ANAESTHESIA FOR RADIOTHERAPY UNDER HIGH-PRESSURE OXYGEN

BY

C. SANGER

Department of Anaesthetics

I. CHURCHILL-DAVIDSON

Department of Radiotherapy

AND

R. H. THOMLINSON

Department of Pathology

St. Thomas's Hospital, London

FOLLOWING experimental work on anim-
als it has been suggested that the
effectiveness of X-ray treatment of
tumours may be increased by the simul-
taneous administration of oxygen under
high pressure (Gray et al., 1953). To de-
termine if these results were applicable to
man eight patients with carcinoma have
been treated while breathing oxygen at
3 atmospheres absolute in a pressure
chamber (Churchill-Davidson et al.,
1955). As anaesthesia was essential for
this type of treatment a suitable technique
had to be developed, and this raised many
problems of anaesthetic interest.

OXYGEN TENSION AND RADIOSENSITIVITY

The sensitivity of many different types
of cells to damage by X-rays may be re-
duced by as much as two-thirds if they are
deprived of their normal oxygen supply,
but will not be greatly increased in the
presence of excess oxygen. In man the
normal environment of most cells contains
oxygen at a tension of about 35 mm Hg,
and a rise in the tension will not greatly
affect the radiosensitivity; similarly, nor-
mally oxygenated tumour cells will not
be made much more radiosensitive by
increasing the oxygen tension.

Many tumours, however, contain large
numbers of cells which, because of poor
blood supply, exist under almost anoxic
conditions. It is believed that these
poorly oxygenated cells may survive such
doses of irradiation as may safely be given
to patients, but that if the oxygen tension
to which they are subjected could be
raised to somewhere in the normal range
they might become much more sensitive
and, further, that this increase in sensi-
tivity may be selective.

Gray and his colleagues have shown
that there is in fact a well-marked increase
in the relative radiosensitivity of the
Ehrlich ascites tumour in mice breathing
oxygen at 3 atmospheres pressure; they
did not feel able, on the basis of their ex-
periments, to predict the response of any
particular human tumours, but believed
that “the possibility of substantial differ-
ential gain . . . is inherent in any situation
in which regions of partial anoxia occur in
a human tumour”. It was in order to test
this possibility that the trial was carried
out.
GENERAL CONSIDERATIONS

The administration of oxygen under high pressure necessitated the use of some form of pressure chamber. Before carrying out treatment it was necessary to consider the physiological effects of high pressure oxygen on the patient. It was then possible to define the anaesthetic requirements. As, during irradiation, the patient could not be seen and no-one could be in the same room, some means of making observations at a distance had to be devised. Finally, the risks of fire or explosion had to be considered.

THE PRESSURE CHAMBER

We have used a modified naval diving recompression chamber (fig. 1). This consists of a heavy gauge steel cylinder measuring internally 7 feet 6 inches in length and 2 feet 6 inches in diameter, with a door at the head end. There are two circular observation windows in the door and on the top a window 25 cm square of 1 inch thick Perspex is provided through which the X-ray beam is directed. Copper pipes lead directly, without reducing valves, from four 120 cu.ft oxygen cylinders to the oxygen inlet manifold, the supply of oxygen to the chamber being regulated by a valve. The main exhaust valve, 1 1/2 inches in diameter, connects with a hose through which waste oxygen is passed to the outside atmosphere, while there is also a fine adjustment exhaust valve near the pressure gauge at the head end. There are two adjustable safety valves.

A flat wooden floor within the chamber allows an aluminium trolley to be wheeled into the chamber from its mobile cradle. The patient lies on a conductive rubber
mattress and the trolley is electrically connected to the wall of the chamber and thence to earth.

Electrical leads from the patient are connected by a cable passing through the wall of the chamber to a twin-channel cathode ray display unit placed outside the treatment room.

