HIGH-PRESSURE OXYGEN THERAPY IN SOUTH AFRICA

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INTRODUCTION

Whenever man dares to transgress the boundaries of his normal environment, be it into the arid desert or the eternal cold of the polar regions, up to the great mountain heights, or into the stratosphere or outer space, his natural adaptability has to be augmented by his ingenuity in supplying himself with the necessary means of survival.

Long before space travel came within the bounds of possibility, the concept of the 'capsule', by means of which the explorer carries a small entrapped atmosphere with him, was applied to exploration of the ocean depths.

With dives being made with ever-increasing frequency and to greater depths, the strange new environment soon claimed its toll of the intrepid invaders. It rapidly became abundantly clear that it was not sufficient to rely on the simple expedient of supplying air to the diver, except in the shallowest of dives, but that the air had to be supplied under compression.

This again seemed simple enough in itself, but the diver was now exposed to the hazards of the formation of nitrogen bubbles in his vessels on re-emerging from the depths.

No single person contributed more to the understanding and the solution of the problems involved than the great physiologist, J. S. Haldane. As a member of the Admiralty Committee on Deep Water Diving, he was jointly responsible for the production of the decompression tables which revolutionized the techniques in use at that time. These tables were so accurate that they are still in regular use.

Arising from his experimental work on the physiology of respiration, Haldane, in 1895,[1] published a report on survival, and recovery, of animals suffering from carbon-monoxide poisoning. By placing these animals in an atmosphere of pure oxygen under pressure greater than that of the atmosphere, he was able to supply the required oxygen to the tissues, purely because of the great increase in oxygen in simple solution in the plasma, in spite of the complete conversion of the haemoglobin to carboxyhaemoglobin. By so doing he could achieve a 16-fold increase in the oxygen in simple solution in the plasma.

On this basic and very important fact is founded the whole concept of the treatment of human beings with oxygen under pressure, which is the subject of this article.

It is a sobering and rather humiliating thought that during the many years since Haldane's observation countless people must have died of carbon-monoxide poisoning, many of whom would undoubtedly have been saved with the aid of a simple apparatus which could have been manufactured in any competent engineeering shop at a reasonable price. Also, had this form of treatment been generally applied the development we are discussing in this paper would have occurred decades ago.

With the accent on diving, such recompression chambers were built and used, and are actually illustrated in Haldane's book, *Respiration,* which is the published record of the Silliman Lectures delivered by him in 1917. Their use was, however, reserved for physiological experiments and the elucidation of the hazards of diving.

In 1953 Lambertsen and his associates[2] published an extensive investigation into the dangers of oxygen intoxication.

So it was that the clinical value of this form of treatment remained unexplored until Boerema and his co-workers[3,4] produced pathological conditions in experimental animals and exposed these animals to oxygen under high pressure.

Since 1957 a number of articles have been published detailing the possible advantages and applications of oxygen under high pressure, with the unit of Prof. I. Boerema of Amsterdam in the lead, followed by the unit of Prof. C. F. W. Illingworth in Glasgow.[5]

The present paper is intended, firstly, to give a short review of the physiological aspects of this form of treatment, the experimental work already published, and the clinical application of the results of these experiments. Secondly, those patients already treated by this method at Karl Bremer Hospital are reviewed, together with a description of the very simple apparatus employed in their treatment, and an indication of the experimental work now proceeding in parallel with the clinical application.

PHYSICAL CONSIDERATIONS

1. *Terminology*

To avoid confusion and cumbersome descriptions, the following internationally recognized abbreviations are used:

ATA=absolute pressure. (The ATA scale includes the atmospheric pressure at sea level.)

ATU=the pressure-gauge reading=the pressure of the artificial atmosphere without inclusion of the sea-level atmospheric pressure. Therefore,

1 ATA=0 ATU
2 ATA=1 ATU
3 ATA=2 ATU
1 ATA=1 atmosphere
=± 15 lb./sq. inch
=1kg./sq. cm.
=735·5 mm.Hg
=pressure-gauge reading of 0 (ATU O)
2 ATA=2 atmospheres
=1 ATU
=pressure-gauge reading of 1 kg./sq. cm. or 15 lb./sq. inch
=pressure at a depth of 10 metres of water (33 ft.)

Barotrauma=injuries as a result of an increase in pressure (recompression).

Reversed barotrauma=injuries as a result of reduction in pressure (decompression).

2. *Barophysiology*

The body is considered incompressible, except for air-filled cavities, viz.:

1. The lungs.

2. The gas-filled intestinal tract.
3. The middle ear.
4. The paranasal sinuses.
5. Carious cavities within the teeth.

The gases in all these air-filled cavities obey Boyle's Law, which expresses the result of pressure changes by the following equation: $P_1V_1=P_2V_2$.

Following this, therefore, if a person with a total lung volume of 6,000 ml. is exposed to a pressure of ATA 3 (ATU 2) without breathing, his lung volume will be reduced according to the formula $P_1V_1=P_2V_2$, thus: $1\times6{,}000=3\times V_2$, i.e. $V_2=2{,}000$ ml. This decrease in volume is the result of recompression.

More important and more dangerous, however, are the problems experienced with decompression. A person exposed to a pressure of ATA 3 with a lung volume of 6,000 ml., would, if he holds his breath during decompression to ATA 1, increase the volume of air in his lungs according to the formula $P_1V_1=P_2V_2$, thus: $3\times6{,}000=1\times V_2$, i.e. $V_2=18{,}000$ ml.

Since the epiglottis is strong enough to withstand such an increased volume, the alveoli of the lungs will tear, with resultant catastrophic air embolism (reversed barotrauma).

If, as a result of fermentation in the intestinal canal, a large volume of gas is released, this will also expand on decompression, resulting in an excessive distension of the intestine, with a danger of rupture.

Similarly, the paranasal sinuses will accommodate a considerable volume of air during recompression, and should there be a partial obstruction to an ostium, as with a cold, the escape of this air during decompression may not be fast enough to prevent a build-up of pressure, which may reach such proportions that fracture of the bony walls of the sinus may occur.

A carious tooth may also suffer rupture as a result of a similar set of circumstances.

The eardrum is subject to a different danger—the possibility of damage with recompression as well as with decompression, should there be a partial occlusion of the nasopharyngeal canal. To obviate this danger divers are taught to pneumatize regularly during recompression, so as to equalize the pressure in the middle ear with that of the surrounding atmosphere. This is done by pinching the nose while forcibly expiring against this resistance.

With decompression, the pressure can again be equalized by constant yawning or swallowing.

PHYSIOLOGY OF OXYGEN CARRIAGE IN THE BODY

1. Oxygen Carriage

Oxygen is carried in the blood:

(*a*) In chemical combination with haemoglobin (oxyhaemoglobin).

(*b*) As a simple solution in the plasma.

