THE USE OF HYPERBARIC OXYGEN IN THE RADIOTHERAPY OF MALIGNANT DISEASE

by

SASHA MORRIS

A thesis submitted for the degree of
Doctor of Medicine at Glasgow University

1972

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

ACKNOWLEDGEMENTS

The practical and clinical work recorded in this thesis was carried out in the Glasgow Institute of Radiotherapeutics. My own interest in hyperbaric oxygen therapy was initiated by Dr. D.L. Phillips who asked me to take charge of the day to day treatment of patients by this method, new to radiotherapy in Scotland. I owe a debt of gratitude to Dr. K.E. Halnan, director, and to all my colleagues in this department. All the consultants recommended hyperbaric treatment for a proportion of their patients. I wish especially to thank Miss Augood and her staff of radiographers who supervised the field settings, the physicists led by Dr. J.S. Orr and Dr. D. McKinnon, who maintained the chamber in working order, and the nursing staff of the Western Infirmary and the Royal Beatson Memorial Hospital who kept high the morale of the patients throughout their therapy.

Mr. Gabriel Donald and his department of Medical Illustration have been outstanding in their help in the preparation of the illustrations. I wish to make special mention of Dr. M.A.C. Cowell, who permitted me to use her results in Figure 9. The histology specimens photographed in Figure 7 were made available by the kindness of Dr. J.E. Craik, Consultant Pathologist, Victoria Infirmary.

Dr. /

Dr. H.M. McCallum, Consultant Pathologist, Royal Beatson Memorial Hospital, was most helpful in giving me her opinion and advice regarding the histological assessment of the biopsy material in the cervix trial. She personally examined all specimens.

Dr. G.E. Flatman's advice and criticism in the preparation of this thesis have been invaluable to me. So has the friendly interest taken by Dr. B. Isaacs. Finally, I am indebted to my husband, Dr. H. Woolfson, for the patient understanding and textual guidance which he has given throughout the writing of this thesis.

In conclusion, I wish that, if this work has any value, it should be dedicated to the memory of the late Hugh McKinlay. "Mac", as he was known to all, gave willing and cheerful service over many years to the Institute of Radiotherapeutics. In particular, he was a tower of strength to this investigation, to the patients involved, and to myself.

INDEX

INTRODUCTION

In the treatment of certain types of cancer, the technique of irradiation in an atmosphere of hyperbaric oxygen is of relatively recent origin and its use is still limited to a number of specially equipped centres.

Can such a novel technique be made acceptable to patients and staff, giving it a place in the normal day to day work of a radiotherapeutic department?

Can the results of this new mode of treatment be shown to better those of radiotherapy in air?

If these two questions could be answered in the affirmative, only then would it be appropriate to introduce this radiotherapeutic technique on a large scale as an accepted form of treatment.

Over the past seven years, the author has had the privilege of working in the Glasgow Institute of Radiotherapeutics where she has had the opportunity of personally treating 164 patients suffering from various forms of malignant disease by the method of radiotherapy in hyperbaric oxygen.

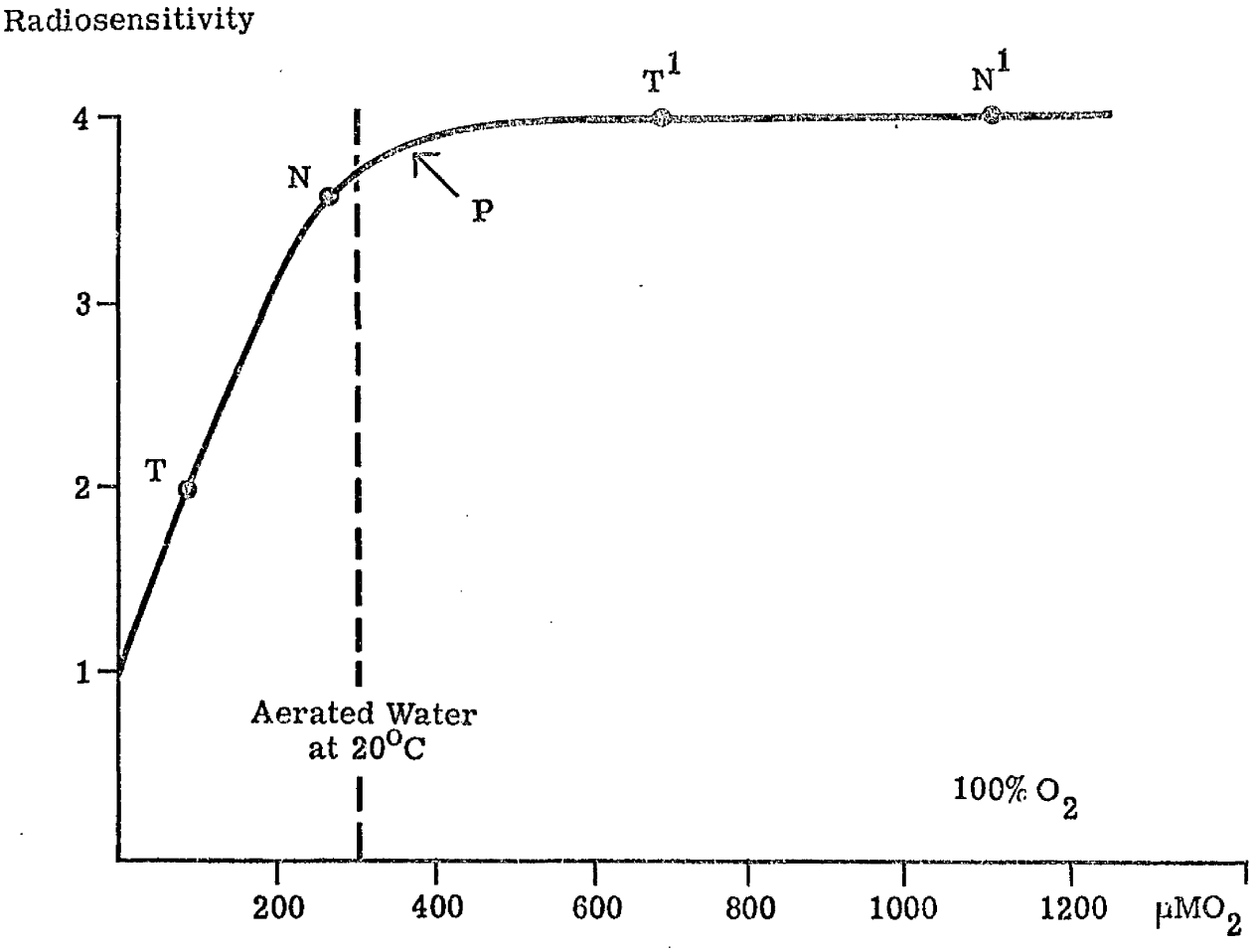
In this thesis, the theoretical and experimental evidence supporting the use of hyperbaric oxygen in the treatment of malignant disease is reviewed and the author's own experience in the treatment of 164 cases is presented.

CHAPTER 1

Historical Review

Today, it is an accepted fact that oxygen must be present in tumour cells at the time of irradiation if the cytotoxic biochemical changes subsequently destroying the cells are to take place. Normal tissue is sufficiently well oxygenated at all times, but circumstances vary with tumour tissue which, by nature, is "out of joint" (Hamlet) with the rest of the body, and which has no system of checks and balances to maintain normal body homeostasis.

The relationship between oxygen and radiosensitivity was clearly established in 1953 by L.H. Gray and his colleagues (1953-1). Their work, involving the irradiation of Ehrlich Mouse Ascites tumour both in vitro and in vivo under varying degrees of oxygen tension, showed that, as the oxygen concentration increased from zero, the radiosensitivity of the cells rapidly rose to reach a plateau where further increase in the concentration of oxygen had almost no further additive effect on the radiosensitivity of the cells (Figure 1). Furthermore, in a variety of experiments, irradiating /



Typical curve of radiosensitivity as a function of oxygen tension at the time of irradiation

From: The Concentration of oxygen dissolved in the tissues at the time of irradiation as a factor in radiotherapy.

L.H. Gray, M. Ebert, S. Hornsey, O.C.A. Scott
British Journal of Radiology 1953, 26, 638-648

Figure 1

irradiating Ehrlich tumours in a series of mice breathing either air at normal atmospheric pressure or oxygen at 1 - 3 atmospheres absolute (ATA) at the time of irradiation, the subsequent tumour regression clearly showed the markedly increased response in the oxygenated mice. At the same time there was little or no change in the normal tissue response to irradiation, skin damage being about equal in both sets of animals. To obtain such a tumour response in mice breathing air, a dose of 1.5 or 2 times the quantity of x-rays must be used. Such a dose would have, moreover, a necrotising effect on surrounding normal tissue.

Gray observed that oxygen appeared to exert influence by being present in the cell at the time of attack by ionizing radiation, thus effecting the "chemical changes which take place". At the same time, its presence was not required if chemical agents or neutrons were used to do similar damage - as was shown by Thoday and Read (1947-2). These facts suggested that oxygen dissolved in the tissues modifies the chemical intermediates formed along the tracks of ionizing particles with a cytotoxic effect.

Gray's /

Gray's conclusions rested not only on his own experimental work, but also on radiobiological evidence which had been accumulating for over 40 years. Experiments with X-rays to prevent the hatching of Ascaris eggs were carried out by Holthusen in 1921 (1921-3). He noted that the dose of X-rays required to stop Ascaris eggs from hatching must be increased by 3 times if the eggs were in an anaerobic state at the time of irradiation. J.C. Mottram in 1924 (1924-4) published the results of his experiments showing the effect of irradiation on the tails of rats subjected to temperatures between $0^{o}C$, and $45^{o}C$ and to blanching of the skin by stopping the bloodflow with ligatures. There was no doubt that reduction of temperature to $0^{o}C$ increased the blood flow and resulted in a greater radiation effect than at normal room temperature whereas the ligatured tails showed a definite reduction in radiosensitivity due to the apparently protective action of a reduced blood supply.

The first experimental work on tumour cells was carried out in the early nineteen thirties by Crabtree and Cramer (1933-5) who /

who found that radiation damage to fragments of mouse tumour cells was markedly decreased by exposure in an environment containing no oxygen. This was proved by bubbling nitrogen through the cell suspension being exposed to radium and showing the continued viability of the cells on re-inoculation into other animals. Mottram (1935 -6, 7) confirmed these findings with experiments on Broad Bean roots (Vicia faba) in which cold rendered the root cells more radiosensitive whereas roots irradiated in water from which the oxygen had been expelled showed a striking reduction in radiosensitivity. He then applied the concept of oxygen as an adjuvant of radiosensitivity to tumour cells, and, using tar warts in mice (1936-8) suggested that small tumour-cell masses are more radiosensitive than large ones because the former cells must all be close to blood vessels and therefore to a more adequate supply of oxygen.

The effect of whole body irradiation in the presence of anoxia was then shown to be diminished by other workers. Lacassagne (1942-9) in 1942 noted a reduction in the mortality of mice while Evans, Goodrich and Slaughter (1942-10) in the same /

same year, reported an increased radio-resistance in new-born rats with marked lessening of skin reactions. All these animals were deprived of oxygen at the time of irradiation.. Dowdy, Bennett and Chastain (1950-11) in 1950 confirmed the reduced mortality in experimental rats, showing at the same time that a histotoxic anoxia caused by intraperitoneal injections of NaCN give no protection against irradiation. This finding pointed towards the vital role in radiation damage being played by radio-chemical reactions involving free oxygen. In 1952 Hall Hamilton and Brues (1952-12) measuring the viability and growth of mouse carcinoma implants irradiated in vitro, came to the conclusion that a varying degree of radiosensitivity in tumours was accounted for by the amount of free oxygen present in the tissues at the time of irradiation. Russell, Russell and Major (1952-13) in 1952 showed that anoxia during irradiation lessened the frequency of embryo abnormalities in pregnant mice. Devik (1952-14) noted a reduction in chromosome damage in the bone marrow of mice under similar conditions. This confirmed the work of Thoday and Read (1947-15) who had observed the increased number of chromosome aberrations produced with the subsequent /

subsequent inhibition of growth when the Vicia faba root was exposed to x-rays in an environment of well-oxygenated water. From further experiments on the Broad Bean root, Read (1952-16) summarised the importance of the presence of oxygen in enhancing the effect of ionizing radiations :-

1. The radiosensitivity of the root which normally has a lower oxygen concentration than the surrounding water, is unaffected by oxygen given immediately after irradiation in anaerobic conditions. This confirmed the results of Riley and Giles (1950-17) on Tradescantia microspores. They had noted that the frequency of chromosome aberrations was unaltered by the addition or absence of oxygen after irradiation in vacuo.

2. The radiosensitivity of the root can be greatly increased by raising the surrounding oxygen concentration within one minute before irradiation. Deschner and Gray (1957-18) subsequently narrowed this time interval down to a few seconds when they irradiated anoxic Ehrlich ascites tumour cells injected into oxygenated saline solution. Howard Flanders and Moore (1958-19) using the dysentery bacillus, showed /

2. (continued)

showed an increase in its radiosensitivity within 20 mseconds of alteration in the oxygen tension.

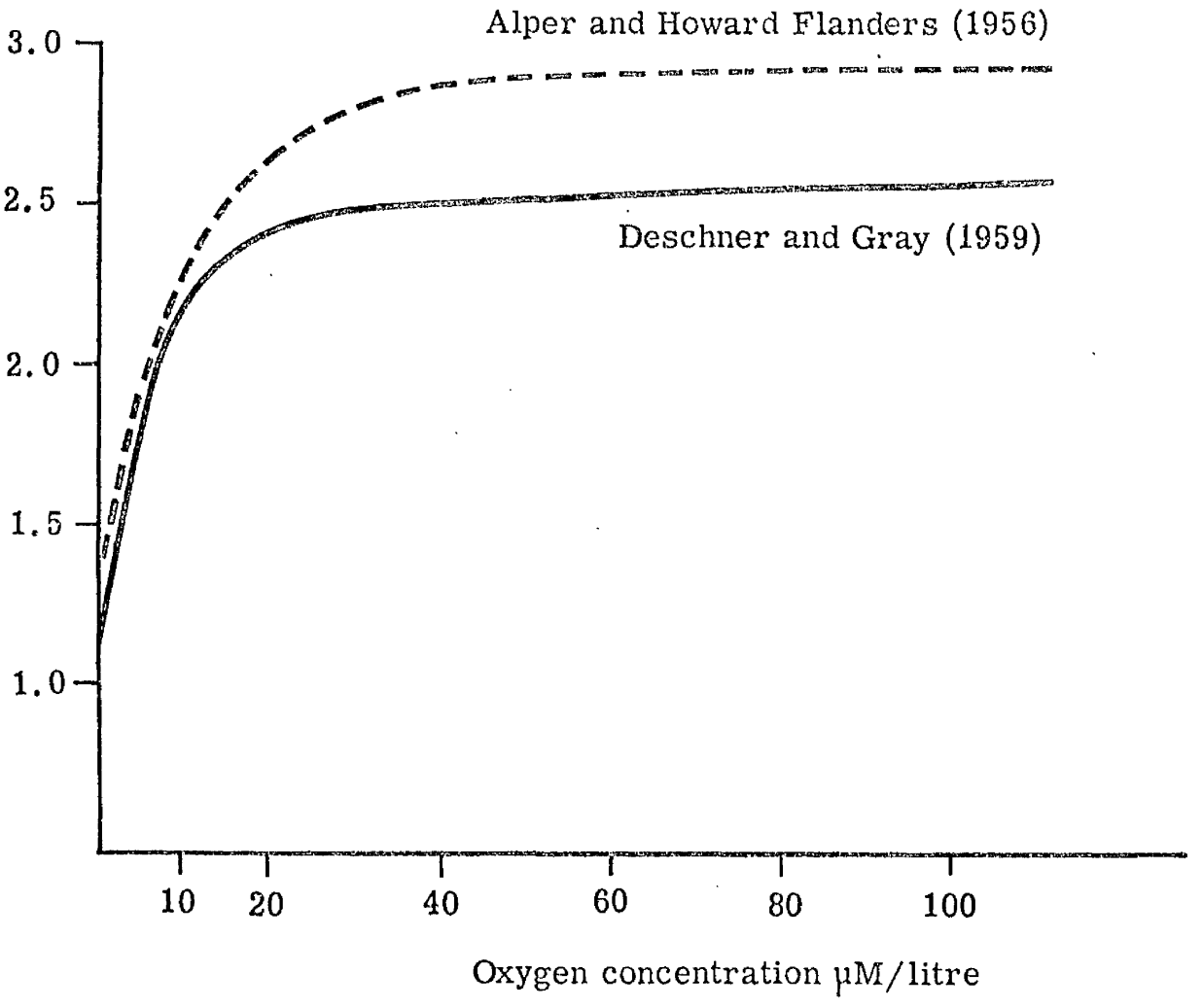
3. The presence of oxygen has a multiplying effect on the radiation dose which would require to be increased three times to give the same inhibitory effect on mitosis without oxygen.

4. Oxygen does nothing to enhance or subtract from the effect of alpha rays or neutrons on plant tissues.

Read postulated that the response of animal tissues - including human tumour tissue - would be parallel to that of plant tissues, and Gray's work (1953-1) mentioned earlier, confirmed this striking similarity of pattern in the oxygen effect on the radiosensitivity of different types of cells. But it was clearly evident that dissolved oxygen affects only the early pathway peculiar to the lesions produced by ionizing radiation, and not lesions induced by chemicals or neutrons. It was not, however, until 1956 that Alper /

Alper and Howard Flanders (1956-20) precisely evaluated the relation between the radiosensitivity of the cell and the oxygen concentration in its environment. They did this using bacteria and yeast cells. Deschner and Gray (1959-18) used mammalian ascites tumour cells with similar results. The response of these tissues from entirely different sources was identical (See Figure 2.)

It must be emphasised that cells which make up mammalian tissues of any kind, exist at oxygen tensions which will vary according to their distance from the capillary supply of oxygen, the concentration of oxygen in that capillary, and the oxygen requirements of the intervening cells. Thus, in turn, the radiosensitivity of the cells is altered, a concept already noted by Mottram (1936-8) and confirmed by the observations of Hall, Hamilton and Brues (1952-12). They appreciated that there is a falling gradient of oxygen tension from the surface to the centre of the tumour. It was only on histological examination of poorly differentiated squamous cell carcinoma of the lung that Thomlinson and Gray (1955-21) noted the absence of capillaries among /



Curves relating radiosensitivity of cells to the concentration of oxygen in their environment at the time of irradiation

(from R.H. Thomlinson - Oxygen Therapy - Biological considerations
Modern Trends in Radiotherapy, Vol. I
Edited T.J. Deeley & C.A.P. Wood 1967,
Butterworths, London.)

Figure 2

among the tumour cells which were arranged in cords whose centres were invariably necrotic if the radius of the cord was greater than 200μ. Ionizing radiation would therefore kill the outer cells but leave unharmed the more central cells in which there must be a greatly lowered concentration of oxygen. At the same time, the oxygen concentration in the capillary will vary with the blood flow. If this is slowed by the sheer mechanical tissue pressure of tumour tissue which has been shown to be definitely greater than that of normal tissue and certainly markedly so in the rapidly growing tumours (Young, Lumsden and Stalker (1950-22), there will be congestion of capillaries with stagnation of blood. Hypoxia of the surrounding cells with consequent diminished radiosensitivity will be the ultimate result. These cells would lie dormant, without losing their inherent ability to proliferate until their nutrient supply improved. It seemed reasonable to suppose that by greatly increasing the oxygen concentration around the periphery of the tumour cords, the radiosensitivity of more tumour cells would be correspondingly increased while surrounding normal well-oxygenated tissues would not be unduly affected.

Thus radiobiological studies over the years have conclusively shown that the response of tissues to ionizing radiation depends on the presence of oxygen within the cells at the time of irradiation. This, in turn, must be determined by an adequate blood supply sufficient to oxygenate all cells. Such a blood supply is not available in tumour tissue which has a defective intrinsic vascular structure. Moreover, the physical bulk of solid tumour cells inevitably obstructs the extrinsic blood supply to and from surrounding tissues.

CHAPTER 2

Techniques of Treatment

From the preceeding data, it is clear that in order to achieve the best radiotherapeutic results, all tumour cells must be thoroughly oxygenated prior to and during treatment. The biological effect on these tumour cells will be increased threefold if their oxygen content is raised from around zero to the level of normal healthy cells. At the same time, normal cells, already fully oxygenated, are not liable to any increase in damage.

These experimental conclusions were first tested clinically by Hultborn and Forssberg (1954-23) in 1954. They studied the effects of irradiation on 4 cases of human skin tumours in vivo. The tumours were divided into 2 equal fields. Treatment was given to each one, using 49KV to 144KV to a dose varying between 700 rads and 3000 rads to field sizes 5 x 5 cms. to 25 x 25 cms. while the patient breathed pure oxygen at normal atmospheric pressure. The other field was treated similarly with the patient breathing air.

On /

2.

On each occasion, the non-irradiated field was shielded with 2mm lead. Within a few days, there was no doubt that the more pronounced reaction had occurred in the tumour areas and surrounding normal skin treated during the inhalation of pure oxygen. They concluded that the increased effect was, in fact, due to the increased formation of deleterious radicals produced on irradiation in well-oxygenated tumour cells normally characterized by an anaerobic metabolism.

They surmised that the effect would be less in older established tumours whose disordered vascular systems did not permit the permeation of oxygen. They made no comment on the increased reaction of the normal skin. Yet, as the epidermis has no direct blood supply, presumably borrowing its oxygen requirements from the dermal capillaries, increased oxygen saturation here would account for the increased radiation effect. This was to be confirmed later by Van den Brenk et al (1965-24) who showed a progressive increase in the radiosensitivity of the skin when doses above 750 rads were given in High Pressure Oxygen (HPO).

3.

To raise the level of oxygenation in tumours of long-standing, it would seem that oxygen must be forced into the intracellular tissues, thereby diffusing directly into the tumour cells. This was achieved by Churchill-Davidson, Sanger and Thomlinson (1955-25) who were the first to irradiate tumours in patients breathing pure oxygen at 3 atmospheres absolute (ATA). This atmospheric pressure was chosen because radiobiological experiments had been successfully carried out at this high pressure at which the oxygen effect appeared to be more marked and more consistent. At the same time, physiological experiments in man by Behnke (1942-26) and Donald (1947-27) showed 3ATA to be near the upper limits of safety. Churchill Davidson used a modified naval recompression chamber for this purpose. It consisted of a steel cylinder with internal measurements 7 ft 6 ins, by 2 ft 6 ins and a door at the head end in which were inset two observation ports. The door also held the monitoring leads connecting the patient with an electrocardiograph to show any alterations in cardiac state, an electromyograph to warn of incipient seizure and a thermistor

to /

to show any changes in the respiratory rate. At the other end of the chamber was the connecting inlet from 4 oxygen cylinders, each holding 120 cu.ft. together with the pressure gauge, safety and exhaust valves. A standard 250KV x-ray unit, filtered to give a half-value layer of 1.7mmCu, was used to irradiate the tumour through a recessed window, 25 sq.cm. in size, made of one inch perspex, on the wall of the chamber.

Prior to treatment the patient was anaesthetised and a bilateral myringotomy was carried out. The patient was then transferred to the pressure chamber trolley and placed in position within the chamber. The chamber was flushed through with oxygen before pressurisation to 3ATA took place.

In the 8 patients treated initially, the tumours were large enough to be divided into 2 fields, each being given a single dose of 1000 to 1500 rads, one in air at normal atmospheric pressure, the other in oxygen at 3ATA. Lead sheets, 2mm thick, were used to protect the surrounding skin and the alternate field. The whole procedure took up to 6 hours to complete. It was for this reason that only a single dose was given.