PHYSIOLOGY

**Effects of raised barometric pressure.**

When the barometric pressure is raised, the tension of the gases dissolved in the blood increases, pressure differentials are caused in those body cavities which do not communicate freely with the atmosphere and there is an increase in the viscosity of the inspired gases (Bean, 1945). If air is breathed, the increased nitrogen in solution in the blood may, on decompression, bubble out and give rise to the "bends" (Caisson disease), but this rarely occurs with oxygen, any bubbles of which are rapidly metabolized. Rupture of the eardrum or even haemorrhage into the middle ear may be caused unless pressures can be equalized; the conscious subject free of upper respiratory infection is able to do this by opening the Eustachian tubes in swallowing and trained individuals can be compressed from 1 to 7 atmospheres in 90 seconds without ill effect (Case and Haldane, 1941). In the unconscious subject a myringotomy, which heals quickly, is necessary and safe. Pressure differentials in the sinuses may cause pain, but those in the gut do not, at 3 atmospheres, give rise to trouble. Valvular bronchial obstruction may cause rupture of the lung if a pocket of gas at high pressure is left beyond it on rapid decompression, and Case and Haldane have reported pneumothorax in an emphysematous subject from this cause.

The increased viscosity of the gases makes breathing harder and magnifies the effect of any obstruction to respiration. Case and Haldane, for instance, found that breathing through some types of canister was unbearable at 10 atmospheres, and there is a noticeable effect at 3 atmospheres. If compression is rapid the gases to be expired become smaller in volume, and elimination of carbon dioxide is impaired (Bean, 1945). Rapid compression or decompression will also cause marked changes in temperature within the pressure chamber.

**Effects of raised oxygen tension.**

The continued inhalation of oxygen at high tensions gives rise to oxygen poisoning. In smaller animals severe pulmonary damage (Lorrain Smith, 1899) may cause death, but in man oxygen convulsions, first described by Paul Bert (1878), occur before this point is reached. Donald (1947) found no evidence of lung damage in over 1,000 experiments, all of which were terminated for central nervous system signs and symptoms. The convulsions resemble epileptic fits and the time of onset varies very greatly not only in different individuals but in the same individual at different times. Thus when 36 healthy subjects breathed oxygen at 3.7 atmospheres the time of onset of symptoms varies from 6 to 96 minutes. One of the early, but not invariable, physical signs is twitching of the lips and facial muscles. Although the fits may be repeated if exposure is continued, no serious after effects have been noted. The electroencephalogram shows the characteristic changes of epilepsy,
although these do not come on immediately. Twitching of the lips may occur without any alteration in the electroencephalogram but is detectable by electromyography.

There has been much discussion as to the cause of these convulsions and three main theories have been advanced to explain them. It was originally suggested by Paul Bert (1878) that oxygen exerts a direct toxic action on the brain and Dickens (1946) has shown that at high pressures there is a diminished uptake of oxygen in brain slices in vitro, probably due to interference with enzyme systems. Although it has not been possible to demonstrate this diminution in vivo, Lambertsen et al. (1953a) are of the opinion that such a toxic action does in fact exist. A second theory has implicated the rise in tissue carbon dioxide tensions which occurs under these conditions.

Because of the high tension of oxygen dissolved in the plasma the tissue oxygen needs are met without the reduction of oxyhaemoglobin. As this substance is more acid than reduced haemoglobin, base is not made available for the uptake of carbon dioxide. Oxyhaemoglobin also combines less readily than does reduced haemoglobin with carbon dioxide to form carbaminohaemoglobin. Thus, the tissue carbon dioxide tension rises (Samson Wright, 1952). Lambertsen et al. (1953b) believe that this rise in the tissue pCO₂ is sufficient to explain the hyperpnoea which follows exposure to high-pressure oxygen, but is not an important contributing cause of the convulsions, and this is supported by the finding of Donald (1947) that symptoms occurred at 2 atmospheres absolute—a level at which carbon dioxide tension is not greatly raised. Finally, cerebral vasoconstriction has been thought to be the cause. Lambertsen found that the cerebral blood flow falls by 25 per cent and cerebral vascular resistance is increased by 55 per cent, but this, he thinks, serves to protect the brain from the direct action of oxygen. This protection may be diminished by the inhalation of carbon dioxide.

Whatever the mechanism may be, it is known that the onset of symptoms is hastened by exercise, heat or cold (Donald, 1947) or by the inhalation of carbon dioxide (Marks, 1944; Kough et al., 1951), and there is evidence that it may be postponed by chloroform (Bert, 1878), barbiturates (Marks, 1944; Taylor, 1954; Churchill-Davidson, 1954) and chlorpromazine (Paton, 1955). While it is possible that the postponement of convulsions may allow time for pulmonary damage to develop, there does not appear to be any evidence in man that this will, in fact, occur; indeed, Donald found that at 2 atmospheres up to 7 hours exposure failed to produce damage.