It is obvious that contact between the haemoglobin and the oxygen is dependent on solution of the oxygen in the plasma and that all transference of oxygen from the alveoli to the red cells, as well as from the red cells to the tissues, must take place through the medium of the plasma.

Under normal circumstances the haemoglobin plays the greater part in the carriage of oxygen. Blood leaving the left heart is 95% saturated, with a haemoglobin value of 15·3 G. per 100 ml., which represents 19·5 volumes % of oxygen.

The oxygen in simple solution in the plasma, on tne contrary, only amounts to 0·25 volumes %. Although this may be a very small quantity it is extremely important because it represents that part of the oxygen immediately available to the tissues.

2. Increase in Dissolved Oxygen

This dissolved oxygen is capable of increase, since it obeys Henry's Law, which states that the solubility of a gas in a fluid is dependent on the partial pressure of the gas to which the fluid is exposed.

We find that plasma at body temperature at ATA 1 will dissolve 0·25 volumes % of oxygen, while at ATA 2 it will dissolve 2·2 volumes %, and at ATA 3 the same volume of plasma will dissolve 4·2 volumes %.

This gives a 16-fold increase in the volume of oxygen carried in solution in the plasma after inhalation at ATA 3, compared with inhalation at ATA 1.[5]

3. Rate of Diffusion into Tissues

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

If air is breathed at ATA 1, the partial pressure of the oxygen in the mixed capillary blood is ±87 mm.Hg. When oxygen is breathed at ATA 3, the partial pressure of the oxygen in the mixed capillary blood is increased 15-fold.[4]

When the main blood supply to a part of the body is so decreased that a definite ischaemia results, there is an increased gradient between the depressed partial pressure in the anoxic tissues and the artificially increased oxygen tension in the plasma, achieved by breathing oxygen at ATA 3. The result is that there is an acceleration of the rate of diffusion of oxygen into these anoxic tissues.

4. Oxygen Intoxication

This condition is well known and is the subject of careful control in the training of frogmen.

Two types of intoxication occur:

(*a*) *Oxygen syncope*. This is the least degree of oxygen intoxication and shows the electro-encephalographic (EEG) changes comparable with those of an attack of petit mal.

(*b*) *Oxygen convulsions*. Here the EEG shows changes comparable with those of an attack of grand mal.

Anticonvulsant drugs can control these epileptic attacks. The exact cause of their development is not clear, but various factors do play a part, such as:

(*a*) 'Stress' and hypoglycaemia.

(*b*) Carbon-dioxide accumulation in the tissues.

(*c*) The surrounding medium. A person immersed in a fluid medium such as water will more readily develop the signs of oxygen intoxication than a person surrounded by an atmosphere of air.

(*d*) The increase in pressure. The interval before the onset of oxygen intoxication decreases in proportion to the increase in pressure. The time varies, however, for each individual and for the same person from day to day.

(*e*) Repeated exposure. By means of repeated exposure,

experimental animals can be made resistant to oxygen intoxication.

The skin divers of the South African Navy may not dive to a depth of more than 33 feet of seawater, which is equal to ATA 2, with pure oxygen. In the recompression chamber, pure oxygen must never be used at a pressure higher than ATA 3.

Oxygen intoxication is treated by placing the patient in an atmosphere of air.

REVIEW OF EXPERIMENTAL WORK WITH HIGH-PRESSURE OXYGEN

1. *Carbon-monoxide Poisoning Treatment*

Haldane,[1] in his experiments with carbon-monoxide poisoning, found that oxygen at ATA 3 (ATU 2) was sufficient to maintain life in a resting mammal, even if no haemoglobin was available for oxygen carriage.

2. *Oxygen Requirements of Resting Body*

Boerema[2] and his co-workers, in experiments on hogs, found that when oxygen at ATA 1 is breathed the haemoglobin value may be reduced to 11 G. per 100 ml. before electrocardiographic (ECG) changes appear.

Exposing these same animals to oxygen at ATA 3 allowed the haemoglobin to be diluted to 0·4 G. per 100 ml. before the same ECG changes appeared. These animals could breathe normally and maintain their blood pressures.

There was a constant fall in the pH, which was of no serious import because the animals recovered fully after blood replacement.

These 2 experiments show that the dissolved oxygen in the plasma is sufficient, under these circumstances, to supply the greater part of the oxygen requirements of the resting body.

3. *Coronary-artery Occlusion in Dogs*

Ligation of the circumflex branch of the left coronary artery results in ischaemia of 40% of the ventricular muscle.

The controls breathing air and oxygen at ATA 1 had a mortality of 56%, while dogs breathing oxygen at ATA 2 had a mortality of 10%.[5]

4. *Cerebrovascular Occlusion in Dogs*

Bilateral occlusion of the carotid and vertebral arteries in dogs still allows a considerable collateral circulation through the muscles of the neck, so that death does not result immediately.

Here again a definite difference could be found between a control group breathing air and oxygen at ATA 1, where cessation of cortical function could be found very early on EEG examination, and a group breathing oxygen at ATA 2, which showed no EEG changes.

5. *Total Circulatory Standstill in Dogs*

High-pressure oxygen and hypothermia to 28°C. allowed a period of circulatory rest of 35 minutes in dogs, without any neurological or other complications. The superior vena cava, inferior vena cava, aorta and pulmonary arteries were clamped after the hypothermia and pressure had reached the desired levels.

In another experiment atriotomy and ventriculotomy were performed on dogs breathing oxygen at ATA 3, with hypothermia of 19°C. – 14·5°C. No extracorporeal circulation was used, and occlusion of the vena cava was found unnecessary. Irritation of the heart with fibrillation did not develop, and 2 days later these animals appeared normal.[5]

6. *Infections with* Clostridium perfringens

Table I indicates the results of Boerema's experiment, in which he injected *Cl. perfringens* into control animals and animals receiving oxygen at ATA 3.

7. *Treatment of Malignancy*

In 1953 Gray[6] indicated that tumour cells in mice became more sensitive to radiation if the oxygen pressure increased during radiation.

TABLE I. RESULTS OF EXPERIMENTAL INJECTION OF CL. PERFRINGENS*

Experiment	*Cl. perfringens*	*Controls*	*Oxygen at ATA 3*
A	0·25 ml. subcutaneously	All ill. 2 with ulcer	None ill. None with ulcer
B	0·5 ml. subcutaneously	All very ill. All with ulcer	None ill. 1 with ulcer
C	0·5 ml. intramuscularly	All very ill. All with ulcer. 2 died	None ill. 2 with ulcer

*In each experiment 8 animals were used — 4 test animals and 4 controls.

Kieler[7] found that blood oxygen tension a little below that in human arterial blood (10%) was the optimum for human leukaemic cells.

Proliferating leukaemic cells, tumour cells and normal immature cells that still have a capacity for multiplication, are sensitive to variations in oxygen tension.