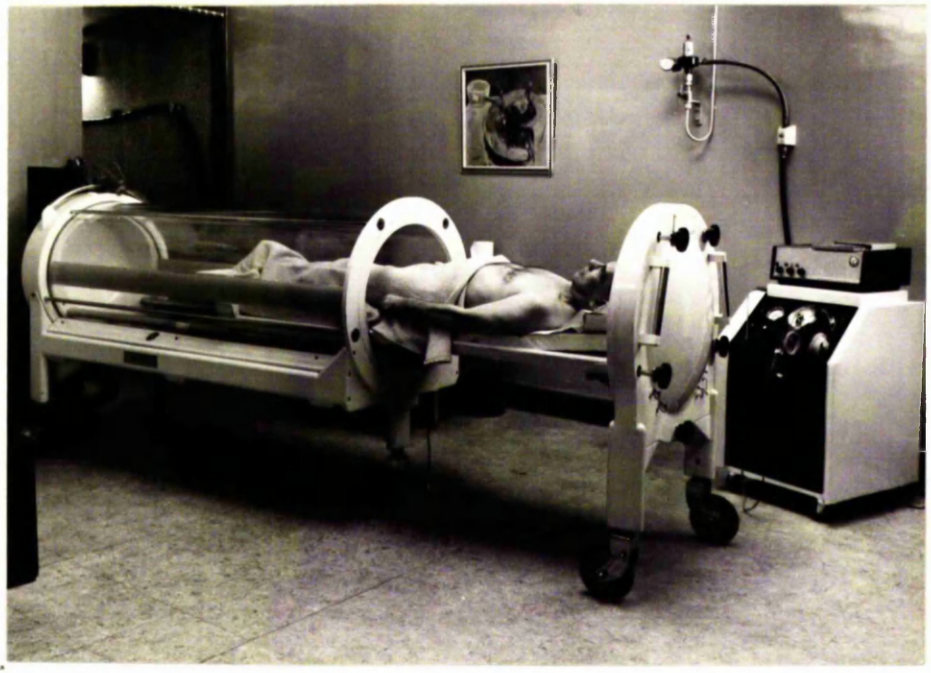
Biopsies from each field were taken up to 3 weeks later and 7 tumours showed markedly greater histological damage in the oxygenated tissue. In the sections of the 8th tumour, no live cells were found in either specimen. Since this initial treatment, Powers and Tolmach (1964-28) have shown that the proportion of resistant tumour cells surviving irradiation drops from 1 in 100 to 1 in 1000 under conditions of hyperbaric oxygen.

Churchill-Davidson's results were sufficient to gain world-wide interest both in the novelty of his technique and in the success of the new treatment.

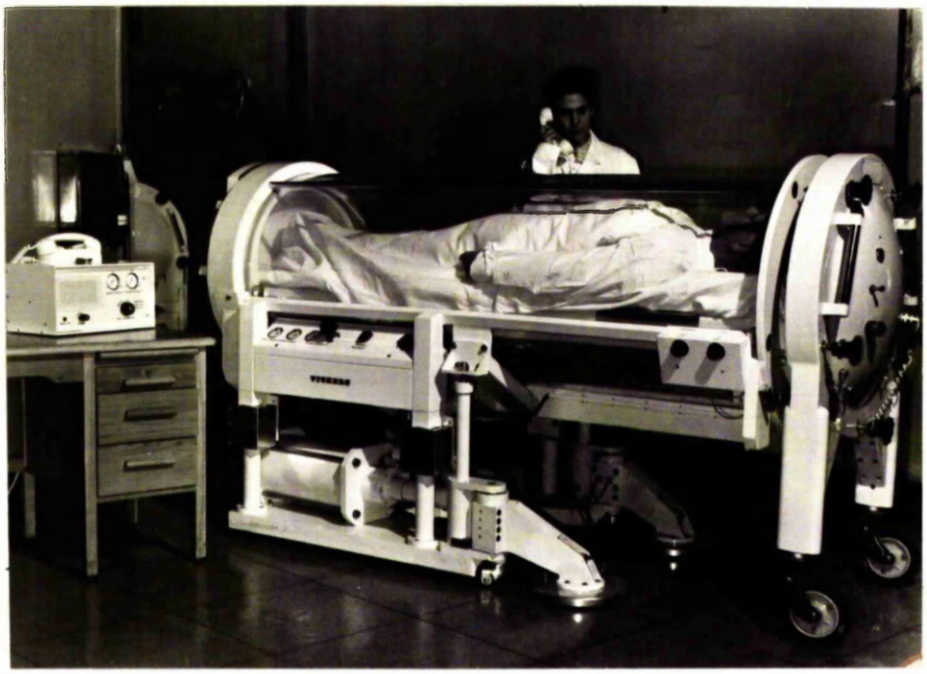
It is now 17 years since hyperbaric oxygen was first used for patients being treated by radiotherapy. In this period the Vickers modification of the original hyperbaric chamber, designed for University College Hospital in 1960 (Emery, Lucas and Williams 1960-29) has become a feature of many radiotherapy departments throughout the world. Basically, it consists of two concentric cylinders 6 feet long. They are made of transparent plastic with metal caps at each end, attached to a chassis mounted on spring castors. The inner plastic cylinder holds the gas under the required /

required pressure, which is generally 3ATA. The outer cylinder, separated from the inner one by an air space, acts as a fail-safe mechanism, holding the pressure temporarily if the inner cylinder should fracture, but not permanently oxygen-tight so that there would be, under these circumstances, a gradual leak of gas and fall in pressure. It is also important in that it protects the inner cylinder from accidental damage by impact with other objects when the chamber is moved for treatment purposes. One end of the chamber is permanently sealed by the metal cap. It is to this end that the oxygen supply and the exhaust duct are connected.

In Glasgow, the Vickers model was used in the treatment of all patients in the preliminary series (Figure 3A). Before the cervix trial was commenced, a trolley, powered by a small electric motor, was added to the chamber to improve its manoeuverability. However, the realisation that the danger of fire was increased by the presence of electrical connections in the environs of the chamber, made further modification necessary. This hazard has been eliminated in the new model, installed in 1970. (Figure 3B). It has no connections with an electrical supply. Instead, it uses the hovercraft principle based on an air pressure system. This not /



The first hyperbaric oxygen chamber in use in Glasgow from 1964.



The second hyperbaric oxygen chamber installed in Glasgow in 1971. This model moves on the hovercraft principle.

Figure 3

not only allows the chamber to be moved with ease, but is also geared to adjust the height of the chamber, bringing the treatment area on the patient to the correct distance from the head of the x-ray unit. The other end of the chamber is secured by 5 screw handwheels which, when released, permit the door to be opened and the stretcher bed to be pulled out onto a trolley.

Two-way communication with the patient, who is slid feet first into the chamber and can be seen to his or her full length, is by microphones set on the inner side of the door and by a telephone receiver attached to the control panel on the side of the chamber, the electrical supply being from a 10 volt battery fitted onto the chassis. There is also a remote control console with communication for use when the patient is being treated and is, therefore, inaccessible to the staff in charge. Physiological monitoring can be carried out through connections on the door of the chamber.

Oxygen is supplied from a liquid oxygen tank, placed in a safe position in the grounds of the hospital. Oxygen from it flows in at a maximum rate of 400 litres per minute, to be piped out through the /

the exhaust duct only via the motorized spring-loaded valve. This valve can alter the pressure within the chamber by a control from the operator's console which can increase or decrease the spring-loading. Safety devices prevent the pressure from rising higher than 30 lbs. per sq.in. As oxygen is constantly flushing through the chamber, carbon dioxide, nitrogen and water vapour are rapidly removed from the patient's vicinity, and the temperature does not vary more than $4^{o}C$.

To minimise the danger of fire and actual injury, patients are required to change into proban-treated cotton gowns and to remove all jewellery, dentures, hairpins, etc. before entering the chamber. Sheets on the stretcher are also proban-treated.

Oxygenation

An essential preliminary to the treatment is the time spent by the patient - generally about 20 minutes - in the oxygen chamber. It is not enough to pressurize the patient to 3 ATA - a procedure which /

which takes 4 to 5 minutes in the majority of cases. The patient at 3 ATA must then be in the chamber for a minimum period of time so that all tumour tissue is thoroughly oxygenated. How long this takes has been a matter for discussion for some time, owing to the difficulty in measuring the level of oxygen tension in living cells. A survey of the work done in this field is discussed in Appendix 1. In fact, it is now generally accepted that the oxygen soaking time should be a minimum period of 15 minutes. In Glasgow, the period is between 15 and 20 minutes.

Beam Direction

Setting up the patient for radiotherapy is not a problem. There is no difficulty in defining the area to be treated through the transparent walls of the chamber. The patient lies in the appropriate position, turning over if required to do so. The normal light-positioning mechanism in use in the treatment of all patients by the linear accelerator can be used in combination with the elevating mechanism of the chamber to attain the correct focus-to-skin distance. For accurate beam direction in the treatment of tumours of the head and neck, where the patient's head

is held in a cast, a method has been devised using an extra lens mounted in front of the treatment head of a linear accelerator (Sutherland and Griffiths, 1966-30, Sutherland 1968-31). Curvature of the cylinder wall is too slight to alter the isodose curves used in planning the treatment, but the thickness of the double wall must be taken into account and the dose of radiation to be given increased accordingly to allow for this. The actual treatment time must vary with the dose of radiation prescribed, but is normally between one and four minutes for each field irradiated. Naturally, during this time, the patient must lie quite still within the chamber and must be alone in the treatment room. Many centres use closed-circuit television to watch the patient during the course of treatment as well as using the two-way communication system. As soon as the treatment is completed, the chamber is returned to the preparation room and the patient is decompressed over 4 to 5 minutes.

Thus /

Thus the initial complicated and time consuming technique has been gradually modified to a simple and straightforward procedure. Patients may travel daily from their own homes for treatment which lasts, on average, half an hour. They only require to be admitted to hospital if their general condition warrants this. They no longer require general anaesthesia. Even premedication is rarely called for. In fact, treatment in hyperbaric oxygen has become an ordinary, everyday exercise.

This technique has been the major one used throughout the world. But it should be mentioned that two others have been developed for the administration of hyperbaric oxygen to patients receiving radiotherapy.

A chamber designed by Oxygenaire consists of a metal cylinder with a transparent plastic head cap. This has been used in Aberdeen for the treatment of head and neck cancer in a way similar /

similar to that already described.

In Japan hyperbaric oxygen has been used in association with the "Ralstron" technique of treating gynaecological cancer since 1968 (Wakabayashi, Ohsawa and Sugawara 1969-32). This combines the administration of pure oxygen by mask within an air-filled chamber pressurized to 3ATA, with the insertion of Cobalt 60 via remotely controlled tubes into applicators which have been inserted into the vagina before treatment. There is a five minute waiting period of oxygen saturation. When the Cobalt 60 sources are in position within the applicators, a dose of 1000 rads may be given in two or three minutes. The whole procedure takes about 40 minutes.

CHAPTER 3

Hazards of Treatment

Although it is now clear that, in the treatment programme, the major obstacle can be the non-co-operation of the patient, other more serious complications may arise. These are :-

1. Fire
2. Barotrauma
3. Oxygen Convulsions
4. Normal Tissue Damage

1. Fire

This is a primary hazard when pure oxygen is being used. This was demonstrated to the world in a most tragic way when American astronauts lost their lives within one minute of their oxygen chamber catching fire due to an aberrant spark. The strictest rules regarding the safety precautions against fire must be observed. Electrical points within the vicinity of the hyperbaric oxygen apparatus must be kept to a minimum and the oxygen leads to and from the chamber must be leakproof. Ideally, the exhaust duct should conduct the oxygen to the outside air. Patients have to change /

change into hospital gowns, proofed against fire, and lie within the chamber on cotton sheets similarly treated.

One accident in the use of hyperbaric oxygen chamber in radiotherapy has been reported in the U.S.A. (Tobin 1971-33). The chamber involved was one of the cantilevered type and consisted of a metal cylinder with a transparent plastic window of single thickness. The patient was being set up for treatment after the usual oxygen soaking period of 15 minutes at 3ATA when spontaneous rupture of the plastic window occurred. The patient, subjected to instantaneous and explosive decompression, sustained a bilateral haemopneumothorax but had no serious skin injuries. Multiple injuries were received by the doctor in charge who was bending over the plastic portion of the chamber at the time of the explosion and experienced its full force. However, further catastrophe and the danger of fire were forestalled by the emergency regulations being put into immediate action. This meant, first and foremost, the shutting off of the main oxygen supply. No-one died.

This incident has served to emphasise the importance which adequate /

adequate safety and emergency regulations must have in the training of staff for this form of treatment.

2. Barotrauma

A frequent but generally minor complication of treatment under hyperbaric oxygen conditions is the temporary discomfort in the ears experienced by the patient as the pressure is raised to 2 atmospheres above normal. There is a sensation of tightness and even pain in the eardrums which disappears when the pressure has stabilised at the maximum level. In fact, it is worthwhile taking as long as 15 to 20 minutes to pressurize the patient on the first occasion so that discomfort is cut to a minimum and the patient learns to adjust to the slowly rising pressure by swallowing, yawning, coughing and the use of the Valsalva technique. Within the space of two or three treatments, the adjustment becomes automatic. Occasionally, a nasal decongestant, such as 1% Ephedrine in normal saline, is administered beforehand to clear the eustachian tubes. Rarely, a myringotomy may be required and grommets can be inserted to ensure complete relief during subsequent treatments.

This was not required in any of the author's preliminary series of 85 cases, and has in fact only been necessary in 2 out of the entire survey. . Both of these patients had a long history of chronic ear disease.

Decompression causes no problems apart from a slight crackling sensation in the ears. The entire procedure takes an average of 35 minutes. Because pure oxygen is used, no danger of nitrogen toxicity can arise during rapid decompression.

3. Oxygen Convulsions

Convulsions have sometimes occurred and appear to be a true toxic effect of the oxygen, although the mechanism for this has not been satisfactorily explained. In 1933 Hill (1933-34) had shown that an accumulation of CO_2 in the tissues appeared to increase the susceptibility to oxygen poisoning in animals. But Donald's work (1947-27), during the 1939-45 war, on the oxygen tolerance of men at 3.7 ATA in dry chambers and under water showed that the alleged CO_2 factor was inadequate to explain oxygen poisoning. Bean (1945-35) suggested that CO_2 by its acid properties, possibly enhances /

enhances the toxic influence of HPO on the enzyme systems of the body. Dickens (1946-36) showed that the effect of HPO on rat brain slices in vitro was progressive poisoning of the respiration of the cortical tissue which appeared to be much more sensitive than any other organ. He postulated that the primary effect was inhibition of the enzyme pyruvic oxidase. This leads to metabolic block of the pyruvate pathway in carbohydrate oxidation. It seemed certain that minute impairment of brain tissue respiration was enough to cause convulsions. Certainly, it is impossible to predict when and in whom the convulsions will occur. There may be no premonitory aura. In the author's preliminary series there were 4 patients who had a single attack, 3 during treatment at the maximum pressure of 30 lbs. per sq.in. and 1 during decompression. All recovered completely within 5 minutes of being released from the chamber by emergency decompression. This was effected within 40 seconds by pressing an emergency button on the end of the chamber or on the console. All were able to complete their courses of therapy without further incident or any evidence of complications.

4. Normal Tissue Damage

The increased liability to radiation damage of certain tissues if included within the treatment area, is the other hazard which has been noted sporadically. Tissues such as the outer layers of the skin, cartilage, bone, the cornea and the lens of the eye, have a poor blood supply and, consequently, oxygen tension is normally low. It is reasonable to suppose that a state of increased oxygenation would enhance their response to ionizing radiations and increase the possibility of damage or necrosis. Nevertheless, no cases of severe skin reaction were noted among the author's 164 patients receiving treatment in oxygen at 30 lbs. per sq.in. pressure. Actual desquamation only occurred if bolus material was applied. Otherwise, a mild erythema was only occasionally seen. It must be noted that this was in spite of the high energy beam having to pass through the double perspex wall of the cylinder and therefore losing some of its skin-sparing properties. In the average case, the dose to the skin was increased to 50-60%, but this varied with the size of the patient and the size of the field.

No /

No damage to cartilage was observed among the patients in the author's survey. However, Churchill-Davidson (1964-37) has reported on 16 cases of laryngeal cartilage necrosis occurring within 9 months of treatment for carcinoma in the neck region. Tumour dose given in oxygen was 4000-4500 rads in 6 fractions over 18 days. No such complication occurred in 36 patients treated similarly in air or in subsequent cases in oxygen when the tumour dose was dropped to 3750 rads with similar fractionation.

Bone necrosis has been rare following treatment in HPO. Bates (1969-38) has reported on 3 cases of subcapital fracture of the femur following treatment for carcinoma of the cervix. No further cases occurred when the field size was shortened to exclude the femoral heads. However, the dose and fractionation of 3500 rads in 6 fractions over 21 days varied from that used for the cases of carcinoma of the cervix in this survey, none of whom have had a subsequent fracture of the neck of femur, although the femoral heads were often, necessarily, within the irradiated zone.

One /

One case of rib necrosis following irradiation for cancer of the upper lobe of left lung was reported by Atkins et al (1965-39). He also noted 3 instances of alveolar ridge necrosis in 8 patients who had been treated for malignancy in the head and neck region. All his patients were given radiotherapy in 4ATA oxygen.

No treatment involving the eye has been given to any patients in the author's series. However, Wildermuth (1968-40) has described one case in whom complete vascularisation of the conjunctiva and destruction of the cornea followed treatment in hyperbaric oxygen of an area in which the eye was unavoidably included.

Work has also been carried out in Melbourne (Van den Brenk 1968-41) to estimate the radiosensitivity of the spinal cord under conditions of hyperbaric oxygen - vitally important when attempting to eradicate malignant disease in the head and/or neck regions without causing radiation myelopathy. It is suggested that there is a higher incidence of this complication after treatment in /

in hyperbaric oxygen than in air, but the data are insufficient to be finally conclusive. In Atkin's series (1965-39) radiation myelopathy occurred in 3 patients between 8 and 29 months after treatment for carcinoma of the base of tongue, upper lobe of lung, and oesophagus, respectively, all in 4 ATA oxygen.

Temporary bowel damage does occur in many patients who receive abdominal or pelvic radiotherapy, in the oxygen chamber. Generally, symptoms are no more than a transient diarrhoea and occasional colicky pain which settles on the completion of treatment. In the author's experience treatment had to be discontinued in only 1 case (No. 38 preliminary series) because of the severity of symptoms which settled thereafter, within one week. Two other patients (Nos. 32 and 39 of the preliminary series) developed signs of intestinal obstruction during their courses of treatment and both died, the former having a rectal perforation, the latter with multiple abdominal metastases but no obvious bowel lesion on post-mortem examination. A fourth patient (No. 51 preliminary series) developed post-radiation necrosis of the small bowel /

bowel 6 months after completion of treatment. A special note is made on this patient on page 13, Chapter 5.

Other centres report similar temporary complications among patients, treated for carcinoma of the bladder and of the cervix. Churchill-Davidson's (1968-42) 5 cases of intestinal obstruction had all been treated for bladder carcinoma. Roulston and Johnson (1968-43) only reported cases of temporary diarrhoea in their series of Stage III and IV carcinoma of cervix, and commented that there were more cases in their retrospective air series, treated similarly. Van den Brenk (1968-44) considered that there was little difference in the sensitivity of the intestine to irradiation in HPO or air.

It follows, therefore, that sensible technical precautions and a careful and constant supervision of the patient will eliminate most hazards. Normal tissues must be protected by adequate shielding, more especially where the blood supply is naturally poor. If such tissues are unavoidably included in the field of treatment, modification of the radiation dosage is essential if complications /

complications are to be minimised and effective treatment secured. Complications of therapy can make a new technique unacceptable to the medical world. This has not happened with hyperbaric oxygen.

CHAPTER 4

Results of Trials in Other Centres

As already stated in Chapter 2, hyperbaric oxygen has been in use in radiotherapeutic departments throughout the world since interest was first aroused by Churchill Davidson and his associates (1955-25). Results have been published by a number of these centres and consideration of them does throw light on the Glasgow project.

In 1966 Churchill Davidson and his colleagues (1966-45) reviewed the results of radiotherapy treatment in high pressure oxygen (HPO) of 235 cases. These patients were generally under 65 years of age and had locally advancing disease which could be treated in a single field of reasonable size. They were regarded as incurable by conventional therapy. A control series of 81 cases was made up of patients suitable for HPO but excluded by reason of an independent medical condition such as coronary insufficiency or severe hypertension or because of their unwillingness to enter the specially designed oxygen chamber. Sites of disease all over the body were treated, the poorest response being in the brain, the best response /

response in the mouth and upper air passages and in the uterine cervix. Clinical assessment of all patients treated before 1st April, 1965 showed 56% of those treated in HPO to be tumour-free. Histological proof of this was obtained in 20% of the oxygen series. This compared with a tumour-free 40% of those treated in air, of which 3% showed no signs of tumour on histological examination. The incidence of distant metastases - 26% in the oxygen series and 30% in the air series was understandably high on account of the advanced nature of the disease prior to treatment. An even more striking response was noted in patients who had treatment of secondary squamous cell carcinoma in lymph nodes. 61 of the 84 oxygen cases (73%) were clinically free of tumour. The same could be said of only 7 out of 28 air cases (25%).

All these results must be viewed with some caution as the standard technique of treatment with daily fractionation was not used. Patients in this series had their course of therapy divided into /

into 2, 3 or 6 fractions with the minimum tumour dosage rising from 2000 rads to 4500 rads accordingly. The authors considered that the improvement in the results of their oxygen series was due partly to this fractionation change.

Van den Brenk, Madigan and Kerr (1964-46) in Melbourne Australia, reported on 203 cases of advanced malignant disease treated by 4 MEV irradiation in a specially constructed hyperbaric oxygen chamber at 4 ATA. Patients received 1 or 2 treatments weekly over 2 to 4 weeks (2000-3000 rads tumour dose). All had advanced inoperable or recurrent disease. The largest assessable group was 91 cases of head and neck cancer, all of whom showed marked regression of tumour following treatment. In fact, 69 of these cases (76%) were freed of neoplasm in the irradiated zone. Survival rates for 6 and 12 months were 81% and 40% respectively.

A later survey (1968-44) was on 614 cases. It was estimated that the rate of eradication of disease at the primary site /

site and at the regional lymph nodes in these head and neck cases should be between 60% and 70%. In fact 64% of these cases treated in HPO showed no recurrence clinically or at autopsy at the primary site. There was no evidence of disease in treated lymph node areas in 75%. These figures compared very favourably with 29% and 27% for air cases.

Van den Brenk (1968-47) has also published results of a small randomised series of 16 cases of carcinoma of the urinary bladder. Eight were treated in oxygen to a tumour dose of 3000 rads in 6 fractions over 22 days; eight were treated in air to a tumour dose of 3300 rads using the same fractionation and overall time. Improvement in survival was significantly better in the oxygen group.

Results published by Atkins and colleagues (1965-39) and, later, by Chang and colleagues (1968-48) from the same institute in New York, were also encouraging. They conducted an initial pilot study followed by a randomized series in which locally advancing cases of malignant disease of the head and neck were treated by irradiation /

irradiation in 4ATA oxygen. It was noted in the pilot study that the degree of normal tissue radiation damage was much higher in the oxygen cases. Modification of the radiation dosage schedule solved this complication. The arrival of a Vickers chamber altered the conditions of treatment from 4ATA to 3ATA and from 2 weekly treatments to 5 or 6 twice weekly sessions within the chamber. Treatment was given to post-operative cases of Glioblastoma Multiforme (3600 rads tumour dose in 9 fractions over 3 weeks). Six of the 12 oxygen cases in the series were alive and free of disease after 6 months. This was true of only 1 of the 22 air cases in the series. Patients with malignant disease of the mouth and upper air passages also showed rapid and impressive tumour response at the primary site and at the regional lymph nodes, when treated in hyperbaric oxygen. No exact figures were given.