The other effects of the inhalation of oxygen at high pressure are of little importance. Donald reported bradycardia in some subjects and a rise of blood pressure of the order of 15 mm Hg. Whitehorn and Bean (1952) have reported electrocardiographic changes in decerebrate dogs which may be delayed by vagotomy.

**CHOICE OF ANAESTHETIC**

To breathe oxygen at a pressure of 3 atmospheres is not in itself unpleasant. The trained subject can rapidly adjust his middle ear pressure, the extra respiratory effort is slight, and indeed there is little
to distinguish the experience from normality. However, general anaesthesia was thought essential in order to minimize the risk of convulsions. It would in any case have been desirable because of the likelihood of ear troubles, sinus pain and claustrophobia in an untrained patient, the necessity of keeping perfectly still during treatment, and the impossibility of an attendant being near the patient.

The inaccessibility of the patient meant that a single-dose technique was required; it also demanded absolute certainty about the airway, which could only be guaranteed by using an endotracheal tube. The first problem, therefore, was to ensure sleep for the requisite time, the second to enable the endotracheal tube to be tolerated, and the third to minimize the risk of complications.

Gaseous anaesthetics were unsuitable because maximum oxygen concentration was wanted, inflammable ones because of the risk of fire, and volatile ones because of the difficulty of control. Intravenous anaesthesia was therefore the choice. Barbiturates, as has been noted, delay convulsions, and sodium pentobarbitone (Nembutal) has a suitable length of action for the treatments used. With improved X-ray apparatus and shorter treatments, sodium thiopentone (Pentothal) or hexobarbitone (Evipan) may suffice. Unfortunately under barbiturate anaesthesia the irritability of the trachea is such that troublesome coughing on the tube occurred in three of the first six cases in spite of careful spraying of the trachea and vocal cords with 4 per cent lignocaine (Xylocaine) and the use of intravenous pethidine. Because it diminishes reflex activity of this type, chlorpromazine (Largactil) was used as well for the last two cases and proved satisfactory. This drug has the advantage of helping to delay convulsions but a theoretical objection to its use is the possibility that changes in the blood flow in the tumour may alter the radiosensitivity; it was thought reasonable to disregard this.

Two further measures to lessen the risk of convulsions were the use of phenobarbitone before treatment and the scrupulous avoidance of carbon dioxide accumulation in the chamber. Because of the increased resistance and the higher temperatures reached by soda lime at 3 atmospheres a modified circle-type absorber (fig. 2) was used which enabled the patient to breathe directly in from the surrounding atmosphere but ensured that all expirations were passed through a Waters canister. Resistance to inspiration was thus minimal and no hot gases were breathed. The slight resistance to expira-
tion offered by the canister could be avoided by relying on a carbon dioxide absorber placed elsewhere in the chamber, but it was thought that this would be less efficient.

Full doses of atropine were given as premedication in view of the finding of Whitehorn and Bean (1952) that vagal section delayed cardiac irregularities, and an opiate was given to allay apprehension. The last two cases were also given pethidine and chlorpromazine.

To keep the bilateral myringotomy incisions open, small polythene tubes were inserted through each drum and removed at the end of treatment. Armstrong (1954), who used this method in the treatment of chronic secretory otitis media, states that even with the tubes in place the hearing loss is only 13.9 per cent.

OBSERVATION OF THE PATIENT

The observations that could be made on the patient during treatment were limited in type by the necessity to avoid using electrical currents within the chamber which could give rise to any risk of sparking. It was thought that an electrocardiograph and a trace of the respiration would give the most useful information. As twitching of the lips is often one of the early signs of a convulsion, one of the electrocardiograph leads was taken from the upper lip; any muscular activity would then instantly be recognizable by the electromyograph tracing which would become superimposed on the electrocardiograph (fig. 4B). For the respiratory trace a thermistor (after Galley and Bareham, 1952) was used. This electronic device, placed at the outlet of the soda lime canister, detects variations in the temperature of the expired gases and thus gives an indication of the frequency and to some extent the volume of the breathing (figs. 3 and 4). Probably further information about the respiration could be obtained from a microphone attached to the endotracheal tube, and it is hoped to incorporate this in future.*

* This has now been done with very satisfactory results.
FIG. 4A
Photograph of ECG and respiratory trace. The notches in the latter are caused by closure of the valves.