It was suggested by Kieler that high oxygen concentrations *per se* might have a cytotoxic effect.

CLINICAL APPLICATIONS OF OXYGEN UNDER HIGH PRESSURE

Recently, a number of reports of the use of high-pressure oxygen in the treatment of various clinical disorders have appeared. These include the following:

1. Injury to the Main Artery of a Limb

High-pressure oxygen was used in those cases where, after repair of the artery, the viability of the limb was in doubt.[5]

2. Peripheral Vascular Diseases

These have been treated, with relief from the ischaemic pain during the treatment, improvement of the skin colour proximal to the lesion, and an acceleration of the development of a demarcation line between the viable and necrotic tissues.[5]

3. Carbon-monoxide Poisoning

This serious condition has been treated where the patients were moribund on admission. Under these circumstances the high-pressure oxygen acts in two ways:

(*a*) It keeps the patient alive during the critical period by means of the high concentration of dissolved oxygen in the plasma.

(*b*) The higher partial pressure of oxygen hastens the conversion of carboxyhaemoglobin to oxyhaemoglobin.

Within ½ - 1 hour after treatment began, the carbon-monoxide value of the blood was found to be nil and the patients had recovered consciousness. The absence of myocardial and cerebral complications was gratifying.[1,5,8] It must be emphasized that over and above the loss of haemoglobin because of its attachment to carbon monoxide, the dissolution rate of oxyhaemoglobin is retarded in the presence of carbon monoxide, thus further impairing the transfer of oxygen from the available oxyhaemoglobin to the plasma and through it to the tissues.

4. Barbiturate Poisoning

Medullary suppression in the more serious cases is apparently due to cerebral anoxia; this is reversed by means of the high-pressure oxygen.[5]

5. Radiation Therapy for Malignancy

Eight patients with either carcinoma of the breast or the lung were subjected to radiation while in an atmosphere of oxygen under pressure.[9]

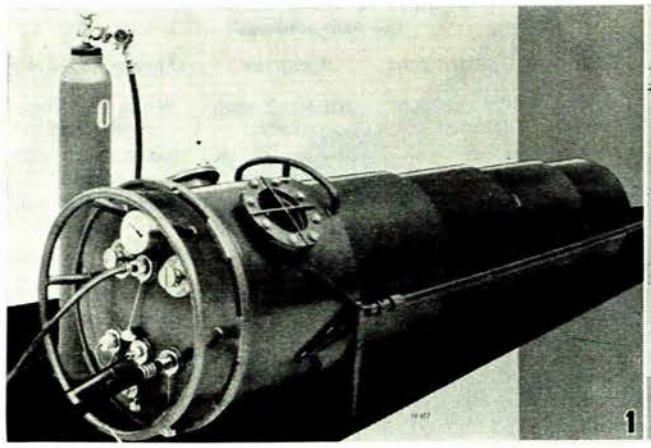


Fig. 1. External appearance of the recompression chamber.

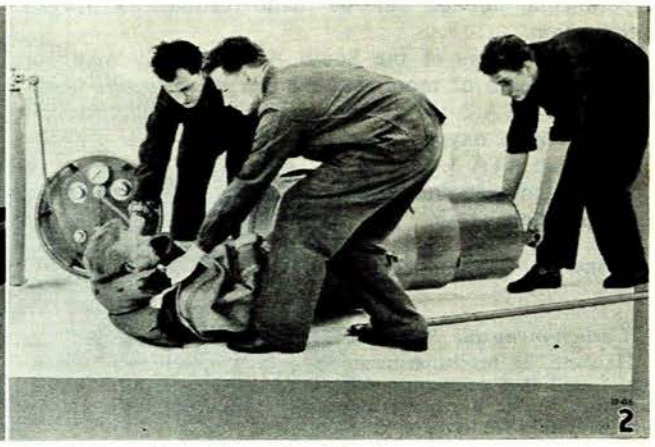


Fig. 2. A patient being placed in the chamber.

Figs. 1 and 2 are reproduced, by permission of the Draeger Co., from the Draeger catalogue.

6. Treatment of Anaerobic Infections

At the present stage of development, the treatment of anaerobic infections appears to be the most promising field, and one which is generally recognized as being past the experimental stage and ready for general clinical application.

Flooding the anaerobic phlegmon with plasma containing oxygen at a high partial pressure makes for cessation of the growth of the anaerobic organisms within the tissues able to be reached by this plasma.

The main reports of this method are those from the units of Professor Boerema in Amsterdam and Professor Illingworth in Glasgow.

THE APPARATUS USED IN TREATING PATIENTS AT KARL BREMER HOSPITAL

Lacking a full-scale recompression chamber, such as is used by the overseas workers, we made use of a one-man Draeger recompression chamber, which can be telescoped for transportation (Draeger catalogue No. 5500). Figs. 1 and 2 show the appearance of this apparatus, and how the patient is put into it.

Pressure is supplied by means of 1,000 cubic foot oxygen cylinders. On an average, 6 - 10 cylinders are required for each treatment lasting 2 hours at ATA 3 and a further 45 minutes for recompression and decompression.

Procedure Followed in the Use of this Recompression Chamber

1. Myringotomy is always performed before treatment to prevent barotrauma and reversed barotrauma to the eardrum. This is essential since communication with the patient does not allow instructions for pneumatization to be given.

2. If the patient is already receiving an intravenous infusion, at least 1,000 ml. of 5% dextrose in water is infused; otherwise glucose is given by mouth to counteract the tendency towards hypoglycaemia, which would predispose towards oxygen intoxication.

3. 'Pethilorfan' and 'phenergan' are given for sedation.

4. The patient is finally carefully examined, particularly with regard to the lungs, and the blood pressure, pulse and temperature are carefully checked. These readings are noted and are compared with those taken after treatment. Any secretions in the throat are sucked off.

5. The trunk is exposed, so that the respirations and the pulse rate can be counted visually, and so that signs of excessive sweating and abdominal distension (during decompression) can be seen. All these signs are important during the constant watch kept on the general condition of the patient.

6. It is ascertained that there is no trace of mineral oil on the patient or his clothing, since spontaneous combustion may occur in the presence of pure oxygen.

