HYPERBARIC OXYGEN

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THE BIOLOGICAL effects of oxygen at increased atmospheric pressure have been studied since both oxygen and atmospheric pressure were discovered. Apart from the specialised interests of compressed air workers and divers, however, careful scientific appraisal of the therapeutic potentialities of hyperbaric oxygen was not begun until the second half of this century. In 1955 Churchill-Davidson used hyperbaric oxygen in the oxygenation of the anoxic centre of tumours as an aid to radiotherapy, while Smith in Scotland and Boerema in Amsterdam investigated the possibilities of using oxygen at increased atmospheric pressure to prolong the period during which the circulation may be totally arrested with safety as an aid to cardiac and neuro-surgery. At this time also the Dutch workers devoted much of their time to an evaluation of the use of oxygen at 3 atmospheres pressure in the treatment of anaerobic infections while the Scottish School investigated the use of oxygen at two atmospheres pressure in resuscitation from coal-gas poisoning.

In carbon monoxide poisoning the tissues are hypoxic since the haemoglobin is no longer available for oxygen transport. The advantage of using hyperbaric oxygen in this condition is that as soon as the patient breathes oxygen at twice atmospheric pressure sufficient oxygen is dissolved in the plasma to oxygenate the tissues, thus by-passing the blocked haemoglobin mechanism. Although the immediate protection of the tissues from further hypoxic damage is the most important action of hyperbaric oxygen in carbon monoxide poisoning we have also shown that the high arterial P_{O_2} ensures a rapid dissociation of carboxyhaemoglobin such that when oxygen at two atmospheres pressure is breathed the blood is half cleared of carbon monoxide twice as quickly as when 7% carbon dioxide in oxygen is breathed (Douglas, Lawson, Ledingham, Norman, Sharp, and Smith, 1962). The use of oxygen at twice atmospheric pressure in carbon monoxide poisoning has proved very satisfactory in clinical practice and a large series of patients have now been treated with success (Smith and Sharp, 1960;

FIG. 1.— External view of pressure chamber at Aberdeen.

FIG. 2.— Interior of pressure chamber at Aberdeen.

Smith, Ledingham, Norman, Sharp and Bates, 1962; Douglas, Lawson, Ledingham, Norman, Sharp and Smith, 1964).

Most of these patients have been treated in large hyperbaric installations such as exist in Aberdeen and Glasgow. Figs. 1 and 2 show the hyperbaric chamber at Aberdeen. It consists of a cylindrical vessel some 21 feet long and 8½ feet in diameter, divided into a main chamber, 14 feet long, and an air-lock, 7 feet long. It is fully air-conditioned and has 8 power points. It is compressed with air, by twin compressors, at a maximum rate of 1 atmosphere in 3½ minutes. When the chamber is

FIG. 3—Mobile pressure chamber.

compressed, the patient breathes oxygen from any of the 6 oxygen inlet points. Frequent air changing prevents the accumulation of CO_2 or oxygen thus safeguarding the health of the staff and obviating the risk of fire. The air-lock is used for changing staff or equipment without decompressing the main chamber and there is a side-hatch in the main chamber which allows access for urgently required equipment in a matter of seconds.

While this type of unit is excellent for patient care and for research purposes it is very costly and is not available to the majority of victims of carbon monoxide poisoning. For this reason it was suggested (Smith, 1962) that small mobile pressure chambers should be built, capable of being transported in an ambulance and pressurised from an oxygen cylinder. These chambers should be sufficiently inexpensive to allow their installation in small hospitals and at sites where carbon-monoxide poisoning is likely to occur, such as at mines. To date, the chambers produced have been clumsy and expensive, but we are developing a model in conjunction with Normair Ltd. (Smith and Norman, 1966) which is light, versatile and inexpensive. This chamber, Fig. 3, could be used for a variety of purposes, such as the transport of patients suffering from carbon monoxide poisoning or traumatic shock to hospital, or for routine use in hospital in the treatment of patients suffering from such conditions as peripheral vascular disease, myocardial infarction or severe burns. It can also be used for radiotherapy.