FIG. 4B
Photograph of ECG and respiratory trace. Superimposed on the ECG is an electromyograph produced by voluntary contraction of the lip muscles.

RISK OF FIRE AND EXPLOSION
Materials, including many which are normally non-inflammable, will burn fiercely in oxygen under pressure, and it was therefore prudent to take careful safety measures against fire and consequent explosion. Besides the obvious steps of prohibiting smoking and avoiding the use of sparking electrical apparatus, or any but the most minute current within the chamber, full anti-static precautions included the careful earthing of the chamber and the use of conductive rubber for the mattress and trolley wheels. All waste oxygen was passed directly to the outside of the building to avoid any accumulation within the treatment room.

TECHNIQUE
Preliminary examination.
In the thorough physical examination before treatment particular note is made of the presence or absence of cardiac irregularity, infection of the upper respiratory tract or middle ear, perforation of the drum, or any evidence of bronchial obstruction. A preliminary electrocardiogram is taken. The patient is told the nature of the treatment and warned that there might be some slight transient hearing loss.
Premedication.
Phenobarbitone 1 gr. (60 mg) is given the night before and repeated four hours before treatment. Atropine 1/60 gr. (1 mg) is given one hour before treatment and pethidine 100 mg with chlorpromazine 50 mg injected intramuscularly.

Anaesthesia.
Pentobarbitone sodium (Nembutal) in 5 per cent solution is injected intravenously through a Gordh needle at the rate of 1 ml per minute until consciousness is lost; 0.25 g usually suffices but up to 0.5 g may be needed. Chlorpromazine 50 mg with pethidine 100 mg is then given slowly through the same needle, followed by succinylcholine 50 mg. The patient's lungs are then inflated with oxygen and the largest convenient endotracheal tube lubricated with 4 per cent lignocaine paste passed under direct vision after spraying the trachea and vocal cords with 4 per cent lignocaine from a Macintosh spray. The tube is secured and a metal airway of sufficient size to prevent biting of the tube is inserted. Controlled respiration is carried out until spontaneous breathing returns; this may conveniently be done with 75 per cent nitrous oxide and 25 per cent oxygen during the myringotomy and placing of the polythene tubes through the eardrums, after which the anaesthetic machine is disconnected and the patient allowed to breathe air.

Preparation of patient.
After the X-ray fields have been defined with lead sheeting, the electrocardiograph electrodes placed, and the carbon dioxide absorber connected, the patient is carefully positioned in the chamber (fig. 5).
The chamber is flushed with oxygen to wash out the air and the door closed. At this stage the oscillograph traces are carefully checked.

Compression.

The exhaust valves are closed and oxygen is allowed to flow into the chamber until the required pressure is reached, about ten minutes being allowed for this. Treatment is then carried out.

Decompression.

Decompression is carried out slowly at the end of treatment, a careful watch being kept on the patient's condition during this stage. If necessary the treatment may be interrupted at any time to enable further doses of pethidine and chlorpromazine to be given, but this involves decompression and recompression and occupies about half an hour. At the end of treatment the polythene tubes are removed from the ears. In an emergency the chamber can be decompressed and opened within two minutes.

RESULTS

The results of the radiotherapy are fully discussed elsewhere (Churchill-Davidson et al., 1955) and it need only be noted here that they were sufficiently encouraging to justify a further and larger trial.

No complications were met with in the eight cases which could be ascribed to the treatment or the anaesthetic. The time of exposure to high-pressure oxygen varied from half an hour to two successive exposures of one hour each. None of the patients had convulsions, nor did any show signs of lung damage. In four patients with carcinoma of the bronchus there was no exacerbation of previously existing symptoms. In one case auricular fibrillation started during treatment; this patient had fibrillated previously and therefore treatment was not interrupted. The fibrillation persisted for some time after treatment but without ill effect. In most cases hearing loss has been unnoticeable to the patient and in the one case in which there was a slight loss for a few days this was due to blood clot on the drum. Drowsiness was prolonged for 24 hours in two cases in which large doses of pentobarbitone were used. Vomiting is likely to occur after X-ray treatment; in this series it was effectively controlled by Dramamine and pyridoxine.

