARY

Increasing the tension of oxygen in the body prior to circulatory arrest by breathing oxygen at 2 atmospheres of absolute pressure increases the time of "safe" circulatory arrest in normothermic dogs.

If this technique is combined with moderate hypothermia of 27 degrees C., the time of safe circulatory arrest is prolonged to 20 minutes by prior ventilation with oxygen at 1 atmosphere of pressure and to 30 minutes if this gas is used at a pressure of 2 atmospheres absolute.

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Oxygen Consumption of Rat Liver Homogenates ($\mu l. O_2$/ mg. N_2). 37° C. with PO_2 150 mm. Hg.

Time (Min.)

Expt.	10	20	30	40	50	60	70	80	90	100	110	120
4A	5.3	8.9	13.0	16.8	17.8	18.8	19.4	20.3	21.0	21.6	22.3	23.9
4B	7.7	10.5	12.6	15.3	19.9	21.1	22.4	23.4	24.4	25.5	26.3	27.2
4C	5.9	9.9	14.0	17.1	19.3	20.8	22.1	23.4	24.5	25.4	26.4	27.0
4D	5.5	12.1	16.1	18.8	19.6	20.0	20.4	21.1	21.8	22.4	23.1	23.8
4E	9.0	12.3	14.9	16.6	18.6	20.1	21.8	23.3	24.7	26.2	27.5	28.9
4F	6.3	10.3	12.5	15.9	18.2	20.4	21.4	22.7	23.6	24.7	25.2	26.3
8A	7.2	12.4	15.8	17.6	20.0	21.8	23.7	24.8	25.7	26.7	27.8	28.6
8B	6.0	10.5	15.3	17.7	18.5	20.3	21.4	22.8	23.9	25.2	25.9	26.4
8C	5.2	9.6	14.5	16.6	19.1	20.4	22.4	23.2	24.1	24.8	25.4	26.3
8D	7.0	10.1	12.4	14.8	16.7	18.2	19.2	20.3	21.4	22.8	23.6	24.6
8E	6.4	10.3	12.6	16.0	19.6	21.9	23.2	24.0	24.9	25.9	26.8	27.6
8F	6.4	10.9	12.7	15.9	19.2	21.2	22.5	23.0	24.1	25.5.	26.1	27.5
6A	6.6	12.3	15.6	17.9	18.8	19.9	21.8	23.6	24.3	25.1	25.9	26.6
6C	7.4	12.0	14.1	15.6	17.8	19.2	20.4	21.5	22.6	23.4	24.7	25.4
6D	8.1	13.0	15.3	17.1	18.9	20.3	21.5	22.7	23.6	24.4	25.2	25.9
6E	8.1	13.1	15.2	16.1	17.8	19.2	20.6	21.5	22.3	23.0	23.9	24.6
6F	5.7	11.4	15.7	17.9	19.9	21.8	23.7	24.8	26.0	27.3	28.2	29.1
6G	5.8	11.3	15.6	17.3	19.1	20.7	22.2	23.4	24.5	25.9	27.0	27.8
10A	8.2	12.7	15.0	16.3	18.0	19.2	20.3	21.3	22.4	23.2	24.0	25.7
10B	6.2	10.3	13.8	15.5	17.4	18.7	19.9	20.8	21.9	23.4	24.8	25.8
10C	7.3	12.2	16.8	18.6	20.6	22.8	24.2	25.4	26.4	27.4	28.5	29.4
10D	8.2	13.7	16.0	17.8	18.6	20.0	21.4	22.3	23.2	24.2	25.0	25.9
10G	6.6	12.7	15.6	16.6	18.3	19.5	20.9	22.0	23.0	23.9	24.7	25.8
10H	8.1	13.0	15.7	17.3	19.4	21.2	24.5	23.7	24.2	25.1	26.2	27.2
12A	6.6	12.5	17.1	19.1	21.3	22.0	23.4	24.9	25.8	26.8	27.9	28.5
12B	6.7	11.7	15.5	18.3	19.6	21.3	22.6	23.9	24.9	25.8	26.9	27.7
12C	7.3	13.8	17.5	19.7	20.8	21.8	22.8	23.4	24.8	25.4	26.4	27.4
12E	7.2	14.3	17.8	20.0	21.5	23.2	24.4	25.4	26.4	27.5	28.4	29.4
12F	4.6	8.9	13.3	15.8	17.6	18.6	20.5	21.4	22.5	23.4	24.1	25.1
12G	7.8	11.6	13.7	15.8	17.5	18.9	20.3	21.5	22.5	23.4	24.2	24.9
TOTAL	204.4	348.3	445.7	511.8	569.4	613.3	655.3	683.8	715.4	745.3	772.2	800.3
MEAN	6.8	11.6	14.9	17.1	19.0	20.4	21.8	22.9	23.8	24.8	25.7	26.7

Oxygen Consumption of Rat Liver Homogenates ($\mu l. O_2$/ mg. N_2). 37° C. with PO_2 760 mm. Hg.