7. The apparatus is checked to ensure that every part is functioning properly.

8. The patient is placed in the pressure chamber and the oxygen flow is started before the door is sealed (Fig. 3).

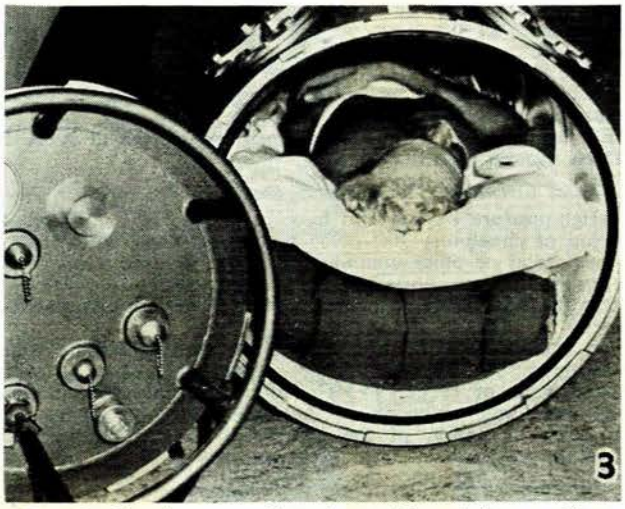


Fig. 3. Showing a patient in position before sealing the door.

9. Recompression to ATA 3 should not take less than 15 minutes, and the increase in pressure must be even.

10. Ventilation, at ATA 3, must be sufficient to prevent any accumulation of carbon dioxide. The exhaust gases are

readily tested for this by means of a simple apparatus (Draeger Gas Detector—model 19/31).

11. The patient is observed constantly, and pulse, respirations, general condition, and carbon-dioxide concentration in the ventilation gases are noted every 15 minutes. Should the patient show signs of excessive sweating the whole chamber can be cooled by covering it with damp towels and directing a large fan over them.

12. After 120 minutes at ATA 3 decompression is commenced. With pure oxygen there is no danger of developing 'the bends', but nevertheless distress is prevented by stepped decompression.

13. During decompression it is particularly important that the patient should breathe normally and not try to hold his breath (because of the danger of reversed barotrauma to the lungs).

14. The abdomen is observed particularly carefully during this period, and should excessive distension be noted it is imperative that partial recompression be carried out at once. The patient must then be encouraged to try to pass flatus, and if necessary even to pass a stool.

In the third case treated by us (a child of 4), this was a very real problem, and transport of the patient within the pressure chamber to the large recompression chamber at the Simonstown naval base was even considered. There, after the large chamber had been recompressed, the small one could have been opened and the child given an enema before further decompression was undertaken. Fortunately we did not need to do this, since the patient managed to pass flatus, thus reducing the abdominal distension.

15. Decompression is carried out in a step-like manner in accordance with Fig. 4.

REVIEW OF THE PATIENTS TREATED AT KARL BREMER HOSPITAL

Case 1

A White male, aged 59 years, was admitted to Karl Bremer Hospital in January 1962 after a massive ischiorectal abscess was drained elsewhere and his condition had deteriorated to a point where he was semi-comatose on admission.

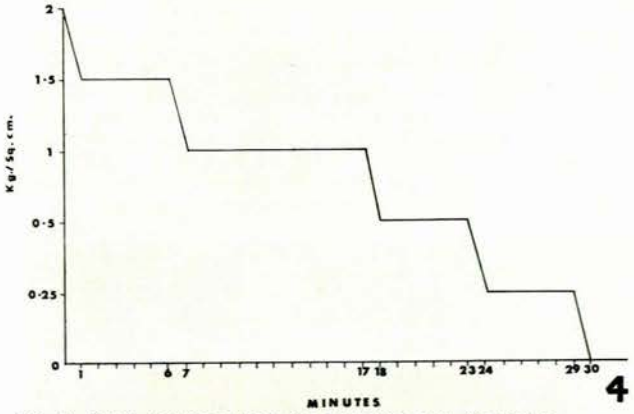


Fig. 4. Graph showing stepped decompression over 30 minutes.

There was an enormous surgical wound around the anus; it was grossly infected and discharging foul-smelling pus. The anus and rectum were virtually suspended freely within this enormous cavity. The left thigh was red, with signs of oedema and with several superficial blisters on the skin.

The serum electrolytes were normal, but the blood-urea level was raised to 72 mg. per 100 ml. Liver-function tests were normal, but the blood-cholesterol level was reduced to 67·6 mg. per 100 ml., while the serum-albumin level was reduced to 2·6 G. per 100 ml. and the globulin to 2·1 G. per 100 ml. Blood culture showed no growth after 17 days. Bacteriology of the pus showed the presence of *E. coli* and *Pseudomonas aeruginosa.*

The condition of the patient deteriorated steadily, and his blood-urea level rose to 142 mg. per 100 ml., together with signs of delirium tremens and early liver failure. On being given intravenous kanamycin and arginine his general condition showed a temporary improvement.

During this period of improvement a sigmoid colostomy was performed, and at the same time the skin and subcutaneous tissue, together with the deep fascia, which had by this time

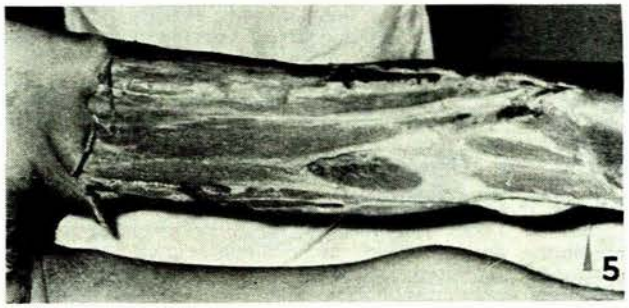


Fig. 5. Case 1—the exposed thigh muscles after excising the slough.

become completely necrotic, were removed from the whole circumference of the left thigh and the posterior aspect of the left leg (Fig. 5). In spite of this treatment the patient's condition again deteriorated and he became comatose.

Approximately a month after the initial abscess drainage the possibility of treating this condition by means of high-pressure oxygen was first mooted. The patient was placed in the chamber and recompressed to ATA 3 for a period of 2 hours. This was repeated on the following day.

In spite of an apparent considerable improvement in his general condition, he again deteriorated and died 24 hours after the second treatment. It was, however, noted that there was a considerable improvement in the appearance of the local lesions before death.

Case 2

A non-White female, aged 60 years, was admitted to Karl Bremer Hospital with an ischiorectal abscess on the left side. She was acutely ill, with gross anaemia and mental depression.

There was tenderness and rigidity over the whole abdomen. The haemoglobin level was 10 G. per 100 ml., the urine was brick-red to Benedict's solution and the fasting blood sugar was 123 mg. per 100 ml.

Incision of the abscess produced no pus, but thin frothy fluid bubbled out of the wound, and a wide excision of the necrotic subcutaneous tissue in the ischiorectal fossa was performed. At this stage the patient developed cardiac arrest; a left thoracotomy was performed and cardiac massage was carried out. The heart responded to this, but an ECG examination subsequently showed signs of an anterior septal infarct. Postoperatively the patient was comatose and active treatment for the diabetes was maintained.