Wildermuth (1964-49) reported on the first 100 cases treated in Seattle up to 1964. Patients of all ages tolerated the hyperbaric/

hyperbaric oxygen chamber well, even when very debilitated. Their malignancies varied widely in origin and case reports showed the markedly improved response of squamous cell carcinoma and the more anaplastic tumours. Lymph node metastases in cases of head and neck cancer appeared especially susceptible to the new technique. However, there was an obvious danger of massive tumour necrosis if care was not taken to modify the dosage regime.

A report by Emery (1964-50) on 17 cases of carcinoma of the bronchus compared the survival times of patients treated in different atmospheres of oxygen. Eight patients treated in 1.5 to 2ATA oxygen survived an average of 8.5 months and 6 of them died of local disease. Seven patients treated in 4ATA oxygen showed a better initial response, survived an average 12.5 months, and only 1 died of local disease.

Cade and McEwen (1967-51) published their experience in the use of HPO in radiotherapy in 1967. The Vickers chamber had /

had been used to treat 96 patients at 3ATA. Of these, 25 had carcinoma of the bronchus and 20 had carcinoma of the urinary bladder. These two groups were part of a controlled clinical trial set up to examine the survival time of patients receiving identical radiotherapy (6000 rads tumour dose in 40 fractions over 8 weeks) in either air or 3ATA oxygen. In the bronchus trial, 5 out of 25 oxygen cases and 6 out of 24 air cases survived 2 years. The incidence of metastases was the same in both series. In the bladder trial, 6 out of 20 oxygen cases and 8 out of 20 air cases survived 2 years. Here, however, the rate of metastatic disease was higher in the oxygen series - 6 out of the latter dying with metastases compared with 3 air cases. This is perhaps not surprising as the oxygen series contained a larger number of advanced cases.

More recent results of a randomized study of carcinoma of the urinary bladder, treated with radiotherapy in HPO, comes from Salt Lake City (Plenk, 1972-52). Using CO^{60} 19 patients were treated in HPO, 21 patients were treated in air. However, the standard technique of 6000 rads tumour dose on 30 fractions over /

over 6 weeks used for all "air" patients was modified to 4800 rads in 12 fractions over 32 days for those treated in oxygen. Results showed a statistically significant higher percentage survival of patients in the oxygen series over 4 years.

A report from Winnipeg, Canada, comes from Roulston and Johnson (1968-43) who have conducted a pilot study of 25 cases of Stage III and IV carcinoma of the uterine cervix treated by radiotherapy in HPO. They compared this with a retrospective series as a control group. The Vickers Chamber was used in combination with whole pelvic cobalt irradiation. All patients received a tumour dose of 5750 rads in 30 fractions over 6 weeks. The Stage III results showed 9 out of 18 cases treated in HPO and 5 out of 16 cases treated in air to be alive and free of disease up to 3 years later. In the stage IV series, 2 out of 7 oxygen cases and 2 out of 9 air cases were alive and well at the time of the report. Distant metastases appeared to occur earlier in the hyperbaric group - generally within the first 6 months. In the control group, metastases appeared up to 4 years after treatment.

The Cardiff trial results were reviewed by Henk et al (1970-53). This was a controlled clinical trial of head and neck cancer in which 213 patients were treated by radiotherapy, 112 in air and 101 in 3ATA oxygen. All patients were given a tumour dose of 3500 rads to 4500 rads in 10 fractions over 3 weeks. Benefit was clearly demonstrated to be greater in the oxygen group. The survival rate at 3 years was 30% for those treated in air and over 50% for those treated in oxygen. The recurrence-free rate was also higher for the latter group. This was particularly marked in cases of laryngeal carcinoma. Subsequent salvage laryngectomy was required in only 1 out of 20 patients treated previously in HPO compared with 7 out of 24 patients treated in air. Kunkler (1970-54) also noted that radical radiotherapy to lymph node metastases gave similar results to radical surgery and that these results were improved by the use of HPO as an adjunct to therapy.

From /

From all these reports, some indications of the value of this form of therapy can be discerned.

1. No deterioration in survival rate has resulted from using hyperbaric oxygen. On the contrary, there has been some improvement.

2. This improvement extends also to the local recurrence-free rate.

3. In the case of squamous cell carcinoma, most authors show improved results when treating affected regional lymph nodes by radiotherapy in hyperbaric oxygen.

4. In the results obtained from Melbourne, Salt Lake City and Cardiff, the oxygen treated series showed a statistically significant advantage in survival over those patients treated in air, for carcinoma of the urinary bladder and for carcinoma of the head and neck region.

11.

A cautionary note in the development of this new technique has been the possibility of an increase in metastatic disease in cases treated in HPO. This has been more noticeable in the immediate post-treatment period.

It must also be emphasised that fractionation is of even greater importance in treatment with hyperbaric oxygen due to an enhanced susceptibility to radiation damage of all cells, normal and abnormal. A slight modification of fractionation may make all the difference between cure and massive tumour necrosis.

CHAPTER 5

1. Practical Application
Personal Preliminary Survey

At the Glasgow Institute of Radiotherapeutics, the hyperbaric oxygen chamber was installed in 1964. Since that time, it has been used for treatment in conjunction with the 4MEV Linear Accelerator. More than 160 patients have been treated and over 3,500 treatment sessions have taken place. At its introduction, however, it was important to see if such a procedure could be accepted daily and without fear by patients receiving a course of therapy lasting up to 6 weeks; that there would be no toxic hazard to patients being treated regularly in this way; and that such an unusual adjuvant to orthodox radiotherapy technique could be integrated into the normal routine work of the Linear Accelerator Unit.

Thus, the first 85 patients constituted a preliminary survey to prove these points at issue. All of them had some form of malignant disease at an advanced stage. They had either local recurrence /

recurrence or dissemination to regional nodes or to other parts of the body. Inevitably, these patients would be considered unrewarding to treat by orthodox methods. It seemed right that one should not be doctrinaire in attempting to arrest such advanced and usually incurable disease. Many consultants took this view, and accepted this new method which might provide, at least, a glimmer of hope.

No patient was rejected for treatment, with the exception that, by reason of deformity or of excessive size, he or she was unable to fit into the chamber and receive irradiation to the tumour area. There have been altogether 5 such patients :-

1. Male - Ca Oesophagus - marked kyphoscoliosis
2. Male - Ca Bronchus - very broad shoulders, unable to turn over within the chamber
3. Female - Ca Cervix
4. Female - Ca Cervix
5. Female - Ca Cervix

Too stout - unable to turn over within the chamber

In /

3.

In order to allay patients' fears, the entire procedure was carefully explained in simple terms. This procedure which was straightforward enough to doctors and technicians, was, for the patient, a step into the unknown which he or she was most fearful to take. Most patients were very nervous indeed of the rather futuristic looking apparatus. In the event, out of 85 patients offered treatment only 6 rejected it. The vast majority, after a trial run, accepted the treatment although all required constant support and reassurance. It must be admitted that the enclosure of the patient in the chamber generated a feeling of claustrophobia even in the most self-reliant. Because of this, the doctor made it a cardinal point to be within sight and sound of the patient throughout every treatment. To pass the time, there was conversation on general topics and the news of the day. Great interest was taken in the social and family background of each patient. In one case (No. 24) it was necessary for the doctor to learn simple Italian conversation in order to establish a good rapport. Other sources of distraction and conversation were found /

found in a changing gallery of pictures kindly lent by the Glasgow Art Galleries. Piped music, both classic and modern, was also available. One patient always carried a paper-back thriller to read in the chamber during the preliminary oxygen-saturating period. Only during the relatively brief period of actual megavoltage x-ray therapy, when, inevitably, no attendant could be with the patient in the treatment room, was the visual contact lost. Then the most was made of the two-way telephone conversation.

As the author has personally treated every one of the 164 patients assessed in this thesis, she realised that it would be worthwhile recording some of their comments and opinions, made spontaneously in the course of this completely new form of treatment.

"I don't mind lying here, Doctor, as long as I know that you are there"

"I feel like a goldfish in a tank"

"It's alright as long as I can talk to you"

"I enjoy the music except when I'm having my actual treatment. Then I like to lie quietly and think"

"I always feel very hot"

"You know, I cannot bear to stand inside one of Pettigrew's lifts. I don't know how you manage to persuade me to lie in here"

"It's /

"It's not uncomfortable for me. I have been to the bottom of the Clyde in a diving bell on many occasions."

"Don't wory about me. I'm determined to go through with it"

"I felt nervous at first, but not now. I can even doze in it"

"I prefer lying on my stomach. It's so much more comfortable reading my book in that position"

"It's not my cup of tea, but I can thole it"

"The time goes so quickly when we talk about the family"

"It's no bother to me at all now. But, at first, I thought that I could never bear it"

"I just pretend that I'm an astronaut"

"I just couldn't have done it without you, Doctor"

"I feel every morning as though I am going to my execution"

"I'm not flattering you, Doctor, but you give me confidence, and I don't worry as long as I know that you are in the room."

The successful integration of hyperbaric oxygen therapy into the existing daily supervoltage programme was essential if the work of the Linear Accelerator was to be carried on smoothly and without undue strain to patients and staff. For the first year, due to the limited adjustment of the chamber, it was necessary to work at an extended focus-to-skin distance (F.S.D.) This prolonged treatment time to nearly twice that of patients treated in air. It was only after 85 patients had been treated that a motorised /

motorised trolley was added to the chamber. This improved the manoeuverability of the chamber and made possible its elevation. The standard F.S.D. of 100 cms. could now be used and thus treatment time became identical with that of patients in air.

Time taken to move the chamber into and out of the treatment room and to arrange the field set-up was increased by an average of one minute. Nevertheless, as many as 9 patients have been treated daily without additional strain to the staff.

As is shown in Figure 4, a very wide range of malignant diseases was covered by the first 85 patients constituting this preliminary survey. Their common denominator was the advanced nature of their illnesses, incurable by orthodox methods of radiation or surgery. There were 33 men and 52 women in this group and their ages varied from 16 to 84 years, covering all periods of adult life. The diagnosis in each case had been proved initially by histological examination following biopsy or operation. These malignancies arose from many systems. There were :-

No.	Age	Sex	Diagnosis	Spread Prior to Radiotherapy	Site	TREATMENT V	T	D	Dose	Fractions	Days	SURVIVAL Months	Quality
1	61	F	Melanotic Sarcoma Urethra	Vagina, R. Inguinal Nodes	Pelvis	14 x	10 x	18	6,000	29	38	14	Local regression - 6 months. Well - 6 months.
2	16	M	Osteogenic Sarcoma, R. Femur	Lungs	Chest	33 x	27 x	19	266	2	2	2	Too ill to complete treatment. No regression.
3	70	M	Anaplastic Ca. Bladder	Pelvic Wall, Pelvic Nodes	Pelvis	9 x	7.5 x	7.5	1,200	6	8	4	Refused to complete treatment. No regression.
4	71	M	Adenocarcinoma Rectum	Ant. Abdominal Wall	Abdomen	10 x	9 x	6	6,000	30	45	8	Local regression and relief of pain - 2 months.
5	76	F	Liposarcoma, R. Thigh	Thigh, and R. Inguinal Nodes	R. Thigh, Groin	36 x	20 x	14	6,000	30	40	7	Local regression. Well till death from unrelated C.V.A.
6	58	F	Squamous cell Ca. Cervix	Rectum, parametria	Pelvis	12 x	9 x	9	6,000	30	41	5	No local regression. Well - 4 months.
7	63	F	Squamous cell Ca. Cervix	Vagina, parametria	Pelvis	12 x	9 x	9.5	6,000	30	40	23	Local regression - 11 months. Well - 22 months.
8	54	F	Squamous cell Ca. Cervix	Parametria, Supraclav. Nodes	Pelvis	12 x	8 x	14	6,500	32	51	10	Local regression - 8 months. Relief of pain - 6 months.
9	57	F	Squamous cell Ca. Bladder	L. Pelvic Wall, Vagina	Pelvis	10 x	12.5 x	10	6,000	30	42	25	Local regression - 6 months. Well - 7 months.
10	64	F	Adenocarcinoma Uterus	Pelvic Mass	Pelvis	22 x	23 x	15	6,000	30	42	25	Local regression - 13 months. Well - 15 months.
11	54	M	Fibrosarcoma, R. Thigh	Lungs	Chest	1st Treatment O_2 Convulsion - treated in air						2	No regression.
12	64	M	Adenocarcinoma Rectum	Anus, Inguinal Nodes	Pelvis	18 x	20 x	20	6,120	26	43	4	Local regression and relief of pain - 3 months.
13	67	F	Squamous cell Ca. Vulva	Vulva, L. Inguinal and Femoral Nodes	Pelvis	17 x	25 x	15	4,650	21	34	2	Too ill to complete treatment. Local regression.
14	71	M	Transitional cell Ca. Bladder	Perivesical tissues	Pelvis	11 x	10 x	9	6,400	32	46	19	Local regression - 15 months. Well - 18 months.
15	64	F	Squamous cell Ca. Vulva	Vulva, L. Inguinal Nodes	Pelvis	Non-co-operative - treated in air						1	Death from acute renal failure.
16	30	F	Adenocarcinoma Cervix	Parametria, Pelvic Nodes.	Pelvis	12 x	10 x	11	6,600	33	45	5	No regression. No symptomatic relief.
17	50	M	Papillary Ca. R. Kidney	Scar R. Loin	R. Loin	10 x	8 x	9	6,000	20	28	28	Local regression - 3 months. Well - 15 months.
18	50	F	Malignant Melanoma Vulva	R. Inguinal Nodes, Pelvic Mass	Groin and Pelvis	20 x	20 x	7	4,320	24	32	2	Too ill to complete treatment. No regression.
19	41	F	Squamous cell Ca. Cervix	Parametria, Pelvic Nodes.	Pelvis	9 x	11 x	17	6,000	30	42	8	Local regression, abdominal metastases. Well - 5 months.
20	49	F	Malig. Synovioma, R. Thigh	Thigh	R. Thigh	30 x	16 x	16	6,600	33	51	24	Local regression - 18 months. Well - 22 months.
21	53	M	Ca. Bronchus	Lower lobe R. lung	Thorax	12 x	8 x	20	5,000	25	39	13	Symptomatic relief - 5 months.
22	64	M	Transitional cell Ca. Bladder	Bladder	Pelvis	10 x	10 x	10	6,500	32	54	79	No recurrence. Well.
23	75	M	Papillary Ca. Bladder	Bladder	Pelvis	9 x	11 x	9	6,400	31	46	30	Complete local regression. Well till death (myocardial infarction).
24	38	F	Squamous cell Ca. Cervix	Parametria	Pelvis	10 x	16 x	9	6,000	30	43	76	Complete local regression. Metastasis R. Ilium treated 15 months later. Well.
25	53	F	Squamous cell Ca. Cervix	Pelvic Mass	Pelvis	15 x	10 x	16	6,000	30	44	8	Complete local regression. Lung metastases - 7½ months.
26	65	M	Malig. Synovioma L. Ant. Axilla	Doubtful if excision complete	L. Axilla	11 x	9 x	6	600	3	3	75	Refused O_2 Chamber - treated in air. Complete local regression. Well.
27	75	F	Squamous cell Ca. Cervix	Bladder, vagina, parametria	Pelvis	14 x	10 x	12	6,000	30	48	17	Local regression - 11 months. Well - 11 months.
28	34	F	Ca. L. Breast	R. Breast, Lungs	L. Breast	20 x	15 x	10	3,500	8	25	2	Local regression (L. Breast) Lung Metastases.
					R. Breast	Similar treatment in air							
29	42	F	Cystadenocarcinoma Ovary	Pelvic Mass	Pelvis	15 x	17 x	11	5,000	28	43	3½	Local regression. Well till death (pulmonary infarct) (Deep venous thrombosis of le
30	53	M	Myosarcoma Rectum	Rectum	Pelvis	17 x	14 x	21	6,000	27	50	43	Local regression - 32 months. Well 32 months.
31	69	F	Papillary Ca. Bladder	Vagina	Pelvis	11 x	15 x	10	6,000	30	43	49	Complete local regression. Well till death (unrelated renal disease).
32	61	M	Adenocarcinoma Rectum	Peri-rectal tissues, Pelvic Nodes	Pelvis	20 x	10 x	12	4,680	26	38	-	Treatment incomplete. Death due to tumour perforating rectum.
33	18	F	Osteogenic Sarcoma L. Upper Tibia	Tibia, Popliteal fossa	Upper tibia, knee	32 x	18 x	11	5,760	25	36	74	Mid-thigh amputation after treatment. Well. (see text)
34	52	F	Leiomyosarcoma R. side Pelvis	Omentum	Pelvis	19 x	12 x	19	5,220	30	48	23	Local regression - 5 months. Well 22 months.
35	72	F	Papillary Ca. Bladder	Perivesical tissues	Pelvis	10 x	14 x	12	5,990	30	44	6½	No regression. Symptom free - 5 months.
36	59	F	Cystadenocarcinoma Ovaries	Pelvic tissues	Pelvis	14 x	14 x	11	6,000	30	42	46	Complete local regression. Lung metastases. Well - 40 months.
37	66	F	Squamous cell Ca. Cervix	L. Parametrium, Vagina	Pelvis	14 x	8 x	12	5,000	25	38	74	Complete regression. Well.
38	61	F	Adenocarcinoma Rectum	Vagina, Pelvic Floor	Pelvis	14 x	15 x	17	4,980	22	30	9	Treatment incomplete (diarrhoea). No regression. Symptom free - 7 months.
39	57	F	Adenocarcinoma R. Kidney	Perirenal Tissues	Abdomen	20 x	17 x	17	4,160	26	33	-	Treatment incomplete. Acute intestinal obstruction. P.M. - tumour regression.
40	56	F	Ca. L. Kidney	Incomplete excision	L. Loin	14 x	20 x	15	6,000	30	42	72	Complete regression. Well.
41	70	M	Squamous cell Ca. Oesophagus	Inoperable	Oesophagus	5@	x 14		6,000	30	43	10	Local regression. Dysphagia relieved. Lung metastases.
42	55	F	Squamous cell Ca. Cervix	Vagina, Rectum, Pelvic Wall	Pelvis	14 x	11 x	12	5,000	25	37	72	Complete regression. Well.
43	53	F	Squamous cell Ca. Anus	Anus, bilateral Inguinal Nodes	Pelvis	18 x	20 x	16	5,000	25	34	28	Local regression - 17 months. Well - 24 months.
44	60	F	Carcinoma R. Breast	R. Breast	R. Breast	27 x	9 x	7	6,000	30	43	40	Complete local regression. Lung metastases. Well - 36 months.
45	53	F	Retroperitoneal Liposarcoma	Inoperable	Abdomen	33 x	27 x	26	640	4	6	-	Treatment incomplete. Pulmonary infarct.
46	28	M	Carcinoma L. Kidney	Incomplete excision	L. Loin	34 x	20 x	17	6,500	40	58	71	Complete regression. Well.

Dimensions of treated volume in cms: V = Vertical, T = Transverse, D = Antero-posterior

Figure 4

						TREATMENT						SURVIVAL	
No.	Age	Sex	Diagnosis	Spread Prior to Radiotherapy	Site	V	T	D	Dose	Fractions	Days	Months	Quality
47	43	F	Squamous cell Ca. Cervix	Vagina, Parametria	Pelvis	14 x	10 x	14	5,000	25	35	32	Complete local regression. Lung metastases. Well - 12 months.
48	60	M	Anaplastic Ca. Bladder	Pelvic Nodes	Pelvis	12 x	10 x	14	6,000	30	42	10	Local regression - 5 months. Symptom free - 7 months.
49	69	F	Anaplastic Ca. Cervix	Vagina, L. Pelvic Wall	Pelvis	14 x	12 x	14	5,500	28	40	8	No regression. Abdominal metastases. No symptomatic relief.
50	64	M	Ca. R. Kidney	Perirenal tissues, Supraclav. Nodes	R. Loin	19 x	20 x	17	6,000	30	44	2	No regression. Generalised metastases.
51	77	F	Squamous cell Ca. Cervix	Vagina, Parametria	Pelvis	17 x	11 x	12	6,400	32	54	48	Complete local regression. Death from chronic renal failure (see text).
52	58	F	Papillary Ca. Bladder	Urethra	Pelvis	11 x	10 x	11	6,000	30	43	16	Local regression - 10 months. Well 13 months.
53	66	F	Squamous cell Ca. Cervix	Pelvic Mass	Pelvis	Non-co-operative - treated in air						-	Treatment incomplete. Acute pyelonephritis and renal failure.
54	76	F	Squamous cell Ca. Cervix	R. Parametrium	Pelvis	14 x	12 x	14	5,000	25	35	50	Complete local regression. Well till death from arterio-sclerosis.
55	55	M	Anaplastic Ca. L. Kidney	Perirenal tissues, Aortic Nodes	L. Loin	18 x	20 x	16	6,000	32	46	2	No regression. Abdominal metastases.
56	54	F	Adenocarcinoma Rectum	Pelvic and Inguinal Nodes	Pelvis	14 x	13 x	13	4,320	20	28	16	Local regression - 12 months. Well - 13 months.
57	75	M	Mucoid Adenocarcinoma Sigmoid Colon	Intra-abdominal	L. Abdomen	19 x	16 x	18	4,500	20	26	2	No regression.
58	77	M	Squamous cell Ca. Bladder	Peritoneum	Pelvis	11 x	11 x	10	6,000	30	42	15½	No regression. Well - 12 months.
59	62	M	Transitional cell Ca. Bladder	Bladder	Pelvis	11 x	11 x	8	5,000	20	28	24	Complete local regression. Well till death from myocardial infarction.
60	61	F	Adenocarcinoma L. Kidney	Incomplete excision	L. Loin	9 x	11 x	8	5,000	20	26	9	Complete local regression. Multiple bony metastases. Well - 3 months.
61	52	M	Anaplastic Ca. Bladder	Bladder	Pelvis	9 x	11 x	8	5,500	25	33	5	No regression. Generalised metastases. No symptomatic relief.
62	59	F	Papillary Ca. Bladder	Pelvic Wall	Pelvis	12 x	10 x	11	204	1	1	10	Refused O_2 Chamber - treated in air. No regression. No symptomatic relief.
63	58	F	Retroperitoneal Sarcoma	Retroperitoneal metastases	Abdomen	19 x	17 x	12	5,000	25	36	8	Local regression and relief of pain. Generalised metastases.
64	70	M	Lipomyxosarcoma R. Groin	R. Iliac Fossa	Lower Abdomen	22 x	7 x	7	6,000	30	44	20	Local regression - 14 months. Lung metastases. Well - 16 months.
65	55	M	Squamous cell Ca. Scrotum	R. Inguinal Nodes	R. Groin	16 x	10 x	14	5,000	25	37	12	Local regression - 9 months. Well - 10 months.
66	53	F	Transitional cell Ca. Bladder	Perivesical tissues	Pelvis	8 x	9 x	9	6,000	24	35	66	Complete local regression. Well. (N.B. Asymptomatic bladder telangiectasia
67	57	F	Squamous cell Ca. R. Leg	R. Inguinal Nodes, R. Pubis	R. Groin	16 x	11 x	7	6,000	24	36	20	No regression. Slow deterioration.
68	58	M	Squamous cell Ca. Bronchus	Mediastinal lymph Nodes	Chest	8 x	8 x	6	6,000	24	32	22	No regression. Symptom free - 16 months.
69	61	F	Adenocarcinoma Rectum	Pelvic Mass	Pelvis	15 x	15 x	19	1,600	8	12	3	Too ill to complete treatment. Generalised metastases.
70	41	F	Anaplastic Ca. Bladder	Bladder	Pelvis	15 x	15 x	17	1,340	6	8	1	Too ill to complete treatment. Lung metastases.
71	62	F	Adenocarcinoma Rectum	R. Iliac Fossa	R. Iliac Fossa	10 x	8 x	16	8,000	26	36	64	Complete regression. Well.
72	63	M	Transitional cell Ca. Bladder	Bladder	Pelvis	9 x	8 x	9	4,750	20	27	9	Treatment incomplete (dysuria). No regression. Symptom free - 4 months.
73	58	M	Transitional cell Ca. Bladder	Bladder	Pelvis	9 x	9 x	11	6,000	24	35	64	Complete regression. Well.
74	76	F	Adenocarcinoma Rectum	Vagina, Pelvic tissues	Pelvis	14 x	14 x	17	6,000	30	43	12	Local regression - 11 months. Well - 11 months.
75	61	F	Adenocarcinoma of Colon	Retroperitoneal metastasis	Abdomen	25 x	22 x	19	3,750	24	34	5	Local regression - 3 months. Multiple metastases. Well - 4 months.
76	50	F	Papillary Ca. Bladder	Bladder	Pelvis	8 x	7 x	7	6,000	24	30	19	No regression. Symptomatic relief - 9 months.
77	66	M	Squamous cell Ca. Bladder	Pelvis Rectum	Pelvis	15 x	15 x	18	4,500	14	26	3	No regression. No symptomatic relief.
78	77	F	Fibro-liposarcoma R. Thigh	Thigh	R. Thigh	20 x	15 x	13	6,000	19	29	23	Complete local regression. Well till death (unrelated Ca. uterus)
79	53	F	Squamous cell Ca. Cervix	Pelvic Mass	Pelvis	20 x	15 x	23	2,690	10	11	3	No regression. No symptomatic relief.
80	57	M	Seminoma L. Testis	L. Kidney	Abdomen	27 x	18 x	24	4,000	20	29	62	Complete regression. Well.
81	61	M	Synovial Sarcoma L. Groin	Groin, Abdominal Wall	L. Groin	24 x	14 x	18	6,000	30	43	4	No regression. Steady deterioration.
82	67	F	Retroperitoneal Neurogenic Sarcoma	Inoperable	Abdomen	28 x	28 x	25	3,500	20	26	12	Local regression - 8 months. Symptom free - 9 months.
83	71	M	Leiomyosarcoma L. Groin	Groin	L. Groin	16 x	12 x	17	4,500	16	23	37	Complete local regression. Well till death (myocardial infarction).
84	79	M	Lymphosarcoma Testis	L. Leg	L. Leg	38 x	14 x	13	3,700	14	18	7½	Local regression. Multiple metastases. Steady deterioration.
85	62	M	Adenocarcinoma Rectum	Abdominal and Perineal scars	Pelvis	12 x	12 x	12	630	3	5	2½	Treatment completed in air (abdominal pain). No regression.