Open Heart Surgery

The considerable advances made in the past 10 years in cardiopulmonary by-pass techniques have made the use of hyperbaric oxygen in adult open heart surgery less attractive but it still

has a useful part to play in neonatal patients suffering from severe intra-cardiac lesions, who require some form of surgery urgently for survival. Hyperbaric oxygen has indeed been used with considerable success in such patients by Gross and Bernhard (Bernhard and Tank, 1963; Bernhard, 1966) in Boston. Our first work in this field was in normothermic dogs, where it was shown that if the animal was given oxygen to breathe at atmospheric pressure then it was possible to arrest the circulation completely for 5 minutes with safety, but if the dog was given oxygen at 2 atmospheres pressure to breathe, then it was possible to arrest the circulation for 8 minutes with safety. While an increase of 3 minutes may be of little value, clinically it represents a considerable percentage increase in the permissible time of total circulatory arrest and hardly seems consistent with the extra quantity of oxygen stored, before the establishment of circulatory arrest, when oxygen was breathed at two atmospheres pressure instead of one. Parallel studies of tissue homogenates examined *in vitro*, however, showed that as the tension of oxygen to which the tissue was exposed rose, the consumption of oxygen fell. Thus the consumption of oxygen by these tissue homogenates was reduced by some 30% when the tissue was exposed to oxygen at 2 atmospheres pressure compared to air at atmospheric pressure (Norman, Douglas and Smith, 1966). This helped to explain the *in vivo* experiments in dogs: more oxygen was supplied and less was required. It also seemed reasonable to expect that if hypothermia was now added to the system, that considerable periods of "safe" circulatory arrest might be obtained since more oxygen would be supplied and two factors tending to reduce tissue oxygen requirements would be at play.

A further two series of circulatory arrest experiments were then carried out at hypothermia, one at 28°C and one at 20°C (Smith, Ledingham, Norman, Douglas, Bates and Lee, 1963; Ledingham and Norman, 1965). In this case it was shown that at 28°C the circulation could be arrested with safety for 20 minutes if the animal breathed oxygen at atmospheric pressure and for 30 minutes if the animal breathed oxygen at twice atmospheric pressure. At 20°C it was found that the circulation could be totally arrested for only 40 minutes whether the animal breathed oxygen at one or two atmospheres pressure. The explanation for the apparently paradoxical results was found by further *in vitro* studies of tissue homogenates. It was observed that, at 28°C , as the oxygen tension

to which the tissue was exposed rose, the oxygen consumption also rose until the exposure P_{O_2} reached about 500 mm. Hg. Thereafter the oxygen consumption fell. The overall reduction in oxygen consumption when the tissue was exposed to 2 atmospheres of oxygen at this temperature, was, however, only 10% compared to exposure of the tissue to air. Again at 15°C, as the oxygen tension to which the tissue was exposed rose, the oxygen consumption also rose until the P_{O_2} reached about 1000 mm. Hg., after which the oxygen consumption fell. There was, however, no difference in oxygen consumption of the tissue exposed at this temperature, to air at atmospheric pressure or to oxygen at 2 atmospheres pressure.

These *in vitro* results can be interpreted as suggesting that hypothermic tissues may require less oxygen than normothermic tissues partly because their requirements are less and partly because they are unable to utilise it unless it is supplied at a sufficiently high pressure. These results suggest that the optimum tissue P_{O_2} for tissue maintained at 28°C is about 500 mm. Hg. and about 1000 mm. Hg. for tissues maintained at 15°C. The better metabolic condition of hypothermic tissues exposed to an adequate oxygen tension is reflected in the biochemical parameters measured in the dogs subjected to 40 minutes circulatory arrest while breathing oxygen at 1 or 2 atmospheres pressure (Table 1).

Local Ischaemia

One of the main clinical applications of hyperbaric oxygen is the treatment of local ischaemia as it occurs in such sites as the heart, limbs or the bowel. We have treated a large series of cases suffering from peripheral vascular disease from various causes, and these cases have been divided into those suffering from some form of degenerative disease such as atherosclerosis, diabetic arteritis or thrombo-angiitis obliterans and those suffering from arterial insufficiency following trauma, due to accidents or from cold. The assessment of the majority of the cases has depended largely upon clinical evaluation and serial photography but the recent improvements in polarographic and other micro-analytical techniques have enabled a more critical judgement to be made of the effect of hyperbaric oxygen on the patients. Our general impression has been that hyperbaric oxygen is only of limited value in the