Culture of the fluid from the wound showed that no clostridium was present, but that the fluid contained *Klebsiella pneumoniae, E. coli* and *Streptococcus faecalis.*

However, since the appearance of the lesion so closely resembled gas gangrene, the patient was recompressed on 4 occasions for 2 hours over a period of 3 days, and there is no doubt that there was a marked improvement of the local wound. Nevertheless, her general condition remained extremely grave, and she died 5 days after admission.

Case 3

A non-White child, aged 4 years, was admitted to the Paediatric Department of Karl Bremer Hospital with pain in the right lower leg, a swelling of the right ankle region, and a high temperature. The haemoglobin level was 6·2 G. per 100 ml. with a white-cell count of 3,000 per c. mm. and the

following differential count: staff cells 1%, polymorphs 37%, lymphocytes 58%, and monocytes 4%. The erythrocyte sedimentation rate was raised to 76 mm. in the first half hour.

From the time of admission the child was given 'bendralan', and tetracycline was subsequently added. The temperature remained elevated and began to swing after 10 days. In the absence of a response to the antibiotics the bendralan was stopped and 'staphcillin' was given in its place. Blood had been transfused, but he remained grossly anaemic.

At this stage a peri-anal swelling was noted, with a small area of necrosis on the surface immediately to the left of the anus. Incision produced no pus.

The necrosis spread very rapidly after this, to cover the whole of the left side of the perineum, extending anteriorly over the medial and anterior aspects of the thigh and the inguinal region. This was accompanied by rapid deterioration in the general condition, despite the addition of several further antibiotics. The rate at which this necrotic process extended was most disturbing; growing from an area 1 inch in diameter late on the day of the incision, to an area more than 9 inches in diameter 18 hours later.

At this stage the patient was recompressed in an effort to stop the spread of the necrosis.

The full 2-hour recompression to ATA 3 was performed, but during decompression the abdominal distension already mentioned developed, requiring partial recompression and later slow decompression. The total decompression time was eventually 155 minutes.

On removal from the chamber the patient passed flatus freely and also belched to help rid himself of the excess intestinal gas.

An X-ray picture of the abdomen (Fig. 6) showed multiple distended bowel loops, but there was no evidence of free gas in the abdomen nor did the lungs appear damaged. At this stage a flatus tube was passed with further relief, and by the next morning the abdominal distension had disappeared completely.

There was an immediate and dramatic improvement in the patient's general condition. Even more noticeable was the complete cessation of spread of the necrotic lesion, and no further recompression was indicated. Thirteen days after this treatment the necrotic tissues could be removed with ease under anaesthesia, a very clear demarcation line having developed (Figs. 7 and 8). At operation it was found that the necrosis included the skin, the subcutaneous tissue, and the deep fascia. The underlying muscles were normal in appearance, and rapid granulation followed this debridement. It was possible to carry out a skin graft two weeks later, which resulted in rapid healing.

Throughout this period the basic diagnosis remained in doubt, the most likely diagnosis being hypoplastic anaemia. There was a marked improvement in his blood picture after the therapy.

Approximately 7 months after oxygen therapy he was readmitted, acutely ill, with gross anaemia and septicaemia from which he soon succumbed. Postmortem examination was refused; therefore there is no further information available.

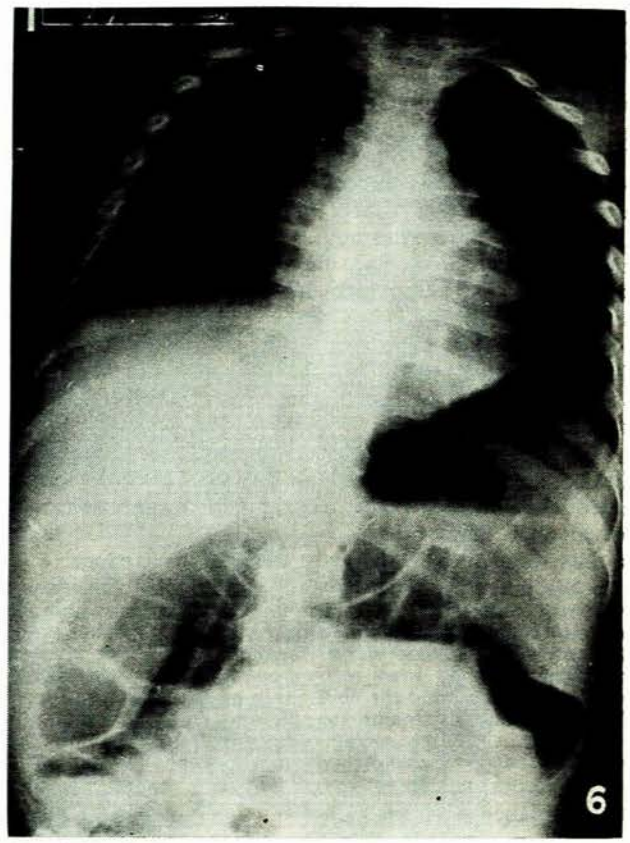


Fig. 6. Case 3—X-ray showing the degree of gaseous distension of the bowel following decompression.

An unconfirmed diagnosis of leukaemia was made, but it was noted that the local lesion for which he was recompressed showed complete healing.

Bacteriological findings: In this case also no clostridial infection could be found and the organisms grown on culture were the following: (1) *Staphylococcus aureus*, (2) *Proteus mirabilis*, (3) *Streptococcus faecalis*, (4) *Klebsiella pneumoniae* and (5) paracolon.

Case 4

A White male, aged 48 years, was comatose when he was admitted to Karl Bremer Hospital with a black necrotic lesion in the peri-anal region, extending posteriorly into the buttock and anteriorly into the region behind the scrotum. Incision released pus and gas with a most offensive odour.

Fig. 7. Case 3—the defect in the upper thigh after excision of the slough.

Fig. 8. Case 3—the mass of necrotic tissue that was removed.

He was dehydrated, the abdomen was tender, and the bowel sounds were very much reduced. The reflexes in the arms were reduced and those in the legs were absent. There was a previous history of alcoholism and pancreatitis, and the urine contained sugar and acetone. The level of the fasting blood sugar was 244 mg. per 100 ml. and the CO_2 content was 10·8 mEq. per litre.

The patient was immediately given treatment for the diabetes and was given penicillin, 'terramycin' and 'reverin', in an attempt to achieve the widest possible antibiotic cover pending the result of the bacteriological examination.

On the day of admission he was recompressed to ATA 3 for a period of 2 hours, and developed convulsions during decompression. The following day he was again recompressed, but after 30 minutes he developed such severe convulsions that it was decided to decompress him. Again during decompression he developed convulsions.

Further attempts at recompression were deferred until such time as his acidosis could be brought under control. There was, however, such a dramatic improvement in the local lesion without any signs of spread that further recompression was considered unnecessary. In parallel with this improvement in the local lesion his general condition also improved.

On the day after the second treatment it was possible to carry out a sigmoid colostomy and a debridement of the necrotic tissues in the peri-anal region.