Figure 4 (continued

27 tumours arising from the urinary tract
23 tumours arising from the reproductive tract
13 tumours arising from the gastro-intestinal tract
13 tumours arising from the musculo-skeletal system
6 tumours arising from the epidermis
2 tumours arising from the respiratory tract
1 tumour arising from the sympathetic nervous system

Radiotherapy was prescribed according to the regular methods used in the department. Although disease tended to be advanced, every effort was made to take the radiation dose to radical levels. A total of 16 out of 85 patients did not complete treatment. In 8 of these (Nos. 2, 13, 18, 69, 70, 72, 79 and 85) this was because the patients became too ill to be moved. Only case No. 85 was able to complete treatment in air. All died within 3 months of the beginning of treatment with the exception of case No. 72, who, having had 70% of his treatment, survived 9 months and had symptomatic relief for 4 months. Case No. 39 suddenly deteriorated with symptoms of a partial intestinal obstruction from which she died in what would have been her last week of therapy. Case No. 45 died of a massive pulmonary embolus when only 4 treatments had been given.

Six patients refused to be treated in the oxygen chamber although all entered it (see Figure 5). Cases Nos. 11, 15 and 26 were not treated at all. Cases Nos. 3, 25, and 62 had 6, 3 and 1 treatment respectively before refusing to continue. All 6 patients were subsequently treated in air and died without signs of regression, with the exception of Case No. 26 who is alive and well 75 months later. Thus, out of 85 patients accepted for treatment, 69 completed it - a total of 80%.

All 69 patients were understandably nervous at the onset of therapy. Two (Nos. 10 and 20) suffered from acute claustrophobia but, with the help of tranquillising drugs and continuous encouragement from the doctor in charge, both completed the courses prescribed. Five cases (Nos. 9, 29, 68, 70 and 72) had difficulty in adjusting their ears to the rising pressure in the chamber. All settled satisfactorily within the first week by the use of Cerumol ear drops to remove wax and a nasal decongestant - 1% Ephedrine in normal saline. Three patients (Nos. 24, 38 and 52) experienced nausea and occasional vomiting during and after decompression.

All /

ANALYSIS OF PATIENT REFUSAL

Trial No.	Age	Sex	Disease	No. of Treatments in HPO	Reason for refusing treatment in HPO.
3	70	M	Ca. Bladder	6	Very disturbed by temporary change of doctor in charge of treatment.
11	54	M	Lung metastases	None	Convulsion after 15 minutes in oxygen chamber increased his acute anxiety.
15	64	F	Ca. Vulva	None	Mentally disturbed and would not co-operate.
26	65	M	Malignant Synovioma of shoulder	3	While at home for weekend, was re-assured by his own doctor that HPO was not an essential part of his treatment.
53	66	F	Ca. cervix (IV)	None	Deaf and demented and unable to co-operate.
62	59	F	Ca. bladder	1	This intelligent lady considered the pros and cons of treatment in HPO and decided against it.

Figure 5

All improved with injections of Prochlorperazine (Stemetil) 12.5 mgs in 1cc. Convulsions occurred in 4 patients (Nos. 11, 23, 32 and 60). No. 11 convulsed on the first day after 13 minutes at full pressure in the chamber. No. 23 convulsed on the 8th day of treatment during actual x-ray therapy after 19 minutes in the oxygen chamber at full pressure. No. 31 convulsed during decompression on the 24th day of treatment. No. 60 convulsed after being in the chamber at full pressure for 13 minutes and before her first x-ray treatment was given. Following emergency decompression, all recovered within 3 minutes of removal from the chamber and, with the exception of No. 11, continued their courses of therapy in the chamber without further incident. Fifty-five patients went through the courses of treatment prescribed for them smoothly and without complaint.

When considering the survival of these patients, one must remember that none would have been considered curable by the usual therapeutic methods, and even with the help of hyperbaric /

hyperbaric oxygen, it was very doubtful indeed if any one of them could have been expected to regain permanent good health. What seemed of value in the assessment of cases at follow-up was the quality of survival obtained in terms of local regression and freedom from symptoms.

Figure 6 puts this in graphic form. The horizontal lines represent the lifelines of the 69 patients who completed therapy. Each lifeline has the case number of the patient. Those on the left are the cases in whom no local regression was achieved between the beginning of treatment and death. There were 17 such cases - 25% of the total treated - and 6 of them had a satisfactory symptom-free period. Eleven deteriorated steadily with uninterrupted advancement of disease.

Those on the right represent the 52 patients who had local regression of disease, a total of 75% of those treated. For 22 patients (32%) regression was only for a temporary period lasting between 3 and 32 months. It was always accompanied /

SURVIVAL OF PATIENTS IN INITIAL SERIES

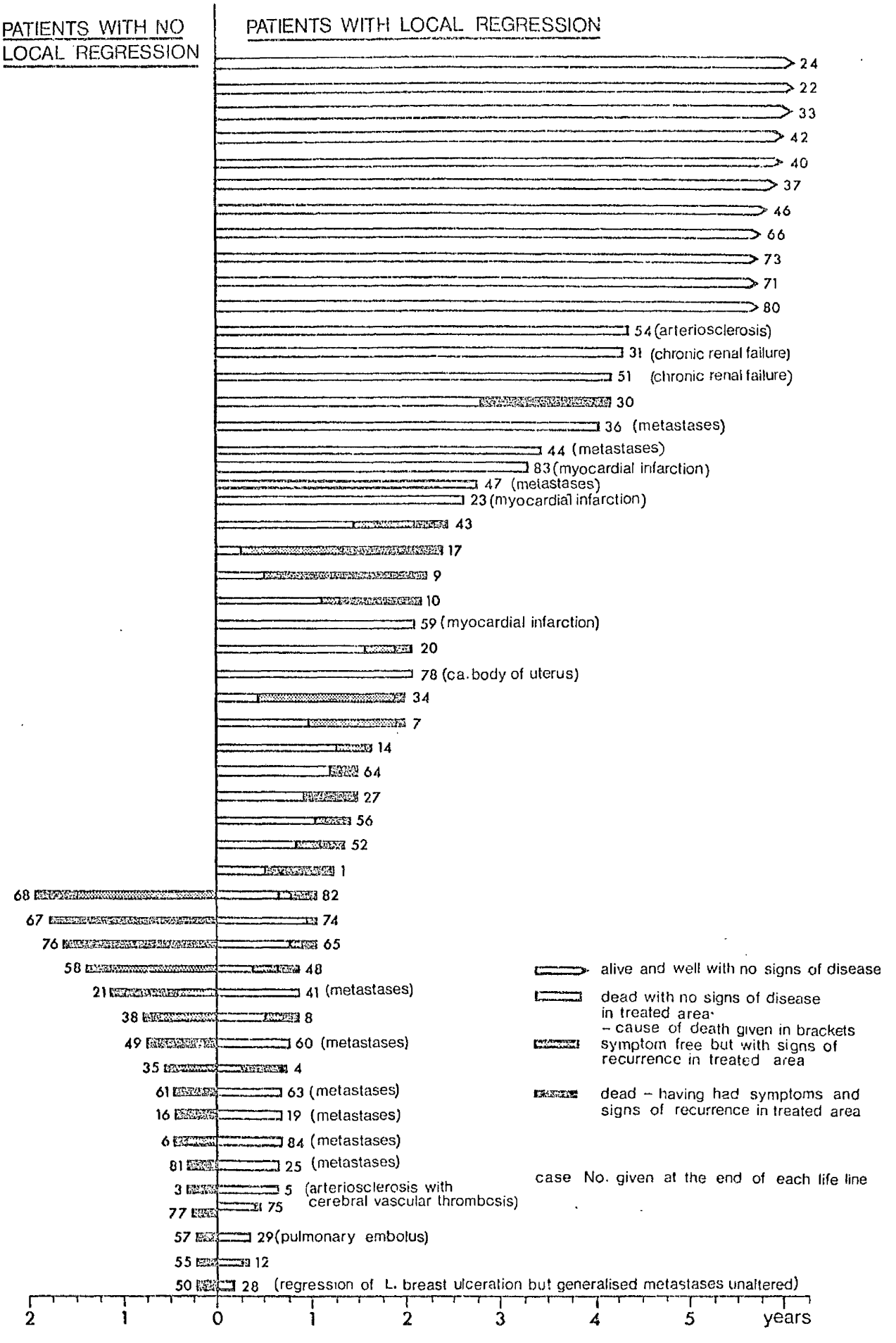


Figure 6

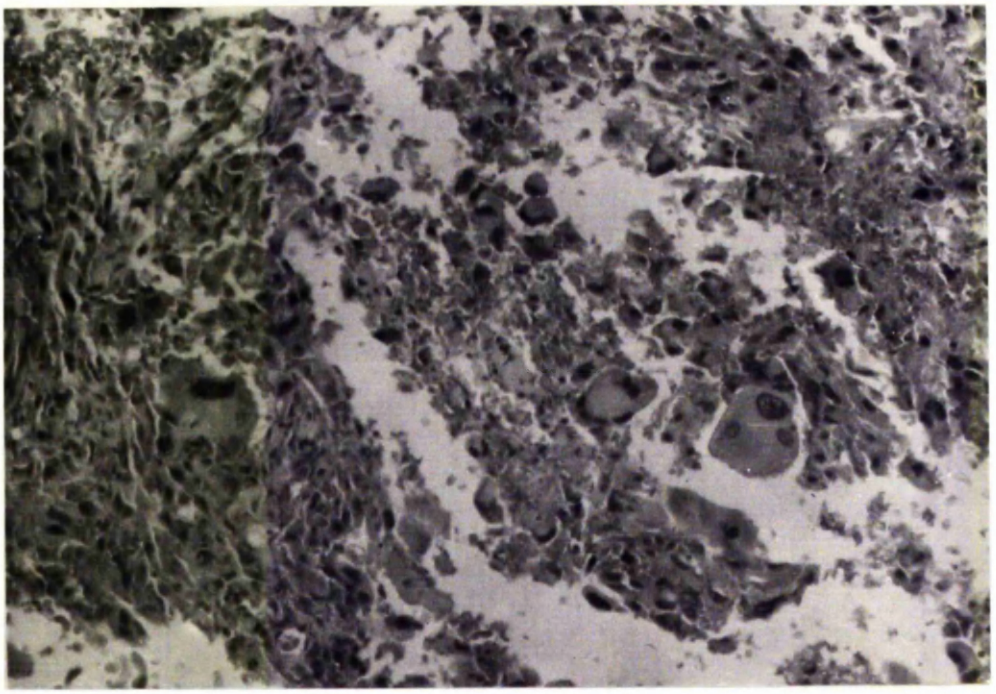
accompanied by a similar or longer period of satisfactory health. In the 10 patients who died from metastatic disease (14.5%), there was excellent regression of the treated tumour as shown clinically or by post-mortem examination. Another 9 patients (13%) died of an unrelated cause, all being clinically free from recurrence at the time of death. Eleven patients (16%) remain alive and well and without recurrence between 62 and 79 months after the commencement of therapy.

In this preliminary survey, two cases are of particular interest and are given in detail, viz.

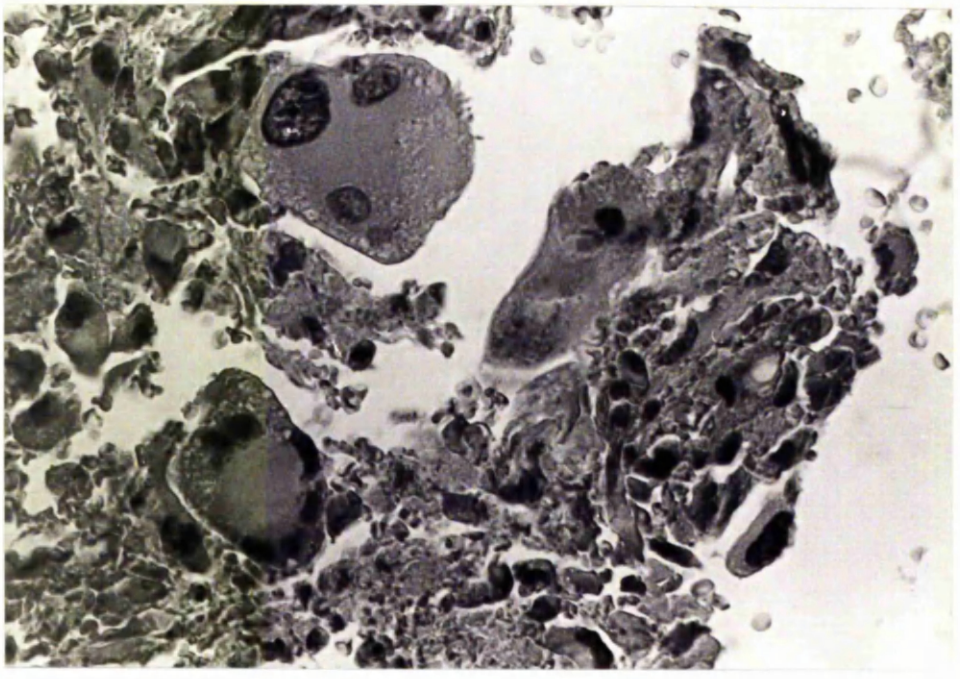
Case No. 33 - This patient, a girl of 17, had a past history of Tuberculous Endometritis treated by the usual triple drug regime of Streptomycin, Para-Aminosalicylic acid (PAS) and Izoniazid (INAH). Four months after the institution of treatment, she developed swelling of the upper end of her left tibia. This was accompanied by pain and stiffness. In view of her history, bone tuberculosis was, at first, suspected but repeated needle biopsies were negative for this. Histological examination of bone tissue obtained at open operation 8 weeks after the onset of /

of symptoms, showed osteogenic sarcoma. (Figure 7a). Following this diagnosis, treatment of the tumour by local arterial perfusion with methotrexate caused immediate but very temporary regression. Four and a half months after the initial appearance of the swelling, she was referred for radiotherapy. This was carried out by combined hyperbaric oxygen and supervoltage x-ray therapy. Parallel opposed fields, 32 x 18 cms. were used at an F.S.D. of 122 cms. and a tumour dose of 5760 rads was given in 25 treatments over 36 days. Mid-thigh amputation of the leg followed one week after completion of radiotherapy. Histological examination now revealed only necrotic tissue and areas of haemorrhage surrounded by a reactive fibrous zone containing hemosiderin-laden macrophages. There had obviously been invasion of the skeletal muscle and of the epidermis by tumour tissue but, in spite of repeated sections being taken from all areas of the affected tissue, not a single viable tumour cell was identified (Figure 7b).

It /

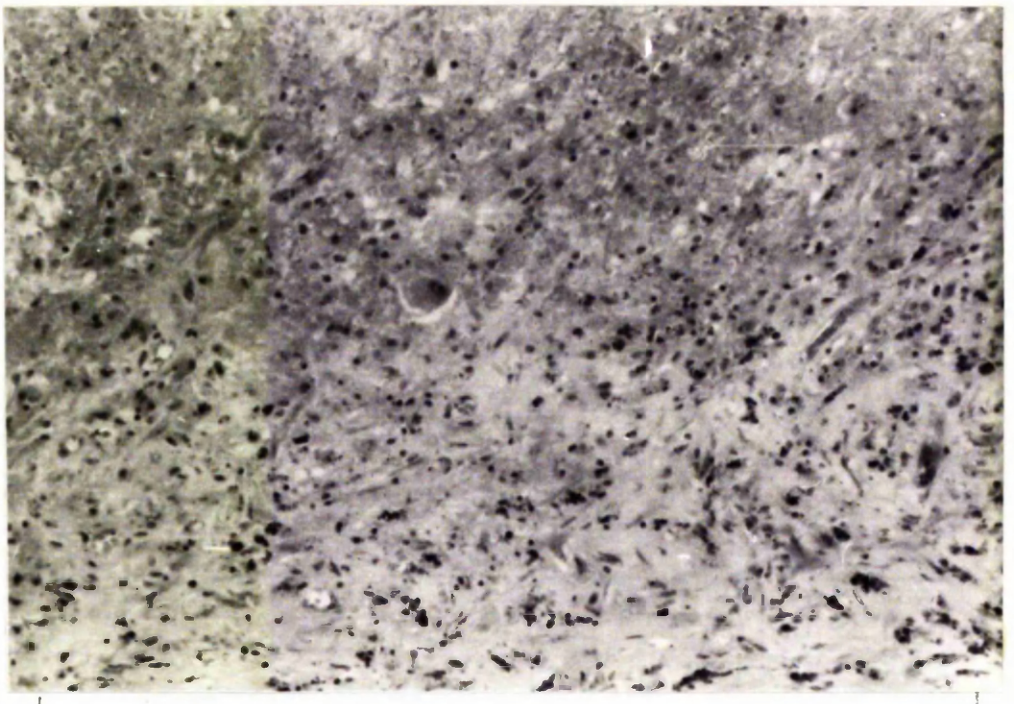


Great cellularity and striking pleomorphism with large numbers of giant cells, many of which have multiple nuclei. Low power x 125.

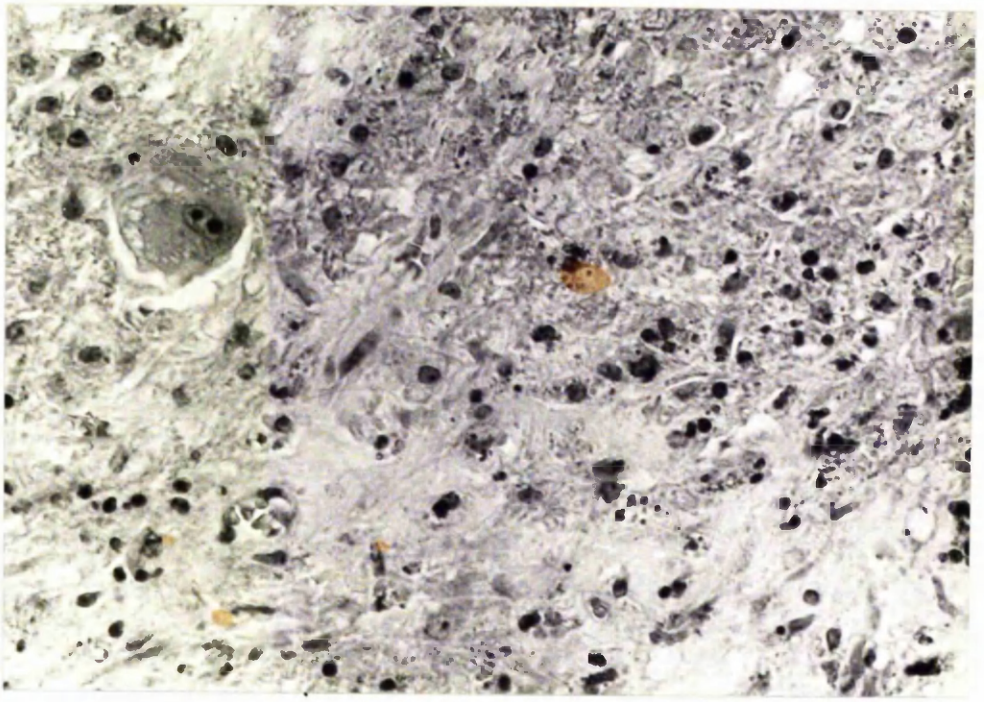


Highly pleomorphic osteogenic sarcoma with two enormous giant cells. High power x 350.

Figure 7a



Necrotic tumour above with reactive fibroplastic proliferation below. Low power x 125



Detailed view of necrotic area of tumour above and reactive fibroplastic proliferation below. There are abundant granules of haemosiderin and of lipofuscins scattered throughout the tumour and the reactive tissue. High power x 350.

Figure 7b

It is of interest to note that 10 months after her amputation and in spite of her previous history of T.B. Endometritis, the patient became pregnant. Unfortunately, she developed hyperemesis requiring hospitalization and termination of pregnancy. She has remained in excellent health since then, a period of over 74 months and is happily married.

Case No. 51 - This elderly lady of 77 was referred for radiotherapy with a Stage III squamous cell carcinoma of cervix. There was extension of the tumour into both uterosacral ligaments, and to the lower third of the vagina as far as the introitus. Because of stenosis of the vagina by tumour, no radium could be inserted. External supervoltage x-ray therapy consisting of 4 pelvic fields, all 18 x 11 cms. was given in 32 fractions over 54 days to a tumour dose of 6400 rads, the patient being pressurized in the oxygen chamber for all treatments without any complication. Subsequently, she /

she remained well for $5\frac{1}{2}$ months before developing abdominal symptoms suggestive of an intestinal obstruction. These settled temporarily but she required an emergency laparotomy for acute symptoms 1 month later. On this occasion, beyond dilated and hypertrophied small bowel, the terminal ileum was found to be grossly thickened, contracted and avascular in appearance (Figure 8). No enlargement of mesenteric nodes or, in fact, any signs of recurrence of malignancy were seen. Clearly, there had taken place a gradual radiation necrosis of this loop of ileum which had healed by intense fibrosis thus causing an obstruction. The patient remained well for another three and a half-years and died without evidence of recurrence.

When a general assessment was made of the results of this preliminary survey, there was shown to be a definite improvement in the quality of survival of 75% of the cases treated. Whether the high pressure oxygen contributed materially /

Case No. 51

Appearance of bowel at operation for acute obstruction showing acute radiation fibrosis of the terminal ileum.