TABLE 1

% INCREASE DURING CIRCULATORY ARREST

	1 At. O_2	2 At. O_2
Potassium	58	36
Phosphate	49	22
Lactate	40	23
Excess Lactate	22	9

Biochemical measurements made after total circulatory arrest for 40 min. in dogs cooled to 20°C. One group breathed oxygen at atmospheric pressure and the other oxygen at twice atmospheric pressure.

treatment of vascular insufficiency resulting from atherosclerosis although it has occasionally been possible to heal an ischaemic ulcer and thereby to delay amputation or to carry out more distal amputation than at first appeared possible. The exception to this general rule is angiitis obliterans: six cases have been treated intermittently with hyperbaric oxygen and in five the ischaemic lesion has healed and amputation averted. Astrup (1964) suggested that patients suffering from thrombo-angiitis obliterans may have a defect in oxygen carriage resulting in the oxygen dissociation curve being shifted to the left and thereby rendering the oxygen carried by the haemoglobin less readily available to the tissues. Although this is a tempting hypothesis which would readily explain the successful use of hyperbaric oxygen in these cases, we have not been able to confirm Astrup's findings.

Greater success has attended the treatment of vascular insufficiency following trauma, however (Smith, Stevens, Griffiths and Ledingham, 1961; Donald and Tankel, 1962; Smith, 1964). These patients have all been treated continuously with oxygen at 2 atmospheres pressure for 2 to 3 days, in the hope that if a trickle of blood is entering a limb it may be possible to dissolve sufficient oxygen in it to maintain the vitality of the limb until a sufficient collateral circulation becomes established. The effect of hyperbaric oxygen on one of the cases may be seen in Table 2. This patient had a compound fracture of the ankle, treated by internal fixation, and the foot subsequently became grossly ischaemic. The greatly improved metabolic state of the ischaemic foot following the institution of hyperbaric oxygen therapy can be seen from the measurements made on the venous effluent of the ischaemic foot compared to that of the undamaged foot (Table 2).

TABLE 2
TRAUMATIC ISCHAEMIA

	Po ₂	O ₂ Sat.	pH	pCO ₂	St. Bic.	Base Excess
1. Before Pressurisation						
(a) Injured leg	43	31.5	7.02	160	14.8	-14.5
(b) Normal leg	—	57.0	7.27	50	20.5	-4.2
2. Following Pressurisation						
(a) Injured leg	70	89	7.27	65	22.8	-1.3
(b) Normal leg	82	92	7.34	51	23.2	-0.8

Biochemical measurements made from the venous effluent of both feet when the patient breathed air at atmospheric pressure and then oxygen at two atmospheres pressure. The injured leg was the site of severe traumatic ischaemia.

Myocardial Infarction

Smith and Lawson (1958, 1962) showed a striking improvement in the survival of dogs whose circumflex coronary artery had been ligated provided the animals breathed oxygen at two atmospheres pressure instead of air. These results have subsequently been confirmed (Chardack, Gage, Federico, Cusick, Matsumoto and Lanphier, 1964) and Trapp and Creighton (1964) have shown that following ligation of the left anterior descending coronary artery in the dog, the mass of the resulting infarct is smaller if the animal breathes hyperbaric oxygen instead of air. Meijne (1965) has also shown an increase in the coronary artery back-flow in animals breathing oxygen at 3 atmos-

pheres pressure. Encouraging reports have been published on the use of hyperbaric oxygen in human myocardial infarction, but the results of a controlled clinical trial are not yet available. It seems reasonable to expect that the patients who may benefit most from this form of therapy are those whose condition is complicated by the development of a marked degree of cardiogenic shock. The course of such a patient treated by us may be seen in Figure 4. This patient was given oxygen at two atmospheres pressure to breathe for 36 hours.

Oxygen Poisoning

The use of hyperbaric oxygen is considerably limited by the occurrence of oxygen poisoning

FIG. 4.— Systemic blood pressure, heart rate and respiration changes occurring in a patient under treatment for cardiogenic shock following myocardial infarction. Acid-base measurements are also shown.

and much of our more recent work has been directed towards the elucidation of this syndrome, which has been variously ascribed to changes in the cerebral circulation, loss of the dual function of haemoglobin or inactivation of thiol-containing enzymes. It is uncertain which of these mechanisms is fundamentally responsible for oxygen toxicity, but it has become apparent that high pressures of oxygen cause numerous changes in the metabolism and blood flow of certain tissues.