Bacteriology: On bacteriological examination of the necrotic tissue, *Clostridium welchii, Proteus mirabilis, Klebsiella pneumoniae* and *Streptococcus faecalis* were isolated.

The diabetes remained difficult to control until 2 metastatic abscesses on his shoulder were found and drained. The pus from these abscesses contained *Staphylococcus aureus*.

A month after admission the patient was discharged with his diabetes completely under control and the peri-anal lesion rapidly healing.

Case 5

A non-White male, aged 35 years, was admitted to Karl Bremer Hospital under the influence of alcohol, with a knife-stab wound in the left forearm, received the previous day.

The arm was swollen, red, and tender from the shoulder to the hand, and there were blisters in the cubital fossa containing blood-stained fluid. Crepitus was palpable up to the shoulder. A sutured wound, approximately 2 inches long, was present over the ulnar aspect of the forearm approximately 2 inches below the elbow.

No peripheral pulses could be felt, and there was glove anaesthesia of the hand and wrist. The only motor functions of the hand were dorsiflexion at the wrist and full movements of the middle finger.

Crystalline penicillin, streptomycin and chloramphenicol were prescribed and the necrotic tissue in the region of the stab wound was excised under general anaesthesia. This material was sent for bacteriological examination and *Clostridium welchii* and paracolon organisms were grown.

Without waiting for the bacteriology report, high-pressure oxygen at ATA 3 was given for 2 hours a day on 2 successive days. A dose of 72,000 units of polyvalent anti-gas-gangrene serum was given intravenously. There was clinical and radiological improvement in the extent of the crepitus subsequent to the treatment (Figs. 9 and 10).

At the time of the excision it was noted that the necrotic process had spread inwards up to both the radius and the ulna and, although the blood supply to the hand itself appeared adequate, it was decided that an amputation was imperative, and this was performed 2 days after the second treatment. The level of amputation was 3 inches below the elbow, i.e. virtually at the height of the original wound.

The stump, which was left wide open, healed satisfactorily, and a month later a skin graft was successfully applied to the raw area. Subsequently an X-ray picture showed what appeared to be sequestrum in the stump. Seven weeks after admission the patient was discharged.

Case 6

A non-White male, aged 47 years, was run over by a train, sustaining bilateral traumatic amputation through the thighs. He was admitted to the orthopaedic department of Karl Bremer Hospital where the stumps were trimmed and left open.

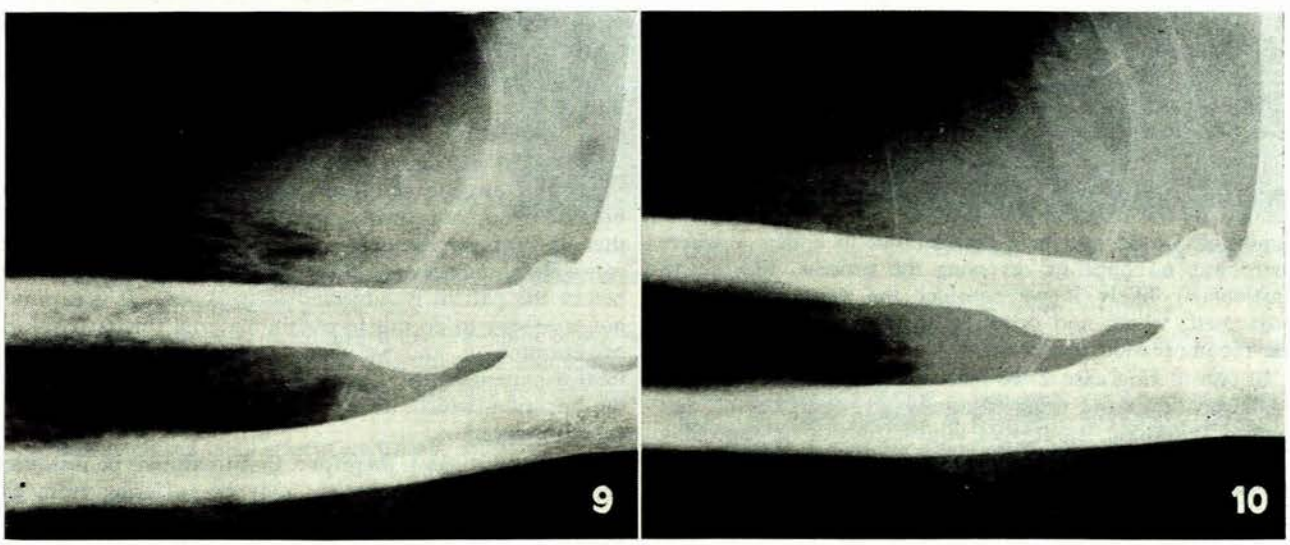
After a week he developed a necrotic area on the right stump and, since there was some discharge from it, a bacteriological examination was performed and *Clostridium welchii* organisms were grown.

Unknown to us an excision of this lesion was undertaken, and it was not until extensive gas infiltration of the tissues over the inguinal region was discovered at operation that the patient was presented for treatment.

Recompression to ATA 3 for 2 periods of 2 hours was undertaken with no further sign of anaerobic infection.

A week later a fresh culture was taken, and although there was no evidence of any inflammatory reaction or infection *Clostridium welchii* was again grown, but was looked on as probably saprophytic.

Recompression for another period of 2 hours was undertaken, and subsequent to this *Clostridium welchii* could not be grown.



Figs. 9 and 10. Case 5—X-rays showing regression of the gas within the tissues after 1 treatment. Fig. 9 (before treatment) and Fig. 10 (after treatment) were taken on successive days.

Case 7

A White female, aged 59 years, and a known diabetic, was admitted to Groote Schuur Hospital with a history of having had a low-grade inflammatory lesion of the right lower abdominal wall for 3 weeks before admission.

When she was transferred to Karl Bremer Hospital on 11 April 1963 she was found to have gangrenous areas of varying size on the abdominal wall, with multilocular abscesses discharging in a number of places. On culture, *Klebsiella pneumoniae* was grown. The patient's general condition was very poor, with a completely uncontrolled diabetes and threatening coma. On palpation there was suspicion of gas in the subcutaneous tissue.

Recompression to ATA 3 was performed for only 45 minutes, since the patient showed signs of claustrophobia and confusion. Even after the short period of treatment there was, however, a considerable improvement in her general condition. She was more orientated and it was possible to carry out a full treatment for 2 hours on the following day.

After this there was a dramatic improvement in the patient's general condition and the diabetes became controllable, so much so that 2 days after the treatment she developed a short period of hypoglycaemic coma after having been given 6 units of ordinary insulin. This was a measure of the drop in her insulin requirements.