Time (Min.)

Expt.	10	20	30	40	50	60	70	80	90	100	110	120
14C	7.2	10.1	13.0	14.4	15.6	17.0	18.0	19.4	20.5	21.6	22.5	23.3
14D	6.8	10.1	12.8	13.8	15.5	16.6	17.7	18.8	19.9	21.5	22.1	22.8
14E	9.3	13.5	16.7	17.9	19.6	21.2	22.4	23.6	24.7	25.0	26.2	27.4
14F	6.8	11.0	13.0	14.4	18.5	20.5	21.3	22.4	23.6	24.0	25.2	26.0
14G	6.6	9.8	13.8	14.1	15.5	16.1	17.1	18.9	19.2	20.2	21.4	22.2
14H	6.3	7.9	10.9	11.3	12.7	13.7	15.4	16.2	17.1	18.0	19.5	20.3
XA	4.2	9.6	11.9	14.2	15.9	16.9	18.3	19.2	20.1	21.0	21.5	22.3
XB	4.8	9.8	12.8	15.1	16.7	17.9	19.0	20.1	20.6	21.5	21.9	22.8
XC	4.8	8.9	11.3	13.9	15.4	16.5	17.6	18.6	19.5	20.5	21.7	22.1
XD	4.8	8.5	11.8	14.3	15.9	17.7	18.2	19.6	19.4	20.3	21.2	22.4
XE	4.3	9.9	12.5	14.9	16.6	18.0	18.9	19.8	19.7	20.4	21.3	22.4
XF	4.6	9.6	13.2	14.7	15.3	16.3	17.4	18.5	19.7	20.3	21.4	22.9
16A	6.0	8.2	11.2	13.0	15.0	16.6	18.1	18.9	20.1	21.0	21.5	22.4
16B	6.6	8.7	10.9	11.3	13.0	15.0	16.7	18.7	20.6	22.3	23.4	24.4
16C	4.7	7.7	9.6	10.8	12.3	13.4	14.4	15.4	16.4	17.4	18.3	18.9
16D	5.5	9.3	12.2	13.7	15.6	16.8	18.2	19.3	20.5	21.3	22.0	22.9
16E	5.9	8.2	11.2	12.8	15.1	16.3	18.0	18.8	20.0	21.0	21.7	22.2
16F	4.6	7.5	9.1	12.6	14.8	16.7	18.5	19.2	20.1	21.7	22.2	23.8
7A	6.0	8.4	12.8	14.9	15.2	16.6	17.8	18.4	19.9	21.8	22.2	23.2
7B	5.6	7.0	11.7	13.0	13.5	14.2	15.2	15.8	18.3	18.6	18.8	19.2
7C	5.7	8.2	12.2	14.3	14.9	15.8	16.9	18.2	19.4	20.3	21.9	22.9
7D	5.5	7.5	10.0	14.8	15.5	16.4	17.5	19.1	19.9	20.7	21.0	21.9
7E	5.6	7.4	10.0	14.6	15.2	16.1	17.2	18.6	19.6	19.8	21.5	22.4
7F	5.8	7.7	10.6	14.7	15.2	16.3	17.5	18.5	19.7	20.8	21.8	22.8
13A	6.1	11.3	14.5	17.2	19.0	20.0	21.3	22.4	23.5	24.7	25.7	26.6
13B	6.1	11.2	14.7	16.7	18.2	19.6	21.3	22.6	23.8	25.0	26.1	27.1
13C	6.5	8.9	12.1	13.9	16.3	17.5	18.8	20.2	21.7	23.1	24.5	25.3
13D	6.2	10.1	12.6	14.7	16.5	17.8	19.2	20.4	21.7	22.4	23.3	24.0
13E	5.6	9.9	12.3	14.0	15.6	17.0	18.2	19.6	20.3	21.5	22.4	23.0
13F	2.0	3.7	4.2	5.2	6.0	6.5	7.1	7.7	8.1	8.5	8.9	9.3
TOTAL	170.5	269.6	355.6	415.2	460.1	497.0	533.2	566.9	597.6	626.2	652.1	679.2
MEAN	5.7	9.0	11.9	13.8	15.3	16.6	17.8	18.9	19.9	20.9	21.8	22.6

SUMMARY

The therapeutic potentialities of hyperbaric oxygen have been intensively investigated in Amsterdam and Glasgow during the past decade but scientists have been interested in the biological properties of high pressures of air or oxygen since the discovery of the phenomenon of atmospheric pressure.