It has been known for some time that hyperbaric oxygen causes cerebral vasoconstriction (Kety and Schmidt, 1946; Lambertson, Kough, Cooper, Emmel, Loeschoke and Schmidt, 1953; Jacobson, Harper and McDowell, 1963) and more recently Jacobson and Lawson (1963) showed that cerebral infarcts created in dogs by ligation of the middle cerebral artery were of greater size if the animal was given oxygen at two atmospheres pressure to breathe instead of air. Nevertheless, Smith, Lawson, Renfrew, Ledingham and Sharp (1961), demonstrated that the hypoxic brain of the dog could be protected if the animal was given oxygen at twice atmospheric pressure to breathe instead of air. This was done by observing that following ligation of the carotid and vertebral arteries while the animal breathed oxygen at 2 atmospheres pressure the EEG activity continued unaltered, whereas if air was breathed the EEG activity ceased within $\frac{1}{4}$ - $\frac{1}{2}$ minute. The reconciliation of these apparently conflicting results was supplied by Harper, Ledingham and McDowall (1965) who showed that cerebral vasoconstriction does not occur when oxygen at twice atmospheric pressure is breathed provided the brain has been first rendered hypoxic by reducing the arterial blood pressure to 50 mm. Hg. by haemorrhage.

Blood flow through the brain thus appears to be regulated to meet the requirements of the brain for oxygen although it has been suggested that reduction in cerebral blood flow in response to a high inspired oxygen tension is a physiological mechanism designed to protect the brain from the damaging effects of hyperbaric oxygen. The site of action of oxygen in the control of cerebral blood flow is not clear, however, since vasoconstriction does not occur in the hypoxic brain despite a high arterial P_{O_2} .

Cowley, Attar, Blair, Esmond, Ollodart and Hamshimoto (1965) have clearly shown that hyperbaric oxygen has an ameliorating effect on haemorrhagic and endotoxic shock and since the protective effect of hyperbaric oxygen on the

hypoxic brain had already been demonstrated by us, it seemed desirable to determine the effect of hyperbaric oxygen on the normal and hypoxic kidney. Renal blood flow was measured directly by collecting the left renal venous effluent into a measuring cylinder and then returning it to the circulation of the dog by means of a sigrumoter pump (Norman, Irvin, Skene and Smith, 1966). It was found that the renal blood flow fell linearly as an inverse function of the inspired P_{O_2} and that the magnitude of the fall was of the same order as that noted by Jacobson and others (1963) for cerebral blood flow under similar conditions of inspired P_{O_2} . Measurements of renal venous P_{O_2} showed that when 1 atmosphere of oxygen was breathed the renal venous effluent was supersaturated with oxygen. When these measurements were repeated at an arterial blood pressure of 60 mm. Hg., however, it was found that when oxygen at atmospheric pressure was breathed, the renal venous effluent was no longer supersaturated with oxygen and the renal blood flow was not altered from the value obtained when air was breathed. When oxygen at 2 atmospheres pressure was breathed, at this level of arterial pressure, the renal venous blood was once again supersaturated with oxygen and the renal blood flow fell by some 28% of the value obtained when air or oxygen at atmospheric pressure was breathed.

These findings suggest that both the hypoxic brain and the hypoxic kidney can be protected by hyperbaric oxygen but they may be damaged by supplying oxygen grossly in excess of their requirements. It could be concluded that these tissues function best within a relatively narrow range of P_{O_2} in much the same way as they function best within a relatively narrow range of pH.

Our investigations into the effects of various oxygen tensions on tissue metabolism has led to a reappraisal of the observation of Ivanov (1959) that high oxygen pressures protect mice from the lethal effects of cyanide. 150 mice were divided into three groups and each group was given 0.85 mg./Kg. potassium cyanide by intraperitoneal injection. The first group was given air to breathe, the second group oxygen at atmospheric pressure, and the third group oxygen at 2 atmospheres pressure. The results are shown in Table 3, where it can be seen that the percentage survival increases markedly as the inspired oxygen pressure increases. Although cyanide poisoning is becoming increasingly common in industry, our interest in these findings was mainly in the mechanism which had