Three days after the second treatment it was possible, without any anaesthesia, to undertake a debridement of the lesions, and all the necrotic skin, subcutaneous tissue and aponeurosis could be removed. A quantity of this material was sent for bacteriological examination and *Clostridium welchii* was grown.

This again supports the statement by Boerema that continued presence of infected necrotic material does not militate against improvement in the patient's general condition.

A week after the second recompression she was again placed in the pressure chamber for a full 2-hour period. Following this, bacteriological examination was negative for clostridia.

In spite of shockingly wide ulceration of the abdominal wall, the patient is progressing favourably, her morale is excellent and no insulin whatsoever is required.

Both cases 6 and 7 are still far from healed, but there is no reason to suspect that they should have any further complications as a result of their anaerobic infections.

Case 7 was referred to us by Prof. J. H. Louw of the Department of Surgery and Dr. H. Muller of the Department of Medicine at Groote Schuur Hospital, and we must express our appreciation that we were given the opportunity of treating her.

DISCUSSION OF THE CASES

In 2 of the 7 cases the anaerobic infection followed injury. In the remaining 5 cases there was a predisposing systemic disease, which must of necessity have contributed to the initiation and spread of the infective lesion.

If the treatment had been instituted at an earlier stage in case 1 it is possible that the infection may have been limited to the original site and that the patient's general condition would not have deteriorated to a degree where there was no hope of reversing the process. This seems particularly likely if we consider the very definite improvement which had occurred in the open lesions after the recompression treatment.

In considering case 2 we must assume that the patient's condition from the time of admission was so poor that the unfavourable result was almost inevitable, especially after the additional complication of cardiac arrest and subsequent respiratory problems.

The third patient very amply demonstrated the powerful effect of high-pressure oxygen treatment. Here we were dealing with a small child who, during intensive treatment with antibiotics, developed a massive, rapidly spreading, gangrenous lesion. The extension of this lesion was interrupted dramatically by means of this treatment. Associated with this improvement there was also a comparable and simultaneous improvement in his general condition and, in particular, his possibly leukaemic picture.

Case 4, also, in spite of the problems experienced, showed a dramatic improvement in his general condition and his local lesion.

Case 5 showed typical gas gangrene following on injury. The improvement experienced was so great that it was possible to perform a forearm amputation at the approximate height of the original lesion. Although the hand appeared to have sufficient blood supply an amputation was indicated by the absence of muscular function, and examination of the amputated forearm showed that the muscle masses were completely necrotic. Without this treatment the patient would, at best, have lost his whole arm.

Treatment was requested for case 6 after the operation for excision of the gas-filled tissues was abandoned because it appeared impossible to get ahead of the gas infiltration. Here again there was an immediate cessation of signs of anaerobic infection.

Case 7, although not presenting the signs of dramatically spreading gas gangrene, nevertheless was in dire peril. The remarkable change wrought in this patient could only be appreciated by observing her condition before and after the treatment. Although her general improvement continued it was not dramatically affected by the subsequent removal of the necrotic tissue.

Conclusions Regarding the Patients Treated

Even if the first 2 patients are considered to have been completely beyond saving, we were nevertheless struck by the considerable improvement achieved by the treatment they received. It is also possible that had these 2 patients been subjected to this treatment earlier their lives might have been saved.

In the third and fourth cases it is probable, if the treatment had been instituted earlier when the lesions were very small, that extensive excisions would not have been required.

In the fifth case it is acceptable that, had the patient been treated early enough, amputation may have been entirely avoidable.

In case 6 we regret that we were unable to treat this patient before any excision whatsoever was undertaken, because from our own experience, and this agrees with that of Professor Boerema and his co-workers, it appears completely unnecessary to excise any necrotic material before the patient is subjected to treatment. It is certainly not necessary to do this to obtain material for bacteriological examinaion, and we would suggest that it is better to treat a patient as early as possible to prevent extension of the infection, which, as is well known, can take place at a fantastic speed.

We would suggest, therefore, that treatment be instituted on suspicion that the patient may be suffering from gas gangrene, and that any debridement be left until after the treatment. The necrotic material will still contain the live organisms, but in this situation they are, for the time

being, innocuous, while those at the spreading edge of the lesion are readily destroyed by the high oxygen content of the plasma.

GENERAL CONCLUSIONS

It appears that we are on the threshold of a new development in therapy, which may prove to be of the very greatest importance.

It may result in a revolution in the treatment of a wide variety of conditions, both medical and surgical, where there is tissue the viability of which is in the balance.

However, before this form of treatment can really progress it is imperative that extensive clinical research on a much larger scale is carried out without delay. In parallel with this clinical research purely experimental work on animals should be continued on the lines indicated by the units of Professors Boerema and Illingworth.

We ourselves already have a small recompression chamber in use where various experiments on animals are being carried out.

PRESENT AND FUTURE EXPERIMENTAL PROJECTS

Apart from its use in anaerobic infections and in those experiments already mentioned above, hyperbaric oxygen therapy can be used whenever anoxia plays a part in a disease process, whether the anoxia is of central origin, viz. respiratory and/or cardiovascular, or whether it is of local origin. We therefore consider the following to be fruitful fields of investigation from this point of view:

1. *Shock*

(*a*) *Oligaemic shock*. In a traumatic unit hyperbaric oxygen therapy and plasma replacement will suffice as emergency treatment pending the preparation of blood for transfusion.

(*b*) *Toxaemic shock*. A patient with a hopeless prognosis following 70% thermal burns was treated, with improvement in his general condition and his mental confusion. Although this patient died the encouraging result left food for thought.

(*c*) *Irreversible shock*. Since anoxia is considered a major contributor to the development of lower-nephron nephrosis, the onset of this condition may possibly be prevented and its course interrupted by hyperbaric oxygen therapy.

2. *Anaerobic Infections*

Since the treatment of clostridial gas gangrene by this method now appears firmly established, treatment of other anaerobic infections must be considered.

Of particular interest is the treatment of tetanus, where the local lesion must obviously benefit, but there is as yet no certainty regarding the effect of the oxygen on the toxins already liberated.

There are, of course, many other less dramatic anaerobic infections, e.g. that caused by intestinal organisms, which may benefit.

3. *Vascular Occlusion*

Peripheral occlusion, both chronic and acute, could benefit from hyperbaric oxygen treatment, inasmuch as the onset of gangrene may be delayed. Furthermore, it may be valuable in helping a limb over the critical stages after operation for relief of such occlusion.

Cerebrovascular occlusion may benefit in the same manner, while cardiac infarction may be reduced in extent and life may be supported during the critical phase.

In mesenteric vascular occlusion doubtfully viable intestine may be saved.

The effect of renal-artery stenosis may be reduced pending preparations for operation, and again in the critical post-operative period.

4. *Respiratory Insufficiency*

Particularly if this is temporary or acute insufficiency superimposed on chronic insufficiency it may very well be a further application of this form of treatment.