The use of hyperbaric oxygen can be classified into three main categories and examples of these form the three principal sections of this thesis:

1. The use of hyperbaric oxygen in anoxic states, such as carbon monoxide poisoning, where tissue oxygenation is maintained at adequate levels until the normal method of oxygen transport is restored.
2. The use of the metabolic effects of hyperbaric oxygen on normal tissues to reduce their oxygen consumption and thus prolong the period during which the circulation may be totally arrested as an aid to heart or brain surgery.
3. The toxic effects of hyperbaric oxygen, which may be

of use as selective toxic agents against malignant tumour cells or pathogenic bacteria.

CARBON MONOXIDE POISONING.

Killick and Marchant (1959) showed clearly that 5% carbogen removed carbon monoxide from the blood more rapidly than pure oxygen only but there was much controversy regarding the administration of carbon dioxide in an asphyxial state in which it was presumed carbon dioxide retention would already exist. Experiments are described which show that hyperventilation occurs during carbon monoxide intoxication causing respiratory alkalosis. When respiratory depression supervenes, the pCO_2 rises to normal levels only and carbogen mixtures are thus not contra-indicated in the treatment of this condition. Controversy next arose as to whether 5% or 7% carbogen would reduce the blood level of carboxyhaemoglobin more speedily and experiments are described which show that there is no difference between the efficiency of these agents in this respect. Experiments are also described in which it is shown that oxygen at two atmospheres pressure will reduce the blood-level of carboxyhaemoglobin about twice as fast as carbogen

mixtures and it is pointed out that the main benefit derived from this therapy is the rapid correction of tissue anoxia by dissolution of oxygen in physical solution in the plasma, thus by-passing the blocked haemoglobin mechanism. An account is also given of a group of patients treated successfully with oxygen at two atmospheres pressure.

METABOLIC EFFECTS OF HYPERBARIC OXYGEN.

In order to determine the metabolic effects on tissues of administering high pressures of oxygen for the relatively short periods of time required for heart surgery, the oxygen consumption of tissue homogenates was measured over a two hour period when the tissue was exposed to pressures of oxygen of 150 mm. Hg., 300 mm. Hg., 760 mm. Hg., or 1520 mm. Hg. at 37° C., 28° C. or 15° C. At 37° C. a linear depression in oxygen consumption was found as the pO_2 rose so that there was a 32% reduction in the oxygen consumption of tissue exposed to a pO_2 of 1520 mm. Hg. as compared to that exposed to a pO_2 of 150 mm. Hg. At 28° C. and 15° C. there was an initial rise in oxygen consumption with increasing pO_2 but beyond a certain level (about 500 mm. Hg. at 28° C. and 1000 mm. Hg. at 15° C.) further increase in oxygen pressure caused a fall in oxygen consumption. In terms of the prolongation of the safe period during which the circulation may be totally arrested

maximum benefit should be found at normothermia and though less is to be gained at hypothermia considerable advantage may accrue by ensuring adequate oxygenation at low temperatures.

Experiments, in dogs, show that the safe duration of total circulatory arrest at 37° C. can be increased from 5 minutes to 8 minutes if oxygen at two atmospheres pressure is breathed as compared to one atmosphere pressure. At 28° C. the time is increased from 20 minutes to 30 minutes while at 20° C. the safe duration of total circulatory arrest is 40 minutes whether the animal is breathing oxygen at one or two atmospheres pressure.

OXYGEN TOXICITY.

Ten rats exposed to oxygen at two atmospheres pressure for 18 hours died while another ten rats exposed for six hours survived. Of ten rats exposed for 12 hours, two died. Mortality was not avoided by administering the same total quantity of oxygen in three divided doses, each separated by twenty-four hours, but mortality was reduced to 50% of that obtained from continuous exposure for 12 or 18 hours. Clinically, neurological signs occurred in association with pulmonary signs and histologically there was patchy atelectasis, pulmonary oedema, thickening of alveolar septa and perivascular oedema in those rats which died.

Exposure of cultures of pathogenic bacteria to oxygen at two atmospheres pressure for 18 hours revealed a bacteriostatic effect which was particularly well marked with Pseudomonas pyocyanea and Aspergillus fumigatus, less well marked with Staphylococcus aureus and hardly seen with Proteus vulgaris or Escherichia coli. This implies a spectrum of bacterial sensitivity to

hyperbaric oxygen, which may prove a valuable adjunct in the treatment of infections by certain organisms.