Figure 8

materially to this could only be surmised as a clinical impression. Some support was derived from the valuable studies of Churchill Davidson, Van den Brenk, Atkins and others, as mentioned in Chapter 3. However, their methods varied, treatment being given at 4ATA in some series. Furthermore, fractionation of treatment tended to be on a once or twice weekly basis rather than on the standard 5 days per week technique used conventionally in Glasgow. Such additional variables make it difficult to equate the results of one centre with another.

Nevertheless, in Glasgow it had become clear that the criteria required of this new technique of hyperbaric oxygen with radiotherapy had been fulfilled. It was acceptable to patients without undue hazard. It was easily assimilated into the daily routine work of the Linear Accelerator team. But, above all, in a series of patients with advanced malignant disease, regarded as incurable by ordinary therapeutic standards /

standards, it had been shown to cause tumour regression in a majority and to hold out a hope of cure in 16% of them.

CHAPTER 6

Medical Research Council Trials

There was now no doubt that radiotherapy combined with hyperbaric oxygen constituted a new form of treatment which showed definite promise. Moreover, many therapists, convinced by their encouraging results of the value of hyperbaric oxygen, thought that it would be morally wrong to withhold this treatment from suitable patients (Churchill Davidson et al 1966-45). However, a true critical evaluation could only be achieved by a controlled clinical trial. Already in 1965 the Medical Research Council had appointed a committee to co-ordinate the work in progress in this field at various centres in Britain. It now seemed appropriate to take part in this.

The Cervix Trial

At the Glasgow Institute of Radiotherapeutics, advanced carcinoma of the uterine cervix was selected as the subject of the trial. Cases were chosen if they fitted into one of the following /

following categories :-

1. Stage III carcinoma of the uterine cervix involving either the lower third of the vagina or extending through the parametrium to the pelvic wall.

2. Stage IV carcinoma of the uterine cervix involving the mucosa of the bladder or of the rectum but not extending beyond the true pelvis.

For these cases, radiotherapy is the only practical form of treatment holding out even the slightest hope of cure. In fact, a 36% five year survival for Stage III cases and a 9% survival for Stage IV cases are the Glasgow figures for the period 1956-63 (Figure 9) prior to the introduction of HPO. It has been shown that the oxygen effect is minimal when low intensity radiation is given over a prolonged period of time, but maximal when high intensity rays are used over short periods. (Hall, Bedford, Oliver 1966-55). It thus seemed reasonable to hope that hyperbaric oxygen added to the treatment technique might improve the results for the Stage III and IV cases. Moreover, the advantages of this site are : /

ADVANCED CASES OF CA. CERVIX

referred to
Radiotherapy Department, Western Infirmary, Glasgow
1956-63

	STAGE III		STAGE IV	
	Radical	Palliative	Radical	Palliative
No. treated	179	6	67	9
No. alive at 5 years	66	0	7	0
5 year survival	37%	0%	10%	0%
Overall 5 year survival	36%		9%	

Figure 9

site are :-

1. Its accessibility allowing biopsy and a clear assessment of the extent of the malignancy which, even in its terminal stages, may still be confined to the pelvis.

2. The fact that there would be a minimum of bone and cartilage involvement in the treatment volume.

3. The ease with which local regression of tumour as well as quality of survival might be assessed.

4. The expectation that there would be sufficient patients available for treatment.

Conditions of Entry

Patients entered in the trial had to satisfy the following criteria :-

(a) The age of the patient must be less than 75 years

(b) The diagnosis of carcinoma must be corroborated by histology prior to treatment

(c) /

(c) Patients must have Stage III or IV carcinoma of the cervix with disease confined to the pelvis

(d) No previous radiotherapy and no surgery other than a diagnostic procedure must have been performed

(e) The patient must be medically fit to undergo treatment in the oxygen chamber and be able to lie flat in the prone and supine positions.

Each patient is admitted to hospital and subjected to a complete clinical examination as well as radiographs of chest and pelvis, intravenous pyelogram, full blood examination (Hb, PCV, MCHC, WBC, Platelets, Film) and blood biochemistry (Na, K, Cl, Bicarbonate, Urea). For acceptance in the trial these indices are all required to be within normal limits. Examination under anaesthetic (E. U. A.) including cystoscopy and biopsy of the cervix, the endometrium and any other suspicious areas, is carried out.

Figure /

Figure 10 shows the extension of disease found at E.U.A. A chart of this kind is made out for each patient.

Documentation of treatment planning is illustrated by Figures 11 and 12. The standard "brick' technique of one anterior, one posterior and two laterial fields, in use since the installation of megavoltage equipment in 1962, is employed. An isodose chart distribution is calculated (Figure 11) and a 4 week course of radiotherapy on the linear accelerator (4MEV) is prescribed (Figure 12). Over 28 days the pelvis, of volume approximately 15 x 15 x 12 cms, is irradiated to a tumour dose of 4250 rads by means of the 4 fields mentioned above. Two are treated daily over 5 days per week so that each field is given a total of 10 treatments.

On completion of this course, a single radium insertion is carried out and charted in the operating theatre (Figure 13).

A /

GLASGOW INSTITUTE FOR RADIOTHERAPY

DIAGRAM No.21

Patient's Name E.N.

Radiotherapy No. 705222

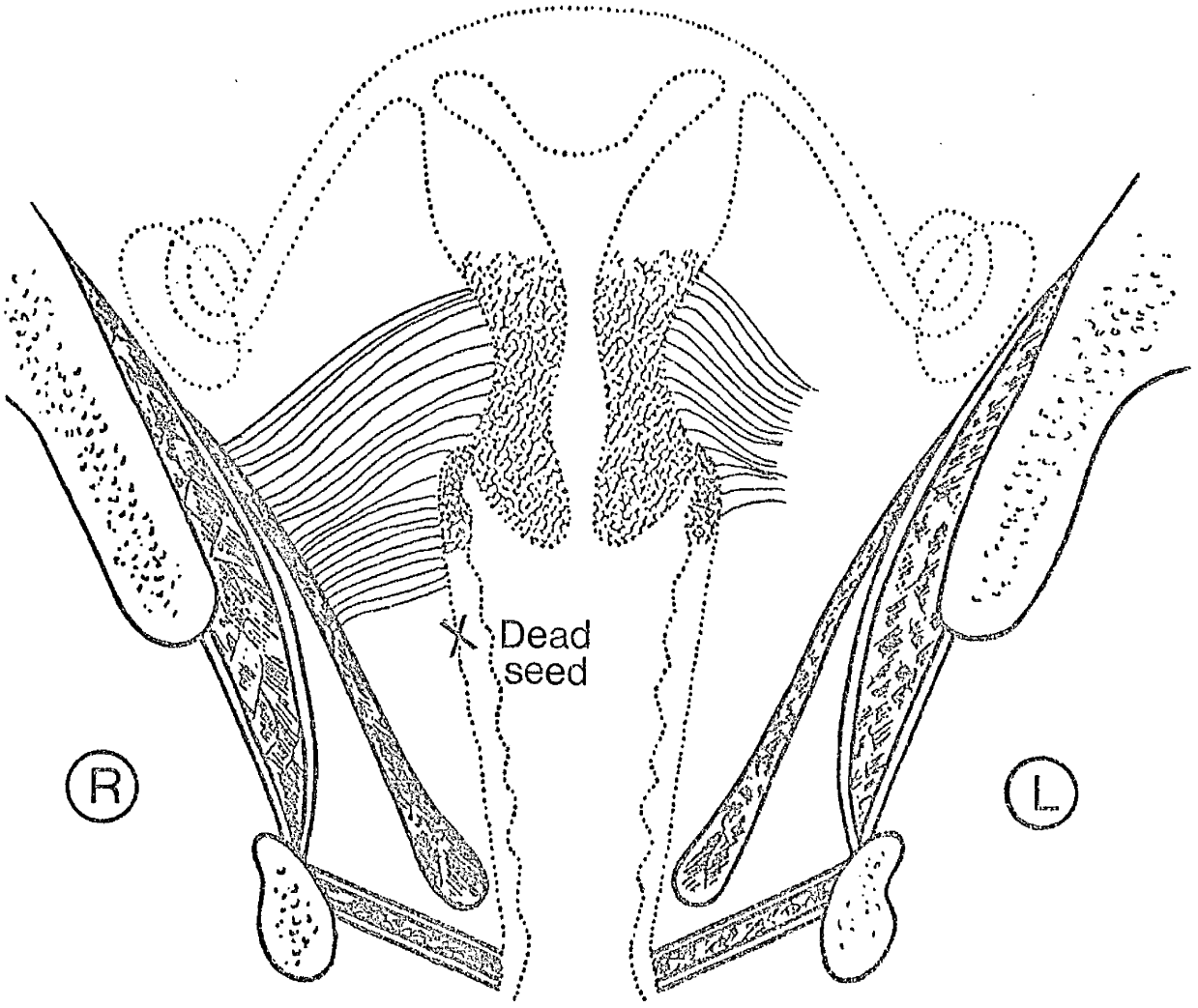
Cystoscopy - capacity 1 pint. Large bulge between ureteric orifices. No mucosal invasion seen.

P.V. Cervix destroyed by large fungating tumour which seems to extend up into body. Difficulty in identifying canal.

P.R. Left side invaded.
Right side invaded and fixed.

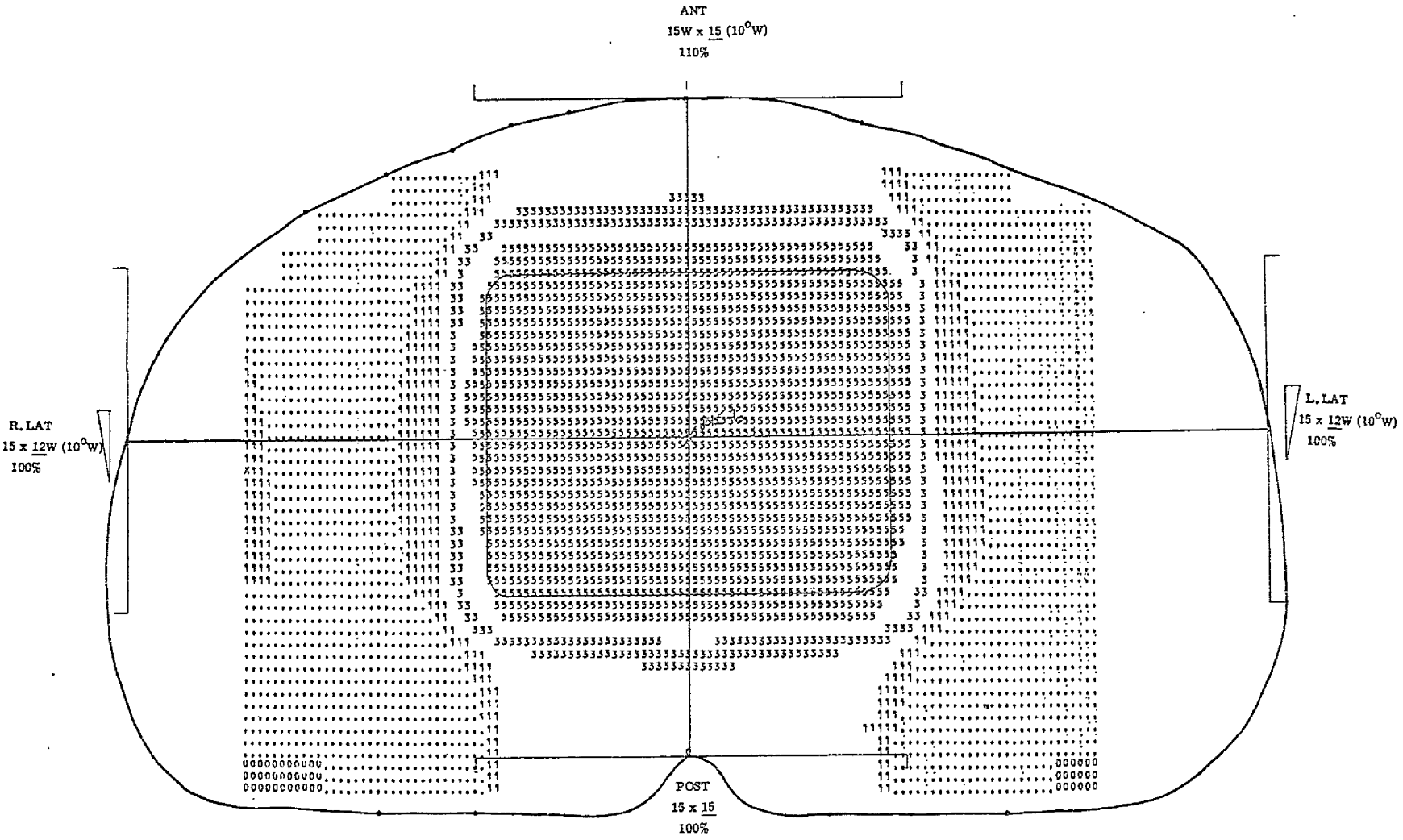
Biopsy of cervix to pathology.

Dead seed inserted on R. vaginal wall opposite lower limit of growth.



Date : 23. 6.70
Operator : E.R.W.

Figure 10



ISODOSE CHART DISTRIBUTION

Modal Dose = 213 Maximum Dose = 216.9

C O D E S U S E D

	0		1	2	3	4	5	6	7
% Modal Dose	0	0	>50	>65	> 75	> 85	> 95	>105	>115
Value	0	0.0	105.5	138.5	159.7	181.0	202.3	223.7	244.9

Figure 11

GLASGOW INSTITUTE FOR RADIOTHERAPY

DIAGNOSIS Ca. Cervix

Western Infirmary R/T DEPARTMENT

PRESCRIPTION SHEET

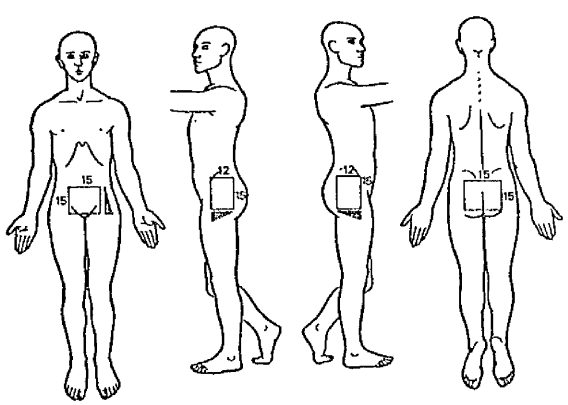
CONSULTANT E.R.W.

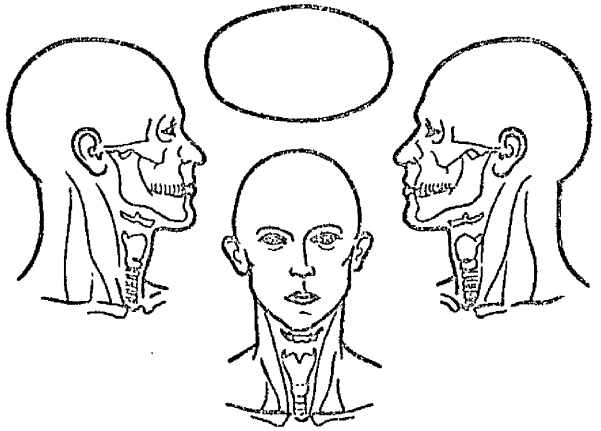
O.P./I.P. WARD F.2.

Name	R/Th. No
Miss E.N.	705222
Address	D.O.B. 12. 0.25
	Ward/Dept. F/2

RADICAL/PALLIATIVE/TRIAL TRIAL (No. 109 - Air)

FIELD	DESCRIPTION	UNIT & H.V.L.	SIZE	F.S.D. RADIUS	WEDGE	DOSE Incident	DOSE PEAK Skin/Subcut.	TUMOUR MAX.	TUMOUR MIN.	TUMOUR MODAL	PIN	ARC	SEPARATION	REMARKS	FIELD
1	Anterior pelvis	4MeV	15Wx15	100	10^0	2200(110%)								Thick end wedge inferior	1
2	Posterior pelvis	"	15x15	"	-	2000(100%)		4290	4200	4250					2
3	Right lateral	"	15x12W	"	10^0	2000(100%)		(215%)	(211%)	(213%)	11.5cm	90^0		Thick end wedge anterior	3
4	Left lateral	"	15x12W	"	10^0	2000(100%)					11.5cm	90^0		Thick end wedge anterior	4





DURATION 4 weeks

REVIEW weekly

FINAL TREATMENT GIVEN & COMMENTS 23. 7. 70

FRACTIONATION 20

BLOOD COUNT twice weekly

DATE COMMENCED/FINISHED 26. 5. 70

DATE 25/6/70

PRESCRIBED BY K.H. Monnais

TECHNIQUE Pelvic Brick

FINAL TUMOUR DOSE 4250 rads

TREATED VOLUME 15 x 15 x 12

Supt. Radiographer M. Augood

Figure 12

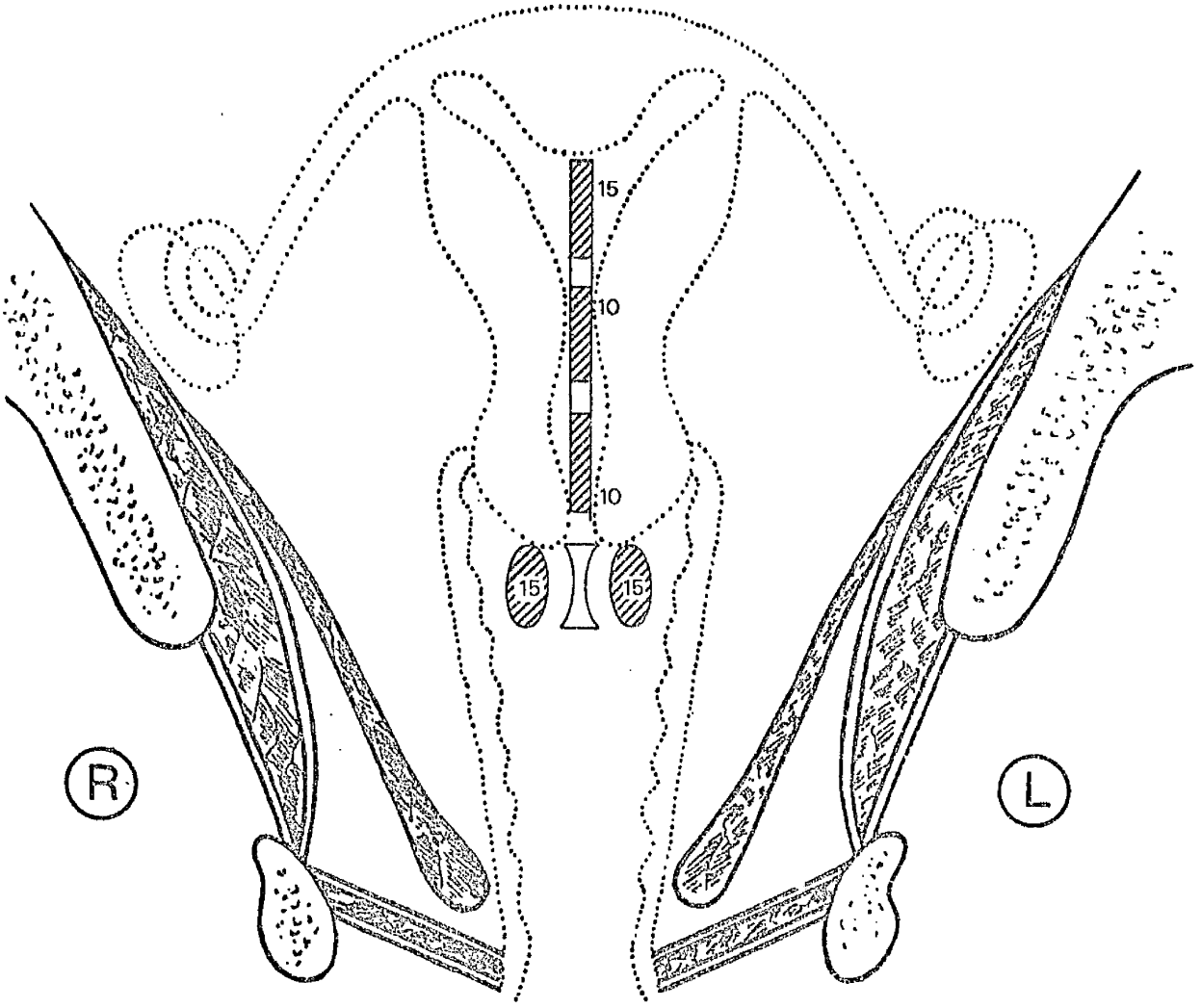
GLASGOW INSTITUTE FOR RADIOTHERAPY

DIAGRAM No.21

P.V. Good tumour regression. Uterus fairly mobile. Cervix completely destroyed. Very narrow at vault. Canal found anteriorly.
P.R. Still tumour to pelvic wall on R. side L. side invaded.

Patient's Name E.N.
Radiotherapy No. 705222

Radium insertion - 1 long central tube 15 mgs.10 mgs.10 mgs.
2 small ovoids with washer 15 mgs.15 mgs.
duration - 60 hours



Date : 24. 7.70
Operator : D.S.A.

Figure 13

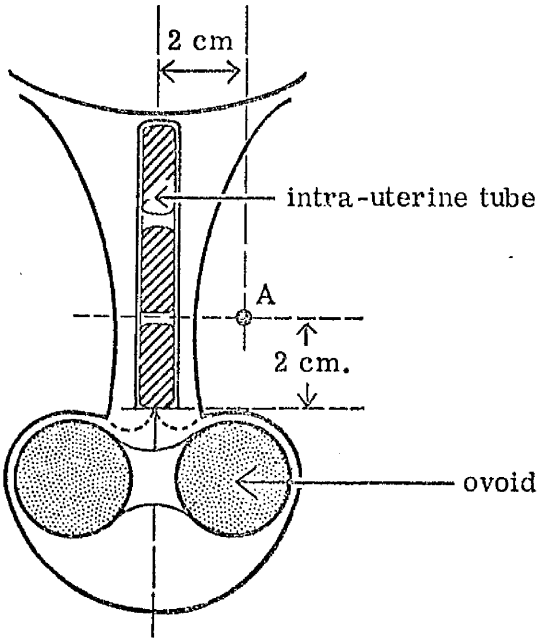
A minimum dose of 3000 roentgens from the radium is given to point A (Figure 14). This point, first defined by Tod and Meredith (1953-56), permits assessment of the dose of intracavitary radium in and around the cervix. Thus the total dose at A, a minimum of 7250r, will be a combination of supervoltage rads and radium roentgens.

Only after all the criteria have been satisfied and the prescription drawn up is the selection for treatment in either air or oxygen made according to the content of sealed envelopes supplied by the Medical Research Council. Thus there has been only a single difference between two randomly selected group of patients - the atmosphere in which treatment is given. Treatment of all patients has otherwise been identical from all points of view.

On the 1st July, 1971, 129 patients had been entered in the cervix trial. Of these, 99 were Stage III and 30 Stage IV (Figure 15). The histologies of all cases are given in Figure 16.

Stage III /

Diagrammatic Uterus and Vagina
showing position of point A.



Point A lies in the paracervical triangle and is defined as being 2 cm. lateral to the central canal of the uterus and 2 cm. above the mucous membrane of the lateral fornix in the axis of the uterus.