5. *Head Injuries*

It has already been experimentally demonstrated that hyperbaric oxygen therapy can maintain normal cerebral function, and it seems clear that the clinical case should benefit where there is severe cerebral vasoconstriction in the early phase.

6. *Tissue Transplantation*

It may be possible to increase the size and length of skin pedicle flaps as well as to shorten the periods of 'delay' by improving the oxygenation of the transplanted tissue.

It is also possible that homotransplants of organs could benefit in the same manner.

7. *Obstetrical Practice*

Toxaemia of pregnancy may lend itself to treatment, both by protecting the kidney against damage and by restoring the rate of growth of the foetus.

If it is true that a constriction ring of the uterus during labour is partly due to ischaemia, it should improve on high-pressure oxygen treatment.

By the same token uterine contractions should in general become less painful, and the condition of the baby should be protected and improved by the high oxygen concentration.

However, retrolental fibroplasia is considered a dangerous complication, which may ensue from exposure of premature infants to high concentrations of oxygen. This is however by no means proved, and it has been shown that anoxia may produce the same changes. It is obvious that until this matter is clarified a mother in labour should not be exposed to hyperbaric oxygen except when it is considered necessary to save her life.

8. *Liver-cell Damage and Regeneration*

These may also be subject to modification by hyperbaric oxygen, and this treatment may be of great importance in hepatic artery damage or after partial hepatectomy.

9. *Certain Congenital Abnormalities*

These have been shown to result from local anoxia, and it may be possible to modify such changes by means of hyperbaric oxygen.

It is clear, therefore, that a wide field for research is offered by this development, and it is to be hoped that this research will be energetically pursued. As already mentioned, we have a small experimental pressure chamber in use for such research.

SUMMARY

Since the publication of the results of pioneer work on the use of oxygen under high pressure by the units directed by Professors Boerema of Amsterdam and Illingworth of Glasgow, a number of cases of anaerobic and suspected anaerobic infections, with extensive tissue destruction, were treated by this method at Karl Bremer Hospital.

Owing to the lack of a full-scale recompression chamber, the treatment was carried out in a small recompression chamber kindly lent by the Diving School of the South African Naval Forces.

The results of the short periods of intermittent recompression possible with this apparatus were so startingly good that the experience obtained in 7 cases is presented herewith.

The first 2 cases proved fatal, but this was not unexpected considering their extremely grave condition before treatment was instituted. In both cases there was a distinct improvement in the condition of the local lesion following

exposure to high-pressure oxygen (hyperbaric oxygen drenching—HOD).

In the remaining 5 cases there was a dramatic cessation of extension of the local lesion with a corresponding improvement in the general condition of the patient.

The possible applications of this new therapeutic measure in both medicine and surgery are as yet undetermined, but without doubt they will be many and varied.

It deserves intensive clinical and experimental research, so as to advance our present scanty knowledge to a stage where it can be made more generally and scientifically applicable.

ADDENDUM

Since the above paper was written, a further patient was offered for treatment.

He is a White male, aged 68 years, a diabetic, who was treated by his general practitioner for a small peri-anal lesion resembling a thrombosed external haemorrhoid. This was opened with relief, but 2 days later pain in the peri-anal region recurred, and after a further 2 days a large ischiorectal abscess was drained. It was noted that the pus was particularly foul.

Relief was immediate, but 1 day later the scrotum started swelling rapidly, and by that evening a small patch of gangrene developed on the surface of the scrotum in its midline. Crepitus could be felt, and at this stage the patient was sent to us for treatment.

On examination at this time we found an obviously gangrenous area extending on to the base of the penis, inferiorly, with an inflammatory phlegmon extending on to the pubis and into the line of the inguinal canal on both sides.

The edge of this was marked and the patient was then recompressed to ATA 3 for a full 2 hours. By the next morning his general condition was much improved, with extension of the phlegmon by approximately 1 cm. in one small area on the left side.

He was again recompressed on that and the following day, with cessation of extension of the phlegmon. The day after treatment stopped the necrotic tissue was excised without anaesthesia and sent for culture.

At this stage it was noted that there was still a steady, although very slow, advance of the black necrotic edge of the lesion, and a fourth recompression was carried out on the day after the excision. It was gratifying to note that the extension stopped forthwith after this last treatment.

This patient is progressing favourably and there has been a complete regression of the phlegmon, except for a small area over the left external inguinal ring. The peri-anal wound and the scrotal skin defect are already showing signs of rapid diminution in size. No clostridia have been isolated.

We are grateful to Drs. A. A. Brown, I. Grayce, S. Stein and J. Gelb for kindly referring this patient to us.

We take pleasure in expressing our appreciation to the Chief-of-Staff of the South African Naval Forces, Rear-Admiral H. H. Biermann, and the personnel of the South African Naval Diving School for the help and cooperation which we have received, and are still receiving, from them.

We must also express our gratitude to Prof. F. D. du T. van Zijl, Professor of Surgery at the University of Stellenbosch, for his encouragement in our treatment of the patients mentioned above, and to Dr. R. L. M. Kotze, Medical Superintendent of Karl Bremer Hospital, for permission to publish the details of the patients.

REFERENCES

1. Haldane, J. S. (1895): J. Physiol., **17**, 104.
2. Lambertsen, C. J., Kough, R. H., Cooper, D. Y., Emmel, G. L., Loeschcke, H. H. and Schmidt, C. F. (1953): J. Appl. Physiol., **5**, 471.
3. Boerema, I. (1961): Surgery, **49**, 291.
4. Boerema, I., Brummelkamp, W. H. and Hoogendijk, J. (1961): Surgery, **49**, 299.
5. Illingworth, C. F. W., Smith, G., Lawson, D. D., Ledingham, I. McA., Sharp, G. R. and Griffiths, J. C. (1961): Brit. J. Surg., **49**, 222.
6. Gray, L. H. (1953): Brit. J. Radiol., **26**, 609.
7. Kieler, J. (1957): Acta pharmacol. (Kbh.), **13**, 301.
8. Lawson, D. D., McAllister, R. A. and Smith, R. A. (1961): Lancet, **1**, 800.
9. Churchill-Davidson, I., Sanger, C. and Thomlinson, R. H. (1955): *Ibid.*, 1, 1091.

BIBLIOGRAPHY

Brummelkamp, W. H., Boerema, I. and Hoogendyk, L. (1963): Lancet, **1**, 235.
Illingworth, C. (1962): Brit. Med. J., **2**, 1271.
Smith, G., Sillar, W., Norman, J. N., Ledingham, I. McA., Bates, E. H. and Scott, A. C. (1962): Lancet, **2**, 756.
Smith, G., Stevens, J., Griffiths, J. C. and Ledingham, I. McA. (1961): *Ibid.*, **2**, 1122.