TABLE 3
MORTALITY

Air	O ₂	O ₂
1 Atmos	1 Atmos	2 Atmos
48/50	28/50	10/50

Mortality of mice given a standard dose of potassium cyanide and treated with air or oxygen at one or two atmospheres pressure for two hours.

allowed oxygen to by-pass an apparently blocked metabolic pathway. It is possible that oxygen exerts its therapeutic effect by increasing the rate of detoxification of cyanide to a non-toxic thiocyanate or that it is due to a disturbance of the equilibrium between cytochrome oxidase + CN and cytochrome oxidase cyanide, driving the reaction to the left and freeing increased amounts of cytochrome oxidase for the continuance of cellular respiration. A third possible mechanism is that sufficient cellular respiration continues by some cyanide-insensitive pathway to enable continuance of life until the cyanide has been detoxified. This problem has not yet been finally elucidated but it has been shown that there is an increase in the oxygen consumption of tissues poisoned by cyanide and studied in a Warburg apparatus if the gas phase is changed from air to oxygen at atmospheric pressure (Skene, Norman and Smith, 1965, 1966).

Another recent observation made in this department of the metabolic activity of high oxygen pressures is the depressant action which it has on the secretion of acid and pepsin by the rat stomach (Caridis, Norman and Smith, 1966). The Shay pylorus ligation technique has been used and it has been shown that progressive increase in the oxygen tension breathed results in a reduction of acid and pepsin secretion until the former is nearly abolished when the rat has breathed oxygen at 2 atmospheres pressures for 9 hours. This is not part of a general depression in gastro-intestinal secretion since the other fractions of the gastric secretion are unaffected as are the secretions of the liver, pancreas and small bowel. The altered gastric secretion is not due to the physical effects of compression nor is it affected by histamine. It appears to be due to a direct action on the parietal cell of the gastric mucosa, probably in the nature of an enzymic inactivation. The precise nature of this action is still under investigation.

Whether these observations on gastric secre-

tion have any bearing on the treatment of peptic ulcer is open to doubt since the effect is transient and is gone within 48 hours of exposure to oxygen. In addition, the duration of treatment required to produce a marked effect is rather close to that needed to cause dangerous side-actions.

Although a gradual appreciation of the nature of oxygen poisoning is being acquired there has been no suggestion, as yet, as to how the susceptible tissues may be protected during hyperbaric oxygen therapy. It seemed reasonable, therefore, to discover whether oxygen toxicity could be used to clinical advantage, such as in the destruction of aerobic, pathogenic micro-organisms. McAllister, Stark, Norman and Rose (1963) re-opened this field by demonstrating that oxygen at 2 atmospheres pressure had a bacteriostatic effect on a variety of pathogenic, aerobic micro-organisms such as *Ps. pyocyanea*, *Staph. aureus*, *E. coli* and *Aspergillus fumigatus*. Further work in this department has suggested, however, that it is unlikely to be possible to use hyperbaric oxygen effectively in the treatment of generalised infections since it would not be possible to raise the tissue P_{O_2} to sufficient levels for sufficiently long to cause bacteriostasis without producing oxygen poisoning in the patient. The more likely application of these *in vitro* observations appears to be in the treatment of surface infections such as occur in burns and superficial wounds. In such cases it is possible to expose the infected surface to hyperbaric oxygen by means of a polythene bag, while the patient breathes air in a pressure chamber. Under these conditions treatment can be continued for as long as necessary. Experiments have been carried out in guinea-pigs to test this hypothesis (Irvin, Norman, Suwanagul and Smith, 1966). Capsules with gas inlet and removable tops were sutured over two wounds, one on each flank of the guinea pig. In one group of experiments the wounds were infected with *Ps. pyocyanea*, while in another group they were infected with *Staph. aureus*. The animals were placed in a pressure chamber breathing air at 2 atmospheres pressure and air was passed over one wound while oxygen was passed over the other. This treatment was continued for 72 hours and swabs were taken at 18 hour intervals, which showed a marked bacteriostatic effect on the wounds treated with oxygen, compared to air controls. This effect persisted for the duration of the treatment and indicates the need for further evaluation of this technique as a form of therapy for widespread surface infection,

which may be difficult to control with antibiotics. Considerable work is also being done on the mode of action of high oxygen pressures on bacteria and the indications are that it may be due to a mutation rather than an enzymic inactivation.

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