Figure 14

CASES REGISTERED AT 1ST JULY, 1971

	Oxygen	Air
Stage III	45	54
Stage IV	20	10
Total	65	64

Figure 15

Histology of all registered cases

HISTOLOGY	STAGE III		STAGE IV	
	Oxygen	Air	Oxygen	Air
Squamous cell ca.	40	49	18	8
Anaplastic Ca.	2	5	2	2
Adeno-carcinoma	3	-	-	-

Figure 16

Stage III

Forty-five of these patients (45.5%) were randomly selected for treatment in HPO. For the majority, this treatment proved uneventful. A few complained of a temporary ear discomfort during compression, which generally settled at the second or third occasion in the chamber. Only 2 patients (Nos. 71 and 91) continued to have pain necessitating myringotomy and the insertion of grommets. No. 71 continued her course satisfactorily, but No. 91, a very nervous person, refused to enter the chamber for her last 5 treatments which were given in air. Three patients had a single oxygen convulsion. No. 3 had her siezure at the beginning of decompression after her 14th treatment. No. 28 convulsed at the beginning of decompression after her first treatment. No. 56 convulsed prior to her first radiotherapy treatment after 15 minutes full pressurisation in the chamber. All recovered rapidly and without ill-effect following removal from the chamber by emergency decompression. Nos. 3 and 56 completed the course in air. No. 28 continued to have treatment in the oxygen chamber without further incident. Three patients were unable to tolerate the oxygen chamber by reason of their /

of their extreme nervousness, in spite of the use of "tranquillising" drugs. These were Nos. 40, 73 and 112. No. 107 was physically unable to turn round within the chamber on account of unusually broad shouders and had only one treatment in it, the remainder in air. Thus, out of 45 patients, 37 completed treatment in the oxygen chamber, a total of 82%.

Fifty-four patients were treated in air. All completed the course without incident, with the exception of No. 72, who developed peritonitis caused by perforation of the uterus and subsequent infection. She unfortunately died.

Stage IV

Twenty of the 30 Stage IV cases were randomly selected for oxygen - just over 66%. Three patients failed to complete their treatment. These were Nos. 24, 46 and 114 in whom renal failure supervened with rapid deterioration of their general condition. /

condition. A fourth case, No. 47, was found to have distant bony metastases after she had completed only one week's therapy in oxygen. Further treatment was modified and completed in air. One patient, No. 95, had a convulsion at the beginning of decompression on her sixth treatment and insisted on being treated in air thereafter. Three patients, Nos. 105, 115 and 127, refused to enter the chamber. Thus, 13 out of 20 patients completed treatment in the oxygen chamber - a total of 65%.

The 10 patients allocated for treatment in air completed the course satisfactorily.

An analysis of patient refusal is given in Figure 17.

Results

All patients have been followed up at regular intervals since their treatment and the results are shown schematically on Figures 18 and 19. Cases are grouped histologically into squamous cell carcinoma, anaplastic carcinoma and adenocarcimona. Each horizontal line represents the life-line of a single patient whose /

ANALYSIS OF PATIENT REFUSAL

CERVIX TRIAL SERIES

Trial No.	Age	Sex	Disease	No. of Treatments in HPO	Reason for refusing treatment in HPO
3	53	F	Ca. Cervix (III)	14	Convulsed during decompression following 14th treatment and insisted on completing the course in air.
40	64	F	Ca. Cervix (III)	None	Too nervous and would not permit pressurisation.
56	42	F	Ca. Cervix (III)	None	Convulsed after pressurisation for 15 mins.
73	61	F	Ca. Cervix (III)	None	Acute pain in ears added to her highly excitable, nervous state, made pressurisation beyond 10 lbs/in^2 impossible.
91	47	F	Ca. Cervix (III)	15	Required myringotomy for barotrauma which developed after 2 weeks' treatment. Refused to enter chamber thereafter.
95	74	F	Ca. Cervix (IV)	6	Convulsed during decompression following 6th treatment and would only be treated in air thereafter.
105	54	F	Ca. Cervix (IV)	None	Complained of feelings of claustrophobia and would not co-operate.
112	50	F	Ca. Cervix (III)	None	Extremely nervous in spite of tranquillising drugs and would not be pressurised.
115	53	F	Ca. Cervix (IV)	None	Would not tolerate pressurisation.
127	67	F	Ca. Cervix (IV)	None	Would not co-operate.

Figure 17

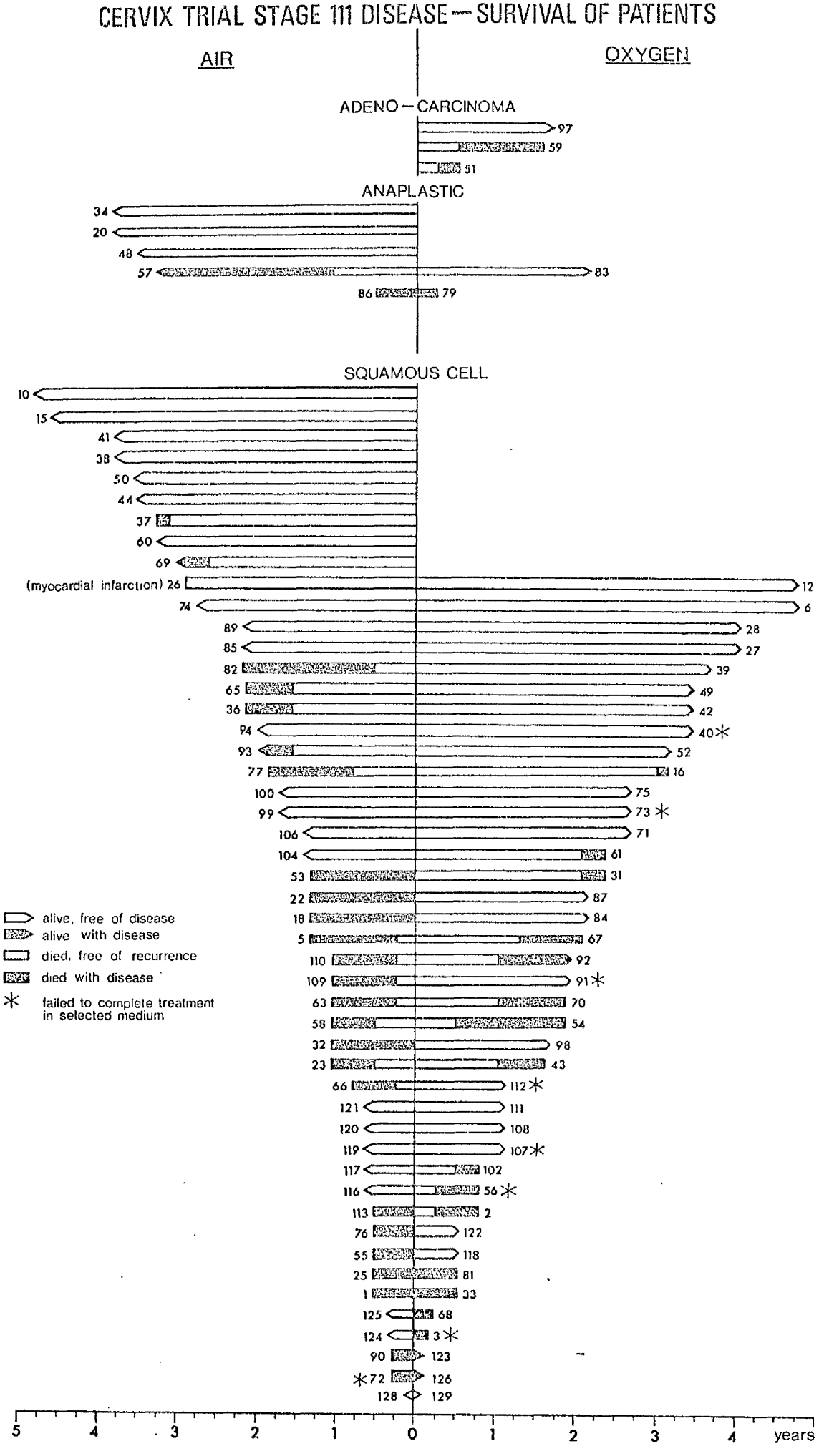

CERVIX TRIAL STAGE III DISEASE — SURVIVAL OF PATIENTS
AIR
OXYGEN
ADENO — CARCINOMA
97
59
51
ANAPLASTIC
34
20
48
57
83
86
79
SQUAMOUS CELL
10
15
41
38
50
44
37
60
69
(myocardial infarction) 26
12
74
6
89
28
85
27
82
39
65
49
36
42
94
40*
93
52
77
16
100
75
99
73*
106
71
104
61
53
31
22
87
18
84
5
67
110
92
109
91*
63
70
58
54
32
98
23
43
66
112*
121
111
120
108
119
107*
117
102
116
56*
113
2
76
122
55
118
25
81
1
33
125
68
124
3*
90
123
*72
126
128
129
alive, free of disease
alive with disease
died, free of recurrence
died with disease
* failed to complete treatment in selected medium
5
4
3
2
1
0
1
2
3
4
years

Figure 18

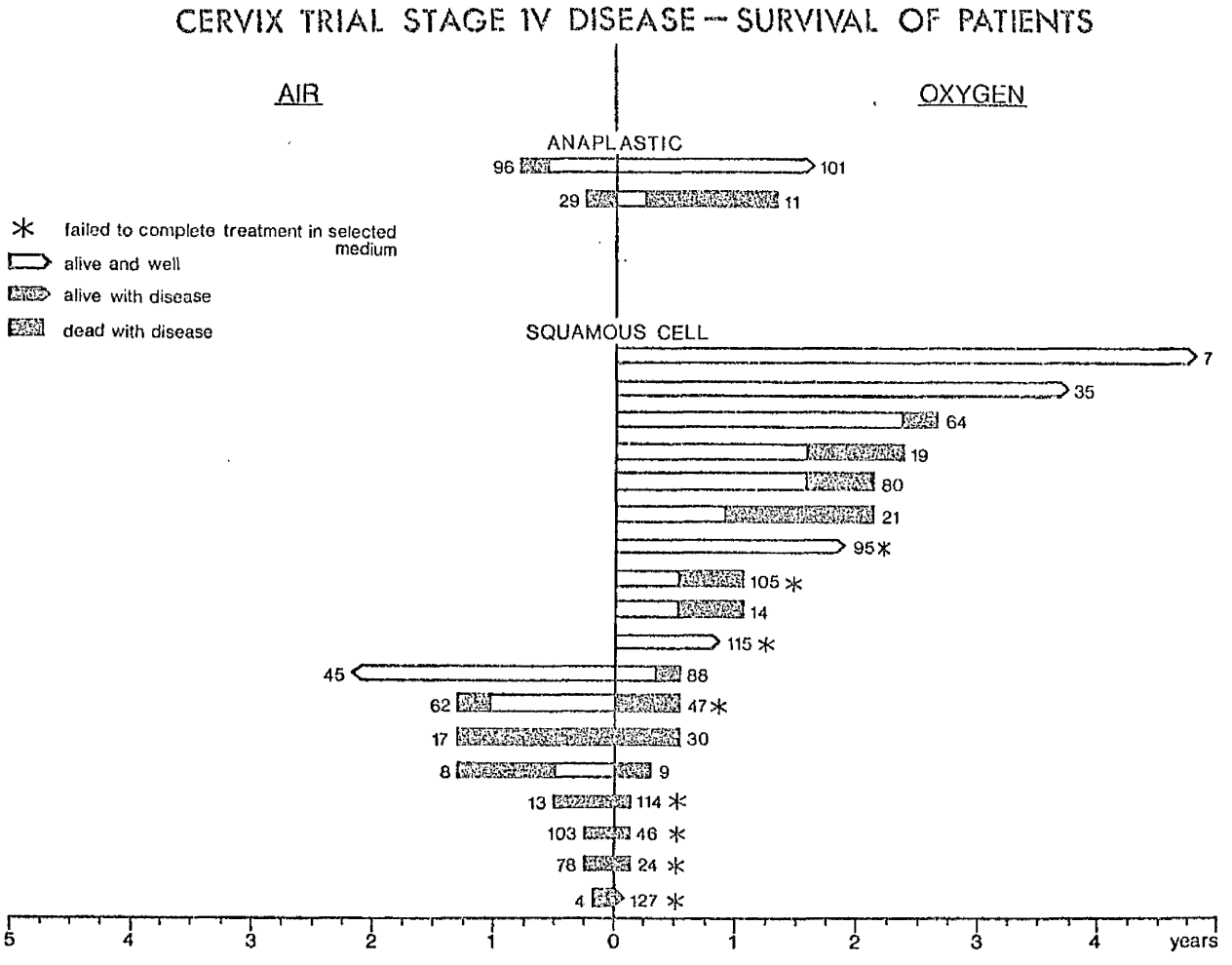

CERVIX TRIAL STAGE IV DISEASE — SURVIVAL OF PATIENTS
AIR
OXYGEN
ANAPLASTIC
96
101
29
11
* failed to complete treatment in selected medium
alive and well
alive with disease
dead with disease
SQUAMOUS CELL
7
35
64
19
80
21
95*
105*
14
115*
45
88
62
47*
17
30
8
9
13
114*
103
46*
78
24*
4
127*
5
4
3
2
1
0
1
2
3
4
years

Figure 19

whose number in the trial is given at the end of the line. Those on the right were all selected for treatment with oxygen, those on the left were treated in air. An asterisk indicates the patients who failed to complete their treatment in the selected medium. The clear arrowed lines represent patients who were alive and clinically free of disease at 1st July, 1971. The solid black lines show those in whom the malignancy has progressed or recurred. Where the line is cut off, the patient has died. In 2 cases (Nos. 3 and 26) the cause of death was unrelated to the malignancy.

It is obviously difficult to assess the results of treatment. Local control of the disease is surely the criterion on which this should be based. But the inaccessibility of pelvic nodes to clinical examination must make vaginal assessment of local control inadequate. Vaginal tumour may heal. But the fibrosed parametria and nodes can hold occult tumour cells with the ability to proliferate in the course of time. One must therefore look for other criteria and /

and in this instance it seems reasonable to consider -

1. The crude survival figures for each stage
2. The quality of survival
3. The local and general spread of disease at the time of death

1. Figures 20 and 21 compare the survival of the oxygen and air patients available for analysis at 1 and 2 years respectively on 1st July, 1971. Figures are given for each stage as a whole and for both stages grouped together. Cases are divided not only by stage but also by histological diagnosis. There were 111 patients for analysis at 1 year and 89 patients at 2 years. In each instance, the oxygen series indicates an increased survival rate, shown as a percentage, the only exception being in the anaplastic sub-group of Stage III where the air cases appear to respond better. However, this group of 5 patients is very small indeed, and therefore hardly conclusive.

In /

Cases for Analysis at 1 year - 1.7.71

Stage III	ALL CASES			OXYGEN			AIR		
	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive
All Histologies	84	43	51.0	39	22	56.5	45	21	46.7
Squamous cell	74	37	50.0	34	20	58.8	40	17	42.6
Anaplastic	7	5	71.5	2	1	50.0	5	4	80.0
Adeno-ca	3	1	33.3	3	1	33.3	-	-	-
Stage IV									
All Histologies	27	5	18.5	17	4	23.5	10	1	10.0
Squamous cell	23	4	17.4	15	3	20.0	8	1	12.5
Anaplastic	4	1	25.0	2	1	50.0	2	0	0
Adeno-ca	-	-	-	-	-	-	-	-	-
Stages III and IV									
All Histologies	111	48	43.4	56	26	46.5	55	22	40.0
Squamous cell	97	41	42.3	49	23	47.0	48	18	37.5
Anaplastic	11	6	54.5	4	2	50.0	7	4	57.0
Adeno-ca	3	1	33.3	3	1	33.3	-	-	-

Figure 20

Cases for analysis at 2 years - 1.7.71

Stage III	ALL CASES			OXYGEN			AIR		
	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive
All Histologies	67	30	44.8	31	15	48.4	36	14	39.0
Squamous cell	58	25	43.3	27	14	51.9	31	11	35.5
Anaplastic	7	5	71.5	2	1	50.0	5	4	80.0
Adeno-ca	2	0	0.0	2	0	0.0	-	-	-
Stage IV									
All Histologies	22	3	13.6	14	2	14.2	8	1	12.5
Squamous cell	20	3	15.0	13	2	15.4	7	1	14.3
Anaplastic	2	0	0.0	1	0	0.0	1	0	0.0
Adeno-ca	-	-	-	-	-	-	-	-	-
Stages III + IV									
All Histologies	89	33	37.0	45	17	37.8	44	15	34.2
Squamous cell	78	29	37.3	40	16	40.0	38	12	31.6
Anaplastic	9	5	55.5	3	1	33.3	6	4	66.6
Adeno-ca	2	0	0.0	2	0	0.0	-	-	-

Figure 21

12.

In all these results, the figures are inclusive of those who failed to complete treatment in the selected medium. There were, in fact, 15 of these cases in the oxygen series and 1 case in the air series. Amended analyses were made to exclude these "failed" cases and are shown for 1 and 2 years respectively. (Figures 22 and 23) These continue to show an improved survival in the oxygen series.

2. The quality of survival is a most important criterion in radiotherapy where so much work is necessarily of a palliative nature. There is no point in giving treatment unless, at the same time, one can reasonably hope for a definite symptom and sign free period during which the patient can carry on and enjoy his normal daily life. Figure 24 shows the life-span after treatment of all patients in the trial who have died. The majority enjoyed a definite symptom-free period of life. This is most marked in both stages of the oxygen series where 65% of stage III cases and 57% of stage IV cases had a period of normal life /

Amended analysis of cases at 1 year excluding cases which failed to complete treatment in selected medium

	ALL CASES			OXYGEN			AIR		
Stage III	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive
All Histologies	77	39	50.6	33	18	54.6	44	21	47.8
Stage IV All Histologies	22	4	18.2	12	3	25.0	10	1	10.0
Stages III + IV All Histologies	99	43	43.5	45	21	46.7	54	22	40.8

Figure 22

Amended analysis of cases at 2 years excluding cases which failed to complete treatment in selected medium

	ALL CASES			OXYGEN			AIR		
Stage III	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive	No. Registered	No. Alive	% Alive
All Histologies	62	28	41.2	27	13	48.2	35	14	40.0
Stage IV All Histologies	19	3	15.8	11	2	18.2	7	1	14.3
Stages III + IV All Histologies	81	31	38.4	38	15	39.5	42	15	35.7

Figure 23

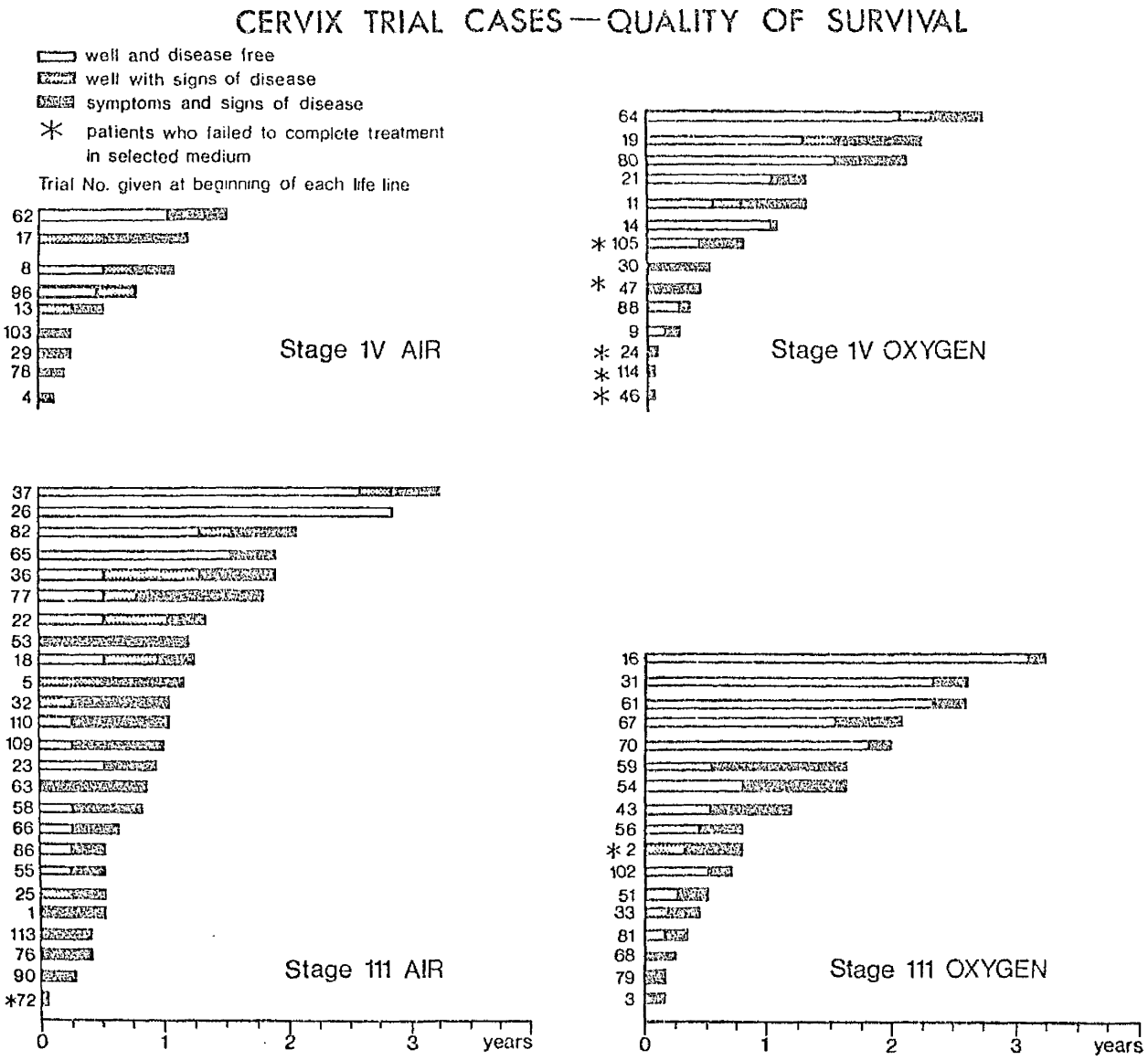

CERVIX TRIAL CASES — QUALITY OF SURVIVAL
well and disease free
well with signs of disease
symptoms and signs of disease
* patients who failed to complete treatment in selected medium
Trial No. given at beginning of each life line
62
17
8
96
13
103
29
78
4
Stage 1V AIR
64
19
80
21
11
14
* 105
30
* 47
88
9
* 24
* 114
* 46
Stage 1V OXYGEN
37
26
82
65
36
77
22
53
18
5
32
110
109
23
63
58
66
86
55
25
1
113
76
90
*72
Stage 111 AIR
16
31
61
67
70
59
54
43
56
* 2
102
51
33
81
68
79
3
Stage 111 OXYGEN
0
1
2
3
years

Figure 24

life and activity of not less than three months. In the air series, the figures are 60% and 33% respectively. If the "failed" cases (marked *) are omitted, the amended stage III and IV oxygen figures rise to 69% and 78%. All these figures point to the worthwhile palliative power of radiotherapy which appears to be enhanced by the addition of HPO.

3. The local and general spread of disease at the time of death is another index of treatment control. Definitive autopsy was not possible in every case, but the regular follow-up examination at stated intervals prior to death, provided the necessary assessment. Of the 111 patients who survived at least one year after entry into the trial, 63 died and the extent of disease at the time of death in these cases is shown in Figure 25. A similar analysis for patients who survived at least two years is made in Figure 26. From these figures, the advantage of oxygen therapy seems to come out best in the local control of the disease. This is shown even more /

CAUSES OF DEATH AMONG CASES FOR ANALYSIS AT 1 YEAR - 1.1.71

Stage III	Oxygen	Air	
Registered	39 (33)	45 (44)	
Dead	17 (15)	24 (23)	
Local recurrence	3 (2)	5 (4)	
Metastases	7 (7)	7 (7)	
Local and metastases	7 (6)	11 (11)	
Other causes	- -	1 (1)	Myocardial infarction No Ca present
Stage IV			
Registered	17 (12)	10	
Dead	13 (9)	9	
Local recurrence	3 (1)	4	
Metastases	5 (4)	1	No failures
Local and metastases	5 (4)	4	
Other causes	- -	-	

Amended figures in parentheses exclude patients failing to complete treatment in selected medium.