DISCUSSION

To obtain the maximum effect from irradiation it would seem that a certain level of oxygen tension in the tumour must be reached. What this level is, and what is the oxygen tension in the inspired gases which is required to produce it, are questions which, unfortunately, cannot be answered yet. With the technique described, analysis of the gases within the chamber at 3 atmospheres showed the oxygen content to be 91 per cent, and this figure will be exceeded when the chamber is slightly modified. This means that the patient breathes oxygen at a tension of about 2,000 mm Hg as compared with 160 mm Hg in air at normal pressure.

Lambertsen et al. (1953c) found that under such conditions the arterial blood contained oxygen at a tension of about 1,700 mm Hg. The extra oxygen is contained in solution in the plasma and must offer a higher head of oxygen pressure to the tissues. Estimates of the tension
reached in the tissues have been made by analysing gas bubbles introduced beneath the skin and by the use of a platinum electrode. Taylor (1949), using the first method, showed that the oxygen tension under the skin of cats was doubled if oxygen at 1 atmosphere was breathed, while Montgomery and Horwitz (1950), using the second method, estimated the tensions reached at 1 atmosphere as 200–400 mm Hg under the skin of human volunteers. Neither of these methods is very reliable, but it is hoped that development of the platinum electrode will enable more accurate estimations to be obtained in some future cases in this work.

In the meantime the optimum conditions in practice will have to be determined empirically. The use of pressures in excess of 1 atmosphere involves a considerable complication in technique and will only be justifiable if the advantage gained is sufficient. The information to be derived, therefore, from a further trial at 3 atmospheres is needed, and will have to be compared with the results obtained at 1 atmosphere.

The anaesthetic technique has been developed to suit the particular requirements of this series of cases and may have to be modified if conditions of treatment are altered. It is, of course, possible to overcome many of the difficulties by training or by using a large chamber and extremely slow compression and decompression as described by Auler et al. (1929), who used high-pressure oxygen in the treatment of cancer, but there would still remain the risk of convulsions. The limited experience so far gained seems to confirm the impression that this risk may be considerably lessened, or even eliminated, by anaesthesia, and this alone is a sufficient indication for its use.

**SUMMARY**

It has been suggested that X-ray treatment given during the breathing of oxygen at high pressure may have an increased effect.

Eight patients with carcinoma have been treated in this way under general anaesthesia.

The physiological and technical aspects of anaesthesia under these conditions are discussed and the method used is described.

No serious complications have been encountered.

The effective rise in tissue oxygen tension is discussed and the necessity for the use of general anaesthesia considered.

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**REFERENCES**


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**BOOK REVIEW**

*Geriatric Anaesthesia.* By Paul N. Lorhan, M.D.
Published simultaneously in the U.S.A. by Charles C. Thomas, in Canada by the Ryerson Press, Toronto, and in the British Congress of Nations by Blackwell Scientific Publications, Oxford. Price 23s. 6d.

It is one of that delightful series known as the Thomas Books. Dr. Lorhan begins with a chapter on the physiological changes that have occurred in the course of years and in the next shows which of these are amenable to therapy and which are not. In the chapter on surgical management he stresses the need of judgment, gentleness and speed, the latter requirement so frequently regarded as of minor importance nowadays. His pre-anaesthetic doses of morphine 1/8 grain (8 mg), atropine 1/300 grain (0.2 mg), strike me as unnecessarily small, particularly as the combination has the advantage of both whilst countering their disadvantages when used alone. There seems to be considerable difference of opinion about N-allylnormorphine. Dr. Lorhan says it "has been found very useful in combating an opiate-induced respiratory depression". Dr. Woolmer seems to agree with him but adds, "because it has some depressant effects of its own N-allylnormorphine should be given cautiously". Dr. Payne, on the other hand, from experiments on 11 volunteers says, "no analeptic effect could be demonstrated while the hypnotic and narcotic actions of the drug were definite deterrents to its use". Of the various anaesthetics in common use, Dr. Lorhan has a good word to say for spinal anaesthesia. He pleads for the use of corrective surgery rather than letting the lesion develop into a possible emergency, and the desirability on the part of the surgeon of employing a competent anaesthetist.

*E. Falkner Hill*