Figure 25

CAUSES OF DEATH AMONG CASES FOR ANALYSIS AT 2 YEARS - 1.7.71

Stage III	Oxygen	Air	
Registered	31 (27)	36 (35)	
Dead	16 (14)	21 (20)	
Local recurrence	3 (2)	5 (4)	
Metastases	6 (6)	5 (5)	
Local and metastases	7 (6)	10 (10)	
Other causes	- -	1 -	Myocardial failure No Ca present
Stage IV			
Registered	14 (11)	8	
Dead	12 (9)	7	
Local recurrence	3 (1)	3	No failures
Metastases	5 (4)	1	
Local and metastases	4 (4)	3	
Other causes	- -	-	

Amended figures in parentheses exclude patients failing to complete treatment in selected medium

Figure 26

more clearly when cases who failed to complete treatment in the selected medium are removed from the analysis (figures in parentheses). Therefore, it may fairly be postulated that cases of carcinoma of the cervix at an earlier, localised stage may well have a better survival rate if external radiotherapy is given in HPO . This, in fact, may turn out to be one of the most substantial contributions which the trial has made to the use of oxygen in radiotherapy.

On the other hand, oxygen therapy does not seem to prevent the appearance of metastases. Figures showing the occurrence of these for oxygen and air cases are about equal in the Stage III section, but are raised for oxygen in the Stage IV section. This suggests that the proliferative ability of well-oxygenated metastatic cells is improved provided that they are able to escape from the radiotherapeutic net.

The /

15.

The Bladder Trial

Another site considered suitable for a trial of treatment by irradiation in hyperbaric oxygen was the urinary bladder. As stated in Chapter 3, Cade and McEwen (1967-51) had been conducting a randomised and controlled clinical trial of patients with advanced carcinoma of the bladder. In Glasgow, a similar trial was commenced in 1966. Cases were considered for selection if they fitted into one of the following categories :-

T1 - Tumour with biopsy evidence of malignancy infiltrating subepithelial connective tissue of the bladder

T2 - Tumour with biopsy evidence of infiltration of superficial muscle of the bladder wall

T3 - Tumour confirmed by biopsy and with infiltration of deep muscle, shown either by biopsy or by bimanual palpation of a hard, freely mobile mass within the pelvis

T4 - Tumour confirmed by biopsy and with evidence on bimanual examination of its fixture to the pelvic wall or of its spread to the prostate, or vagina, but not extending beyond the true pelvis.

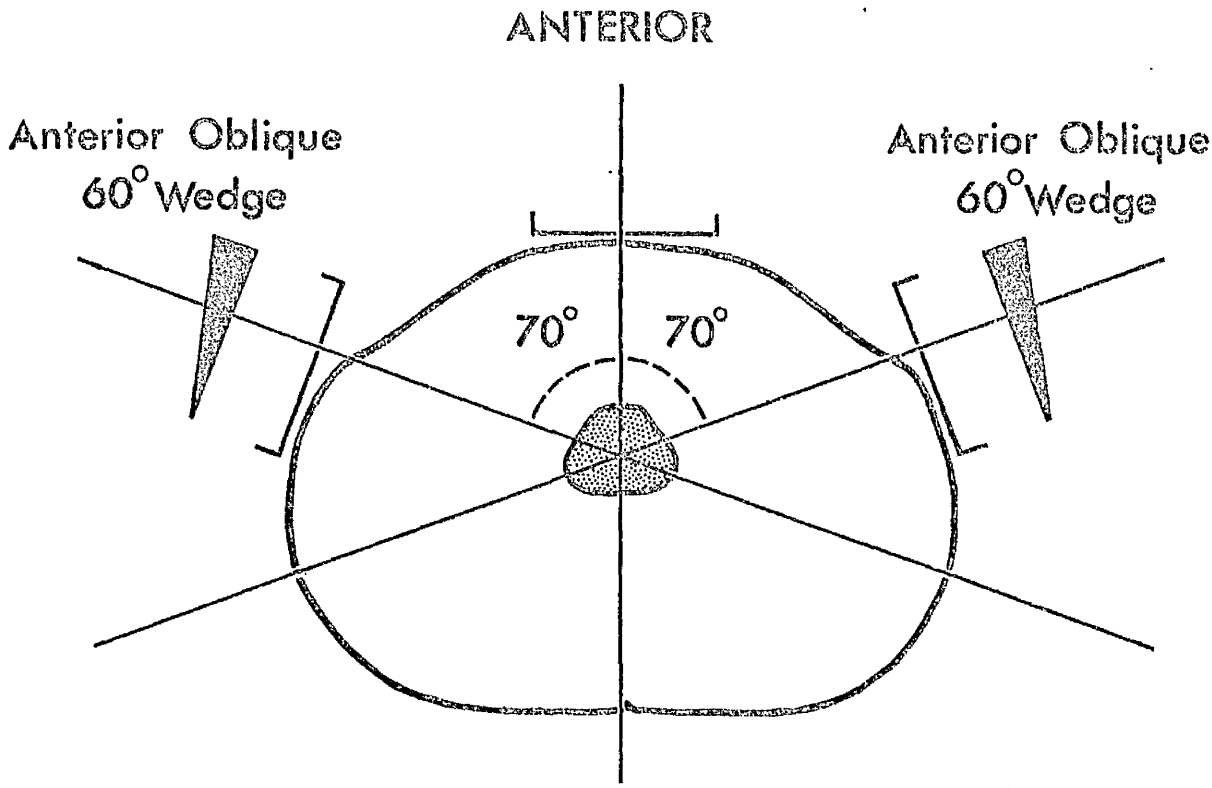
The /

The criteria of entry were similar to those of the cervix trial. They included all of the appropriate clinical, radiological and biochemical investigations, before the same random selection for treatment in air or oxygen.

To date, 27 patients have been entered. The standard technique of treatment, used in the department since the introduction of the 4MeV linear accelerator, was varied slightly. (Figure 27) Three fields, one anterior and two anterior-oblique, had been used and a tumour dose of 6000 rads in 25 fractions over 5 weeks, given on the 4MeV linear accelerator, each field being treated daily (Treatment plan B - Figure 27). With the introduction of the oxygen trial, the oblique fields were treated on alternate days. This shortened the treatment time within the chamber from 10 minutes to about 5 minutes. The total fractionation was altered to 24 (Treatment plan A - Figure 27).

Twenty /

TREATMENT SCHEME FOR BLADDER TRIAL CASES



Slope of anterior abdominal wall
may require wedge in vertical axis

Plan A - Anterior field treated daily
Oblique fields treated on
alternate days
} 24 fractions in 32 days

Plan B - All fields treated daily — 25 fractions in 33 days

Figure 27

Twenty-two patients were treated by plan A, 12 in oxygen and 10 in air. In all cases, the course of therapy was uneventful. It was in the aftermath of treatment that complications arose. As is shown in Figure 28, four patients (Nos. 4, 6, 7 and 10) subsequently required cystectomy for repeated attacks of haematuria, which were the result of radiation changes in the bladder. Seven other patients (Nos. 9, 22, 1, 12, 16, 17 and 20) developed symptoms of presumed local recurrence. They were treated by cystectomy, also. Although it was only in Nos. 9, 1, and 12 that histology was positive for tumour, in all these cases there was found to be similar gross radiation changes in the bladder. As these effects were noted in both the oxygen and the air series, the fault appeared to lie with the type of fractionation used. Accordingly, later patients (5 in all) were treated by the original departmental method (plan B). Two were treated in oxygen, three in air. None of these have had haematuria requiring surgical interference. Two of these subsequent patients have died /

OXYGEN SERIES

Trial No.	Prior to Operation	Operation	Histology	Results
4	Bleeding 12 mths	Cystectomy	Negative	Died - metastases 1 year later
6	Bleeding 12 mths	Cystectomy	Negative	Died - post-op. complications
9	Bleeding 9 mths	Cystectomy	Positive	Died - post-op. complications
22	Recurrence 18 mths ?	Cystectomy	Negative	Well

AIR SERIES

Trial No.	Prior to Operation	Operation	Histology	Results
1	Tumour still present	Cystectomy	Positive	Died within two weeks of operation
7	Bleeding 18 mths	Cystectomy	Negative	Well
10	Bleeding 21 mths	Cystectomy	Negative	Well
12	Recurrence 18 mths ?	Cystectomy	Positive	Died - post-op. complications
16	Recurrence 12 mths ?	Cystectomy	Negative	Died - post-op. complications
17	Recurrence 9 mths ? (Biopsy +)	Cystectomy	Negative	Died - post-op. complications
20	Recurrence 18 mths ?	Partial Cystectomy	Negative	Well

Figure 28

died (Nos. 23 and 24). Autopsies on them have shown no undue radiational changes in the bladder.

All the results are shown in Figures 29 and 30. Five out of 13 air cases and six out of 14 oxygen cases are alive and well without signs of recurrence, eighteen months to four years after their treatment. Of those who died, 3 air cases and 1 oxygen case showed no signs of local or metastatic tumour at the time of death. In 3 of these, death was due to the post-operative complications of cystectomy.

This trial was discontinued in 1970. The Portsmouth trial had been stopped because results of hyperbaric oxygen therapy showed no advantage over those obtained by conventional techniques. Under these circumstances, it seemed unethical to continue. However, new methods of fractionation are being worked out and may form a satisfactory basis for resumption of this trial in the future.

BLADDER TRIAL - OXYGEN CASES

Trial No.	Sex	Age	Histology	Stage	Treatment Plan	First Year 3	6	9	12	Second Year 3	6	9	12	Third Year 3	6	9	12	Fourth Year 3	6	9	12
4	M	40	Anaplastic	T_1	A	o	o	H	C	o	o	o	o	o	Died (metastases)						
6	M	73	Transitional	T_1	A	o	H	H	C	Died (No tumour)											
3	M	53	Anaplastic	T_2	A	o	o	o	o	o	H*	o	o	o	o	o	o	o	o	o	o
8	M	63	Adenoca.	T_2	A	o	o	o	o	o	o	o	o	o	Died (metastases)						
14	M	63	Transitional	T_2	A	●	●	●	●	●	Died (metastases and local tumour)										
18	M	64	Transitional	T_2	A	o	o	o	o	o	o	o	o	o	o	o	o	o			
19	M	58	Anaplastic	T_2	A	o	o	o	o	o	o	o	o	o	o	o	o	o			
21	M	57	Transitional	T_2	A	●	Died (metastases and local tumour)														
26	F	72	Anaplastic	T_2	B	o	o	o	o	o	o										
9	M	64	Anaplastic	T_3	A	o	H	C	Died (local tumour)												
11	M	60	Transitional	T_3	A	o	o	o	o	o	o	o	o	o	o	o	o	o	Died (mets.)		
15	M	52	Transitional	T_3	A	●	●	Died (metastases and local tumour)													
25	F	66	Transitional	T_3	B	o	o	o	o	o	o										
22	F	59	Anaplastic	T_4	A	o	o	o	o	(?R)	C	(No tumour)						o	o		

o - no sign of local recurrence
● - local tumour present
H - Haematuria
H*- Treated by diathermy
C - Cystectomy
R - Recurrence

Figure 29

BLADDER TRIAL - AIR CASES

Trial No.	Sex	Age	Histology	Stage	Treatment Plan	First Year 3	6	9	12	Second Year 3	6	9	12	Third Year 3	6	9	12	Fourth Year 3	6	9	12	
5	M	45	Transitional	T_1	A	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	
7	M	45	Transitional	T_1	A	o	o	H	H	H	C	o	o	o	o	o	o	o	o	o	o	
10	M	53	Transitional	T_1	A	o	o	H	H	H	H	C	o	o	o	o	o	o	o	o	o	
23	F	67	Transitional	T_1	B	◉	◉	◉	Died (myocard. infarct. - local tumour present)													
1	M	65	Anaplastic	T_2	A	◉	◉	C	Died (local tumour)													
2	M	64	Anaplastic	T_2	A	o	o	o	o	o	o	o	o	o	o	o	o	o	Died (mets.)			
16	M	57	Transitional	T_2	A	o	o	(?R)	C	Died (radiation changes only)												
17	M	62	Transitional	T_2	A	o	◉	C	Died (No tumour found in operation specimen)													
27	M	60	Transitional	T_2	B	o	o	o	o	o	o											
12	M	64	Transitional	T_3	A	o	o	o	o	◉	C	Died (local tumour)										
20	M	65	Transitional	T_3	A	o	o	o	o	(?R)	C (No tumour)	o	o									
24	F	51	Transitional	T_3	B	◉	Died (metastases and local tumour)															
13	M	66	Transitional	T_4	A	o	o	o	o	o	o	o	o	Died (myocard. inf. - no tumour)								

o - no sign of local recurrence
◉ - local tumour present
H - Haematuria
C - Cystectomy
R - Recurrence

Figure 30

CHAPTER 7

Conclusions

The use of hyperbaric oxygen in radiotherapy constitutes a new technique outwith the conventional practices of a radiotherapeutic department. The preliminary survey (Chapter 5) which covers a period of two years has shown that the vast majority of patients will accept its conditions. Such morbidity, directly due to its use, was negligible and temporary in nature. The author felt confident that an optimistic attitude was ethically correct. It seemed right to recommend this form of treatment to patients. Equally, after the first teething troubles, hyperbaric oxygen proved easy to dovetail into the work of the department. It became part of the daily routine.

Now, after seven years' experience, certain conclusions as to its value can be drawn. The initial enthusiastic predictions have not, in fact, been fulfilled. The reasoning and experimental evidence behind its use have been excellent. But, /

But, in practice, hyperbaric oxygen does not constitute a "giant leap forward" (Mao Tse Tung). If there is an advantage over conventional radiotherapy in air, one must look closely and assess results carefully.

The findings in the cervix trial point to an improved survival time of oxygen treated cases although these figures are not as yet statistically significant. Palliation of neoplastic disease and its clinical features by which radiotherapy gives worthwhile quality to remaining life, was definitely enhanced by the additional use of hyperbaric oxygen. Only metastatic disease remained apparently unaffected by the new technique. This has been a matter of some controversy in other centres. As a result of the Canadian trial (see Chapter 4) Johnson (1968-57) was of the opinion that the number of deaths from early distant metastases in cases of carcinoma of the cervix increased when hyperbaric oxygen was used. On the other hand, Van den Brenk (1967-58) noted that there was a definite fall in the lymphatic dissemination of disease in the head and neck /

neck region when comparison was made with a similar series treated in air. He speculated that endogenous corticosteroids released by a state of "stress" may cause a depression of the immune mechanisms and explain the growth of metastases. Accordingly, in his series, stress was cut to a minimum by the use of routine bilateral myringotomies, barbiturate anaesthesia and by reduced fractionation of treatment (6 fractions over 3 to 4 weeks).

It is possible that both these workers are correct, though at first sight their views appear contradictory. Hyperbaric oxygen therapy at different primary sites may influence the subsequent appearance of metastases in different ways and at different times. It may be that its indication is more for one site than for another.

The Glasgow results support neither the Canadian nor the Australian results. They only emphasise the need to reconsider /

reconsider the treatment of the earlier and more localised forms of carcinoma of the cervix where the addition of hyperbaric oxygen to therapy might well improve the survival figures even more than it does in the later stages.

This is in line with Bates' report (1969-38) on an uncontrolled series of 21 patients with Stage III carcinoma of the cervix. They were treated by a four-field brick technique to give 3500 rads maximum tissue dose in 6 fractions over 3 weeks. Fourteen were alive at periods varying from 22 months to 5 years. (Bewlay 1970-59) It seemed that this result was significantly better than that of patients with early disease, treated in air. Yet the early cases had intracavitary radium in addition to external x-ray therapy.

The bladder trial is temporarily at a standstill. Nevertheless, the early results from this trial have served to underline the importance of fractionation, still something of an enigma in the practice of radiotherapy. Churchill-Davidson's early cases were treated by a few large fractions rather than by /

by conventional daily treatment spread over several weeks. This was done simply because the first hyperbaric treatments were necessarily elaborate, difficult and time-consuming. The use of the Vickers chamber and the realisation that a general anaesthetic was not required, made daily treatment possible. When the Medical Research Council's trials were begun, it was thought ideally that the only difference between the two randomly selected groups should be the use of hyperbaric oxygen, and that there should be identical fractionation of treatment on both sides. However, it became apparent, especially from the Portsmouth survey, that improvement in the results from hyperbaric oxygen under these circumstances (i.e., the use of many small fractions) might only be minor, perhaps even negligible. It seemed that the full benefit of HPO treatment might only be achieved with small numbers of large fractions. It has even been suggested that any apparent benefits shown in the Cardiff series might have been demonstrated, not because the hyperbaric oxygen results were better, but because the results of treatment of the conventional air series were worse, due to the method of fractionation /

fractionation used, i.e. 10 fractions over 3 weeks. This question will obviously be difficult to resolve. However, with the recent advances in the theoretical understanding of the time factor and dose fractionation by the use of the Ellis formula (1968-60) and CRE formula (1971, 1972-61), it has become possible to choose biologically equivalent tumour doses. Thus, in the future, trials may take place, using large doses in few fractions in HPO and small doses in many fractions in air, so that the best possible curative effects may result and may be compared.

Substantial improvement in the quality and duration of survival of patients treated by radiotherapy and hyperbaric oxygen has not yet been fully demonstrated. Work is continuing to this end. There has been sufficient encouragement by the modest improvement so far achieved by its use to make this worthwhile.

APPENDIX 1

Tissue Saturation with Oxygen

An essential preliminary to treatment is the time spent by the patient - generally about 20 minutes - in the oxygen chamber. It is not enough to pressurise the patient to 3ATA, a procedure which will take 4 to 5 minutes in the majority of cases. The patient, at 3ATA, must remain in the chamber for a minimum period of time so that all tumour tissue is thoroughly oxygenated. How long this takes has been a matter for discussion for some time, owing to the difficulty in measuring the level of oxygen tension in living cells.

Electrodes had been used for many years in the measurement of the partial pressure of oxygen in an aqueous medium. Danneel (1897-62) was the first to show that this oxygen pressure is directly proportional to the current which flows when a voltage is applied to the electrodes resulting in electrolysis of the dissolved oxygen. This was applied to the measurement of oxygen tension in living animal tissues in 1942 by Davies and Brink (1942-63). They experimented with 2 types of platinum electrodes :-

1. /

2.

1. The recessed electrode in which the wire was partially enclosed within a cylindrical glass tip. This had the disadvantages of being difficult to make and to use, and of being very slow to equilibrate between readings - taking between 5 and 20 minutes.

2. The open-ended electrode, in which the wire was directly exposed to the surrounding medium. This gave continuous readings of oxygen tension. But the gradual precipitation of proteins and insoluble salts on the surface of the wire, and its possible proximity to well-oxygenated capillaries or blood cells released by trauma around the platinum surface, resulted in inaccurate measurements.

In an attempt to overcome inaccuracies of the open-ended type, Clark (1953-64) constructed the membrane-covered electrode. A permeable cellophane membrane enclosed and protected the surface of the platinum electrode from coagulating proteins.

Since /

Since then, Cater et al (1959-65) have modified the open-ended electrode by insulating the platinum or gold wire with araldite resin. They ground down the flush end of the electrode between experiments to give a fresh, protein-free surface which is coated with collodion before use. This modified electrode was used to make quantitative measurements of the oxygen tension in normal and tumour tissues of patients before and after radiotherapy. They reported (1960-66) that patients required 7-8 litres oxygen/minute for 30 minutes to obtain a maximum tumour oxygen tension.

Evans and Naylor (1963-67) reported on the slower rate of oxygen saturation in tumour tissue. For patients being treated in air, oxygen tension values appeared to vary considerably. In patients being treated in 100% oxygen at 1ATA, the oxygen tension in the tumour was increased in most areas. In patients breathing 100% oxygen at 4ATA, the oxygen tension at all tumour sites was increased. Cater's work in both human and animal tumours (1964-68) confirmed the increase in tumour oxygen tension with /

with the increased atmospheric pressure of oxygen. Radiosensitivity also increased with oxygen tension. However, a fall in blood pressure would cause a similar fall in tumour blood flow and in the oxygen tension levels. Also, oxygen tension readings taken at the same time within the same tumour area could vary widely due to other factors. These are the irregular nature of the tumour's vascularisation, the areas of necrotic tissue and of intercellular fluid and, not least, the trauma with damage to surrounding cells caused by the insertion of the electrodes.

Jamieson and Van den Brenk (1963-69, 1965-70) tried to avoid this by the use of flexible gold electrodes which, they hoped, would cause less vascular stasis and damage. However, they found that it was difficult to confirm the accurate positioning of the electrode tip in the centre of the tumour. Oxygen tension levels varied widely throughout the tumour, although there appeared to be a general rise when the patient was pressurised to 4ATA oxygen. Moreover, the oxygen tension levels continued to rise if the oxygen pressure was held at 4ATA for 30 minutes. Normal tissue oxygen tension levels did not rise so quickly, or so high, in similar circumstances /

circumstances and these was no evidence of a difference in tissue oxygen tension levels in irradiated or non-irradiated tumour tissue. Jamieson and Van den Brenk were rightly cautious about the value of individual oxygen tension readings because of the many artefacts encountered.

Further experimental work on mice sarcomata has been carried out by Baker et al (1968-71). They found that there was a definite increase in the oxygen levels in a significant number of hypoxic regions during pressurisation at 4ATA. They postulated that cells which remained hypoxic might, in fact, become necrotic in due course. On the other hand, Badib and Webster (1969-72), studying the tumour and surrounding normal tissue oxygen tension levels in 68 cases of lymphoma and carcinoma during radiation therapy, showed that there was a positive correlation between poor oxygenation and persistent tumour.

New atraumatic methods of measurement of tissue oxygen tension levels are not yet available. Meanwhile, it can be said that a saturating period of time in oxygen at full pressurisation is essential. /

essential. In fact, the Medical Research Council Working Party on hyperbaric oxygen have suggested that a minimum of 15 minutes should ensue between full pressurisation and the onset of treatment.

APPENDIX 2

The Prognostic Value of Histology and its Relation to Treatment with Hyperbaric Oxygen

An interesting sidelight on the work of the Cervix Trial has been the histological examination of serial biopsies. These were taken prior to treatment and again four weeks later, at the conclusion of external radiotherapy, when Radium was about to be inserted. An attempt has been made to assess these histological findings in terms of a prognosis and to correlate this prognosis with the use of hyperbaric oxygen and the actual survival of the patients. Only patients with a histological diagnosis of squamous cell carcinoma or anaplastic carcinoma were included in the assessment.

In the histological survey, biopsies taken before and after radiotherapy were compared and graded according to the criteria suggested by Walter et al (1964-73). The pre-treatment biopsies were divided histologically into well-differentiated, moderately-differentiated, poorly-differentiated squamous cell carcinomata and /

and anaplastic carcinoma. A mitotic count per high power field was estimated for each and this generally corresponded to the degree of differentiation of the tumour.

Certain features found on examination of the post-radiation specimen were taken as indicators of the response of the tumours to irradiation (Glucksmann 1965-74). These were:-

1. The presence of viable tumour cells. Radiocurability depends on the death of all tumour cells. If viable ones are found in the biopsy, the prognosis in such a case must be poor, especially where large numbers of tumour cells remain unchanged by irradiation.

2. The presence of normal-looking mitotic figures. Finding these within the tumour cells suggests that there has been a poor response to irradiation. Bizarre cells and abnormal mitoses may also be noted but their presence is of little significance. It is the cells with normal mitoses which will determine the regrowth of the tumour.

3. The presence of increased keratinisation. This may begin in the centre of the tumour foci within 24 hours of the first treatment. It spreads peripherally to cause an increase in differentiation and a sterilisation of tumour cells. Such an increase in keratinisation is indicative of a good tumour response to irradiation and therefore is a good prognostic feature.

Thus the best prognosis would be given to a case which showed well-differentiated squamous cell carcinoma with very few mitotic figures and which showed response to irradiation by greatly increased keratinisation. There would also be an absence of viable tumour cells and of normal looking mitotic figures.

A bad prognosis would be indicated if the tumour was of the anaplastic, highly cellular type with many mitotic figures. Its response to irradiation would show little or no reduction in the number of viable tumour cells or of normal mitoses. There would be a complete absence of keratinisation.

There /

4.

There are certain tumours to which a doubtful prognosis must be given because their response is not clear cut. In this type of case, there might be some slight increase in the differentiation of the tumour cells but a negligible increase in keratinisation. Cellular necrosis and the presence of many abnormal mitotic figures might also be noted, but as stated before these would be of little significance.

Although these criteria appear simple and straightforward it is essential to realise that sections can only be made and observed from the biopsy specimen, which may or may not be representative of the whole range of histological variation shown by the tumour.

Of the 129 cases in the Cervix Trial, pre and post-treatment biopsies were available in 85 diagnosed as squamous cell or anaplastic carcinoma. Figure 31 shows the survival of all these patients who have been included in the trial for one year or more on the 1st July, 1971. Stage III and Stage IV cases are grouped separately, each being divided into those treated in hyperbaric oxygen /

STAGE III - OXYGEN

Trial No.		PRE-TREATMENT BIOPSY Degree of differentiation	Mitotic Rate	SURVIVAL Months	State at 1. 7.71
		Good Prognosis (keratinisation)			
84		Well	1	26	Alive - disease free
98		Well	1 - 2	20	Alive - disease free
27		Moderate	5 - 7	47	Alive - disease free
42		Moderate	3 - 5	41	Alive - disease free
71		Moderate	3 - 4	31	Alive - disease free
73	Ø	Moderate	1 - 2	31	Alive - disease free
75		Moderate	2 - 3	30	Alive - disease free
87		Moderate	2 - 4	25	Alive - disease free
107	Ø	Moderate	2 - 4	15	Alive - disease free
39		Poor	10 +	42	Alive - disease free
		Doubtful Prognosis (Bizarre cells/Necrosis)			
31		Well	1	29	Dead - local recurr. and mets.
56		Well	2	9	Dead - local recurr. and mets.
67		Well	1	24	Dead - local recurrence
68		Well	< 1	2	Dead - local recurrence
28		Moderate	5 - 7	46	Alive - disease free
61		Moderate	2	29	Dead - metastases
102		Moderate	3 - 4	7	Dead - local recurr. and mets.
108		Moderate	6 - 8	13	Alive - disease free
6		Poor	5 -10	55	Alive - disease free
79		Anaplastic	-	2	Dead - local recurr. and mets.
83		Anaplastic	4 - 5	27	Alive - disease free
		Bad Prognosis (Viable Cancer Cells)			
12		Well	1 - 3	54	Alive - disease free
40	Ø	Well	2	42	Alive - disease free
91	Ø	Well	4 - 5	23	Alive - disease free
111	Ø	Well	< 1	19	Dead - metastases
16		Moderate	5	37	Dead - unknown
49		Moderate	2 - 3	39	Alive - disease free
52		Moderate	1 - 2	38	Alive - disease free
81		Moderate	6	4	Dead - local recurr. and mets.
92		Moderate	1 - 2	22	Alive - metastases
105	Ø	Moderate	< 1	9	Dead - local recurr. and mets.
2		Poor	6 - 8	8	Dead - local recurrence
33		Poor	10 +	5	Dead - metastases
54		Poor	5 - 6	19	Dead - local recurr. and mets.

Ø Failed to complete treatment in oxygen

Figure 31 (i)

STAGE III - AIR

Trial No.	PRE-TREATMENT BIOPSY Degree of differentiation	Mitotic Rate	SURVIVAL Months	State at 1. 7.71
	Good Prognosis (keratinisation)			
89	Well	< 1	24	Alive - disease free
104	Well	4 - 5	16	Alive - disease free
10	Moderate	2 - 3	54	Alive - disease free
37	Moderate	2 - 3	37	Dead - local recurrence
86	Anaplastic	10 +	5	Dead - metastases
	Doubtful Prognosis (Bizarre cells/Necrosis)			
58	Well	< 1	10	Dead - metastases
90	Well	< 1	3	Dead - local recurr. and mets.
23	Moderate	6 - 8	16	Dead - local recurr. and mets.
36	Moderate	12	22	Dead - local recurr. and mets.
38	Moderate	1 - 5	42	Alive - disease free
69	Moderate	4	37	Dead - metastases
85	Moderate	1 - 2	26	Alive - disease free
94	Moderate	20	21	Alive - disease free
100	Moderate	2 - 3	19	Alive - disease free
106	Moderate	6 - 7	15	Alive - disease free
44	Poor	5	41	Alive - disease free
55	Poor	< 1	4	Dead - local recurr. and mets.
66	Poor	10	7	Dead - metastases
74	Poor	-	30	Alive - disease free
20	Anaplastic	5 - 7	50	Alive - disease free
34	Anaplastic	10	45	Alive - disease free
	Bad Prognosis (Viable Cancer cells)			
77	Well	1 - 2	20	Dead - local recurr. and mets.
99	Well	1	19	Alive - disease free
1	Moderate	10	6	Dead - unknown
22	Moderate	10	16	Dead - local recurr. and mets.
41	Moderate	1 - 3	42	Alive - disease free
50	Moderate	< 1	38	Alive - disease free
53	Moderate	5 - 6	14	Dead - local recurr. and mets.
65	Moderate	7	22	Dead - local recurr. and mets.
82	Moderate	1 - 2	23	Dead - local recurr. and mets.
93	Moderate	6	21	Alive - disease free
109	Moderate	6	11	Dead - local recurr. and mets.
110	Moderate	3	10	Dead - local recurr. and mets.
5	Poor	5	12	Dead - metastases
25	Poor	4 - 5	9	Dead - local recurr. and mets.
32	Poor	3 - 5	11	Dead - local recurrence
76	Poor	2 - 3	5	Dead - metastases

Figure 31 (ii)

STAGE IV - OXYGEN

Trial No.	PRE-TREATMENT BIOPSY Degree of differentiation	Mitotic Rate	SURVIVAL Months	State at 1. 7.71
	Good Prognosis (keratinisation)			
19	Well	< 5	26	Dead - local recurr. and mets.
88	Well	< - 1	4	Dead - local recurr. and mets.
64	Moderate	7 - 8	33	Dead - metastases
	Doubtful Prognosis (Bizarre cells/Necrosis)			
30	Well	1 - 3	5	Dead - local recurr. and mets.
14	Poor	5	12	Dead - metastases
	Bad Prognosis (Viable cancer cells)			
21	Moderate	3 - 5	23	Dead - metastases
30	Moderate	10	22	Dead - metastases

STAGE IV - AIR

Trial No.	PRE-TREATMENT BIOPSY Degree of differentiation	Mitotic Rate	SURVIVAL Months	State at 1. 7.71
	Good Prognosis (keratinisation)			
29	Anaplastic		2	Dead - local recurr. and mets.
	Doubtful Prognosis (Bizarre Cells/Necrosis)			
78	Well	2 - 3	2	Dead - local recurr. and mets.
17	Moderate	10	14	Dead - local recurrence
96	Anaplastic	1 - 2	8	Dead - local recurrence
	Bad Prognosis (Viable Cancer Cells)			
13	Well	3 - 5	5	Dead - local recurr. and mets.
8	Moderate	1 - 5	13	Dead - metastases
62	Moderate	3 - 4	17	Dead - local recurr. and mets.

Figure 31 (iii)

oxygen or in air. There are three categories within each group. Each category is a prognostic one established by histopathological findings from the serial biopsies. The single most ominous feature in each specimen defines its category. It follows that all trial cases, which showed viable tumour cells in the post-treatment biopsy, were placed in the category of Bad Prognosis. The category of Doubtful Prognosis is distinguished by necrosis or by bizarre cells. The category of Good Prognosis shows increase in keratinisation.

Results are shown in Figure 32. Those with a good histological prognosis have done well in hyperbaric oxygen. 100% are alive at one year or more. Those with a doubtful prognosis have done worse in oxygen than in air. Those with a bad prognosis have done better in oxygen. The numbers in each group are too small to be of statistical significance. A better correlation between histological prognosis, HPO treatment and survival rate could only be established by the study of a large number /

STAGE III - OXYGEN			
Prognosis	Cases	Alive 1 year or more	Dead with local disease
Good	10	10 (100%)	0 (0%)
Doubtful	11	4 (36%)	6 (55%)
Bad	13	6 (46%)	4 (31%)

STAGE III - AIR			
Good	5	3 (60%)	1 (20%)
Doubtful	16	9 (56%)	4 (25%)
Bad	16	4 (25%)	9 (56%)

These figures do not include patients who died with metastatic disease only

Figure 32

number of cases. Nevertheless, the 100% one year survival shown by Stage III oxygen cases with a good histological prognosis is encouraging for the use of hyperbaric oxygen. The predictive value of the histological findings also appears to deserve further study.

INDIVIDUAL AND JOINT PUBLICATIONS

Some of the material in this thesis has been incorporated in publications. The following are the relevant references :-

Phillips, D.L., Morris, S., and Orr, J.S. (1966)

Report on the First year's use of hyperbaric oxygen in supervoltage radiotherapy at the Western Infirmary, Glasgow.

Clinical Radiology 17. 173-176

Watson, E.R., Morris, S. and Halnan, K.E. (1971)

A controlled clinical Trial of Hyperbaric Oxygen in the Radiotherapy of Advanced Carcinoma of the Cervix Uteri.

Modern Trends in Radiotherapy Vol. 11, pp. 53-60
Deeley, T.J. (Ed.)
London : Butterworths

Morris, Sasha (1971)

Radiotherapy in Hyperbaric Oxygen

Recent advances in Cancer and Radiotherapeutics
pp. 309 - 322
Halnan, K.E. (Ed.)
Churchill-Livingstone

BIBLIOGRAPHY

1. L.H. Gray, Conger A.D., Ebert M., Hornsey S., Scott O.C.A., (1953)

The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy

British Journal of Radiology 26:638-648

2. Thoday, J.M. and Read, J. (1947)

Effect of oxygen on the frequency of chromosome aberrations produced by Alpha rays

Nature, 163 : 134-135

3. Holthusen, H. (1921)

Beitrage zur biologie der strahlenwirkung untersuchungen an askerideneiern

Pflugers Archiv fur die Gesampte Physiologie 187 : 1-24

4. Mottram, J.C. (1924)

On the skin reactions to radium exposure and their avoidance in therapy; an experimental investigation

British Journal of Radiology 29 : 174-180

5. Crabtree, H.G. and Cramer, W. (1933)

The action of radium on cancer cells - factors determining the susceptibility of cancer cells to gamma radiation.

Eleventh Scientific Report, Imperial Cancer Research Fund 103-117

6. Mottram, J.C. (1935 a)

On the alteration in the sensitivity of cells towards radiation produced by cold and by anaerobiosis

British Journal of Radiology 8 : 32-39

7. /

7. Mottram, J.C. (1935 b)

Variations in sensitivity of the cell to radiation in relation to mitosis

British Journal of Radiology 8 : 643

8. Mottram, J.C. (1936)

A factor of importance in the radiosensitivity of tumours.

British Journal of Radiology 9 : 606-614

9. Lacassagne, A. (1942)

Chute de la sensibilite aux rayons X chez la souris nouveau - née en etat d'asphyxie.

Compte Rendu Academie Sciences Paris 215 : 231-232

10. Evans, T.C., Goodrich J.P. and Slaughter J.C. (1942)

Temperature and radiosensitivity of the skin of new-born rats - effects of decreased circulation and breathing during irradiation

Radiology 38 : 201-206

11. Dowdy, A.H., Bennett L.R. and Chastain S.N. (1950)

Protective action of anoxic anoxia against total body roentgen irradiation of mammals

Radiology 55 : 879-885

12. Hall V., Hamilton K., and Brues A.M. (1952)

Clarification of differences in radiosensitivity of tumours irradiated in vitro and in vivo on the basis of the effect of oxygen on radiosensitivity

Cancer Research 12 - 268

13. /

13. Russell L.B., Russell W.L. and Major M.H. (1952)

The effect of hypoxia on the radiation induction of developmental abnormalities in the mouse

Nuclear Science Abstracts 6 : 137

14. Devik F. (1952)

Cytological investigation of bone marrow of mice after administration of protective agents and subsequent x-radiation.

British Journal of Radiology 25 : 481-484

15. Thoday J.M. and Read J. (1947)

Effect of oxygen on the frequency of chromosome aberrations produced by x-rays

Nature 160 : 608

16. Read J. (1952)

The effect of ionizing radiations on the broad bean root; the dependence of x-ray sensitivity on dissolved oxygen.

British Journal of Radiology 25 :89-99 and 154-160.

17. Riley, H.P. and Giles N.H. (1950)

The effect of oxygen on the frequency of x-ray induced chromosomal aberrations in Tradescantia microspores

Genetics 35 : 131-132

18. Deschner E.E. and Gray L.H. (1959)

Influence of oxygen tension on x-ray induced chromosomal damage in Ehrlich ascites tumour cells irradiated in vitro and in vivo

Radiation Research 11 : 115

19. /

19. Howard Flanders P. and Moore D. (1958)

Time interval after pulsed irradiation within which injury to bacteria can be modified by dissolved oxygen - a search for an effect of oxygen 0.02 sec. after pulsed irradiation.

Radiation Research 9 : 422-437

20. Alper T. and Howard Flanders P. (1956)

The role of oxygen in modifying the radiosensitivity of E.Coli B.

Nature 178 : 978-979

21. Thomlinson R.H. and Gray L.H. (1955)

The histological structure of some human lung cancers and the possible implications for radiotherapy

British Journal of Cancer 9 : 539-549

22. Young J.S., Lumsden C.E. and Stalker A.L. (1950)

The significance of "tissue pressure" of normal testicular and of neoplastic (Brown-Pearce carcinoma) tissue in the rabbit.

Journal of Pathology and Bacteriology 62 : 313-333

23. Hultborn K.A. and Forssberg A. (1954)

Irradiation of skin tumours during pure oxygen inhalation

Acta Radiologica Stockholm 42 : 475-484

24. Van den Brenk H.A.S., Kerr R.C., Richter W. and Papworth M.P. (1965)

Enhancement of radiosensitivy of skin of patients by high pressure oxygen

British Journal of Radiology 38 : 857-864

25. /

25. Churchill-Davidson I., Sanger C. and Thomlinson R.H. (1955)
High pressure oxygen and radiotherapy
Lancet 1 1091-1095

26. Behnke A.R. (1942)
The physiologic studies pertaining to deep sea diving and aviation, especially in relation to the fat content and composition of the body
Bulletin of the New York Academy of Medicine 18 : 561-585

27. Donald K.W. (1947)
Oxygen poisoning in man.
British Medical Journal, May 17th-24th : 667.672, 712-716

28. Powers W.E. and Tolmach L.T. (1964)
Demonstration of an anoxic component in a mouse tumour cell population by in vivo assay of survival following irradiation.
Radiology 83 : 328-335

29. Emery E.W., Lucas B.G.B. and Williams K.G. (1960)
Technique of irradiation of conscious patients under increased oxygen pressure.
Lancet 1 : 248

30. Sutherland W.H. and Griffiths D. (1966)
Beam direction in hyperbaric oxygen therapy
British Journal of Radiology 39 : 696-698

31. /

31. Sutherland W. H. (1968)

A new method of beam direction, with particular application in hyperbaric oxygen therapy

British Journal of Radiology 41 : 633-636

32. Wakabayashi M., Ohsawa T. and Sugawara T. (1969)

Intracavitary radiation therapy under the hybaroxic condition.

XIIth International Congress in Radiology - Tokyo 1969

33. Tobin D. A. (1971)

Explosive decompression in a hyperbaric oxygen chamber

American Journal of Roentgenology and Radium Therapy 111 : 622-624

34. Hill, L. (1933)

The influence of carbon dioxide in the production of oxygen poisoning.

Quarterly Journal of Experimental Physiology 23 : 49-50

35. Bean J. W. (1945)

Effects of oxygen at increased pressure - aetiology of reactions to oxygen at high pressure

Physiological Reviews 25 : 1-147

36. Dickens, F. (1946)

The toxic effects of oxygen on brain metabolism and on tissue enzymes.

Biochemical Journal 40 : 145-187

37. /

37. Churchill-Davidson I. (1964)

Oxygenation in radiotherapy of malignant disease of the upper air passages.

Proceedings of the Royal Society of Medicine 57 : 635-638

38. Bates T.D. (1969)

The treatment of Stage III Carcinoma of the cervix by external radiotherapy and high pressure oxygen

British Journal of Radiology 42 : 266-269

39. Atkins H.L., Seaman W.B., Jacox H.W. and Matteo R.S. (1965)

Experience with hyperbaric oxygenation in clinical radiotherapy

American Journal of Roentgenology and Radium Therapy 93 : 651-663

40. Wildermuth, O. (1968)

Problems in the management of patients with hyperbaric radiotherapy

Frontiers of Radiation Therapy and Oncology
Vol. 1 pp. 127-133 Karger, Basel/New York

41. Van den Brenk H.A.S., Richter W. and Hurley R.H. (1968)

Radiosensitivity of the human oxygenated cervical spinal cord, based on analysis of 357 cases receiving 4MeV x-rays in hyperbaric oxygen

British Journal of Radiology 41 : 205-214

42. /

42. Churchill-Davidson I. (1968)

Long term effects of hyperbaric oxygen and irradiation on non-neoplastic tissues

Frontiers of Radiation Therapy and Oncology Vol. 1 pp. 134-140 Karger, Basel/New York

43. Roulston J.M. and Johnson R.J.R. (1968)

Treatment of carcinoma of cervix Stages III and IV using cobalt therapy and a hyperbaric oxygen chamber

Journal of Obstetrics and Gynaecology of the British Commonwealth. 75 1279-1280

44. Van den Brenk H.A.S., Madigan J.P. and Kerr R.C. (1968)

Experience in Melbourne with the use of hyperbaric oxygen combined with megavoltage radiation in 614 cases of advanced malignant disease

Frontiers of Radiation Therapy and Oncology Vol. 1, pp. 162-174 Karger, Basel/ New York

45. Churchill-Davidson I., Foster, C.A., Wiernik G. Collins C.D., Pizey, N.C.D., Skeggs D.B.L., Purser P.R. (1966)

The place of oxygen in radiotherapy

British Journal of Radiology 39 : 321-331

46. Van den Brenk H.A.S., Madigan J.P. and Kerr R.C. (1964)

Experience with megavoltage irradiation of advanced malignant disease using High Pressure Oxygen

Clinical Application of Hyperbaric Oxygen pp. 144-160 Ed. I. Boroema, Brummelkamp, Meijne

47. Van den Brenk H.A.S. (1968)

Hyperbaric oxygen in Radiation Therapy

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine 102 : 8-26

48. Chang C.H., Seaman W.B., Jacox H.W. (1968)

Clinical Aspects of Hyperbaric Oxygen and Radiotherapy New York Experience

Frontiers of Radiation Therapy and Oncology
Vol. 1 pp. 183-188 Karger, Basel/New York.

49. Wildermuth, O. (1964)

Hybaroxic Radiation Therapy in Cancer Management

Radiology 82 : 767-777

50. Emery E.W. (1964)

Clinical Trial - Patients treated with radiotherapy under High Pressure Oxygen

British Journal of Radiology 37 : 722

51. Cade I.S. and McEwen J.B. (1967)

Megavoltage radiotherapy in hyperbaric oxygen; a controlled trial.

Cancer 20 : 817-821

52. Plenk H.P. (1972)

Hyperbaric Radiation Therapy. Preliminary results of a randomised study of cancer of the urinary bladder and review of the "oxygen experience"

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine 114 : 152-157

53. Henk J.M., Kunkler P.B., Shah N.K., Smith C.W. Sutherland W.H., and Wassif S.B. (1970)

Hyperbaric Oxygen in radiotherapy of head and neck carcinoma.

Clinical Radiology 21 : 223

54. /

54. Kunkler P.B., Henk J.M., Shah N.K. and Smith C.W. (1970)

Radiotherapy and hyperbaric oxygen in malignant tumours of the oral cavity and oropharynx with lymph node metastases

Gann Monograph No. 9 1970 (Maruzen) Tokyo.

55. Hall E.J., Bedford J.S. and Oliver R. (1966)

Extreme hypoxia; its effect on the survival of mammalian cells irradiated at high and low dose rates

British Journal of Radiology 39 : 302-307

56. Tod M. and Meredith W.J. (1953)

Treatment of Cancer of the Cervix Uteri - a revised "Manchester Method"

British Journal of Radiology 26 : 252-257

57. Johnson R.J.R. (1968)

Gynaecological cancer treated with cobalt under hyperbaric conditions

Frontiers of Radiation Therapy and Oncology
Vol. 1 pp. 149-155 Karger, Basel/New York

58. Van den Brenk, H.A.S., Madigan J.P. and Kerr R.C. (1967)

An analysis of the progression and development of metastases in patients receiving irradiation in hyperbaric oxygen

Clinical Radiology 18 : 54-61

59. Bewlay D.K. (1970)

Treatment of Stage III Cervix by external radiotherapy and high pressure oxygen

British Journal of Radiology 43 : 498-499

60. /

60. Ellis F. (1968)

The relationship of biological effect to dose-time-fractionation factors in radiotherapy

Current topics in Radiation Research Vol. 4 pp. 359-397
Edited by Ebert and Howard
North Holland Publishing Company, Amsterdam

61. Kirk J., Gray W.M. and Watson E.R. (1971, 1972)

Cumulative Radiation Effect
Part 1 - Clinical Radiology 1971 22 : 145-155
Part 2 - Clinical Radiology 1972 23 : 93-105
Part 3 - Clinical Radiology, in press

62. Danneel H. (1897)

Uber den durch diffundierende Gase hervorgerufenen Reststrom

z. Elektrochem 4 : 227

63. Davies P.W. and Brink F. (1942)

Microelectrodes for measuring local oxygen tension in animal tissues

Review of Scientific Instruments 13 : 524-533

64. Clark L.C., Wolf R., Granger D., Taylor Z. (1953)

Continuous recording of Blood oxygen Tension by Polarography

Journal of Applied Physiology 6 : 189-193

65. Cater D.B., Silver I.A. and Wilson G.M. (1959)

Apparatus and technique for the quantitative measurement of Oxygen tension in living tissues

Proceedings of the Royal Society (Biological) 151 : 256-276

66. /

66. Cater D.B. and Silver I.A. (1960)

Quantitative measurements of oxygen tension in normal tissues and in the tumours of patients before and after radiotherapy.

Acta Radiologica, Stockholm 53 : 233-256

67. Evans N.T.S. and Naylor P.F.D. (1963)

The effect of oxygen breathing and radiotherapy upon the tissue oxygen tension of some human tumours

British Journal of Radiology 36 : 418-425

68. Cater D.B. (1964)

Oxygen tension measurements in human and animal tumours

British Journal of Radiology 37 : 720-721

69. Jamieson D. and Van den Brenk H.A.S. (1963)

Comparison of oxygen tensions in normal tissues and Yoshida sarcoma of the rat breathing air or oxygen at 4ATA

British Journal of Cancer 17 : 70-78

70. Jamieson D. and Van den Brenk H.A.S. (1965)

Oxygen tension in Human Malignant Disease under Hyperbaric Conditions

British Journal of Cancer 19 : 139-150

71. Baker D.J., Lindop, P.J. and Hewitt H.B. (1968)

Effect of breathing oxygen at high pressure on the oxygenation of a sarcoma in CBA mice

British Journal of Radiology 41 : 318-319

72. /

72. Badib A.C. and Webster J.H. (1969)

Changes in Tumour Oxygen Tension during Radiation Therapy

Acta Radiologica (Therapy), Stockholm 8 : 247-257

73. Walter L., Harrison C.V., Glucksmann A. and Cherry C.P. (1964)

Assessment of Response to Cervical Cancers to Irradiation by Routine Histological Methods

British Medical Journal 1 : 1673-1675

74. Glucksmann A. (1965)

Histological Factors in the Radiotherapy of Tumours

The Treatment of Cancer pp. 72-88
Edited by J.S. Mitchell
Cambridge University Press