Hyperbaric Oxygen Therapy For The Treatment And Prevention Of Osteoradionecrosis

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Erratum

The following typographical errors are noted and amended as follows:

1. page 9 line 21
   "supervoltage", meaning "megavoltage".

2. page 33 line 26
   "floor" should read "flora".

3. Page 67 line 13
   "PO_2 concentrations" should read "PO_2 values"

4. page 77 line 9
   "Streptococcus" has been omitted.
   It should read "aureus and albus, Strept. Haemolyticus and viridans, Pneumococcus,".

The following are additional inserts into the respective pages.

Page 52 Line 8

The history of Hyperbaric Medicine is misquoted on page 52 as "Hyperbaric Medicine had its beginnings in 1939". In fact Hyperbaric Medicine using air and other gases was proposed by Paul Bert in 1873. Hyperbaric Oxygen Therapy was introduced in 1939 by Albert Behnke, initially for divers.

Page 57 Line 19

Monoplace chambers are quoted on page 57 as being oxygen filled. This is not always the case. There are monoplace chambers available like that manufactured by Hyox in which the patient breath oxygen or air from a mask within an air filled chamber.

Page 63 Line 11

The complication of acute or CNS Oxygen toxicity has been reported at an incidence of 1 in 400 patient treatments in some units. Hence, all staff should be trained in its management or HBO patients require informed consent of this complication.

Mathematical errors are noted in tables 9.10 and 9.27. Both tables have been corrected respectively and should read as follows:

Table 9.10 Oral surgical procedures requiring prophylactic HBO.

HBO PROPHYLACTIC GROUP			
Patients (n)	**Surgical Procedure**	**Perioperative Antibiotic**	**Outcome (Post-op)**
22	Extraction of teeth Md +/- Mx + primary closure	19 Yes	21 Healed 1 ORN
1	Marginal mandibulectomy, resection of tumour recurrence + extraction of lower teeth	Yes	Healed
1	Removal of bone plates + 2 molars Insertion 5 x implants in mandible	Yes	Healed
1	Insertion 5 x maxillary implants + bone graft to maxillary alveolus	Yes	Healed
1	Removal of Mx Radicular cyst + extraction 3 Mx + 3 Md teeth	Yes	Healed
1	Insertion 2 x implants mandible	Yes	Healed
1	Cryofreeze R. Mandibular nerve for pain + removal of bone plates mandible	Yes	Healed
1	Insertion 5 implants into bone grafted mandible	Yes	Healed
29		26 Yes	1 ORN 28 HEALED

Table 9.27 Hyperbaric oxygen experience of patients treated prophylactically.

PROPHYLACTIC HBO PATIENTS			
HYPERBARIC OXYGEN EXPERIENCE: HOW THEY FELT AFTER COMPLETING HBO TREATMENT.			
	SAME	**BETTER**	**WORSE**
GENERALLY	37%	58%	5 %
EATING ABILITY	74%	21%	5 %
TALKING	84%	11%	5 %
JAW OPENING	74%	21%	5 %
MOUTH DRYNESS	53%	31%	16%
PAIN	58%	37%	5 %
CHAMBER EXPERIENCE	26% PLEASURABLE	69% BEARABLE	5 % UNBEARABLE (pulmonary oxygen toxicity)
HAVE SAME TREATMENT AGAIN?	95% YES	5 % NO	
RECOMMEND HBO Tx TO SOMEONE ELSE	100% YES		

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SUMMARY

Hyperbaric oxygen (HBO) therapy has been proposed by Marx (1984) to be an essential component to the successful management of osteoradionecrosis (ORN). To date however, there have been few formal studies to confirm the efficacy of HBO in ORN.

The aims of this study were to:

1. Evaluate the effectiveness of hyperbaric oxygen in the management of osteoradionecrosis of the facial bones.

   This includes determination of :

   (i) Optimum dosages of HBO.
   (ii) The inter-relationship between HBO and surgical resection and grafting.
   (iii) The place of dental treatment in initiating osteoradionecrosis and in subsequent return to normal function.

2. Evaluate the effectiveness of HBO in preventing the development of osteoradionecrosis.

3. Replicate Marx's clinical findings on HBO.

4. Create an osteoradionecrosis animal model.

5. Determine the optimum radiotherapy dose required, and time taken, to create osteoradionecrosis in an animal model.

This investigation involved a detailed evaluation of 51 patient records from the Oral and Maxillofacial Surgery Unit of the University of Adelaide and the Hyperbaric Unit of the Royal Adelaide Hospital for all patients who were treated for either osteoradionecrosis or osteoradionecrosis prevention.

The patients were divided into three groups:

1. Osteoradionecrosis Group

This group consisted of all patients with osteoradionecrosis. (n=15)

The effectiveness of HBO in the treatment of osteoradionecrosis was evaluated in this group.

2. Hyperbaric Oxygen Prophylaxis Group

This group consisted of all patients with a history of irradiation therapy to their head and neck region for malignancy and requiring dental extractions or other oral surgical procedures. (n=29)

The prophylactic role of HBO against osteoradionecrosis was evaluated in this group.

3. Control Group for Hyperbaric Oxygen Prophylaxis

This group consisted of patients who effectively did not receive any therapeutic HBO prior to oral surgical procedures. (n=7)

Patients were evaluated pre and post HBO therapy over a minimum of 12 months for any evidence of osteoradionecrosis.

The results confirmed the findings of previously published research strongly advocating that HBO and surgery should be the primary treatment modality in the treatment and prevention of osteoradionecrosis. There was a 100% success rate in the treatment of osteoradionecrosis, and a 96% prevention rate, through the use of HBO. The failed HBO prophylactic case illustrated that although HBO increases the healing capabilities of irradiated tissue, it is still somewhat compromised. However, generally HBO has a prophylactic role and should be considered when postirradiation dental care involving trauma to tissues is necessary.

A trial was also carried out to create an osteoradionecrosis animal model in lower vertebrates. This involved the use of 11 Sprague Dawley rats that received a range of increasing doses of irradiation to their mandibles and salivary glands. The rats were allowed 6 months to develop hypovascular-hypocellular-hypoxic tissue. Following this period, standard surgically induced traumatic wounds were created in the rat jaw and observed for a further 6 months for any evidence of osteoradionecrosis.

Clinical observation over this period showed complete healing of the lesions. Further histological evaluation of specimens showed no evidence of radionecrosis. It is recognised that creation of an osteoradionecrosis animal model in lower vertebrates is difficult to achieve.

This study confirms that HBO is an essential component in the successful management of ORN. ORN can also be prevented by careful preirradiation management and HBO prior to surgery in previously irradiated jaw bones. The factors involved are presented in detail. Attempts at establishing an animal model were essentially unsuccessful.

STATEMENT

This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Dental Surgery. I declare that the text of this thesis has not been previously published or written by another person except where due reference is made. The findings are the result of my personal investigations. No part of this work has been previously submitted for a degree in any University.

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I give consent to this copy of my thesis, when deposited in the University Libraries, being available for photocopying and loan.

SIGNATURE: ..... DATE: 15-06-2000

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I

INTRODUCTION

CHAPTER 1

HISTORY AND GENERAL INTRODUCTION ON OSTEORADIONECROSIS

Osteoradionecrosis (ORN) of the facial bones, particularly of the mandible, is a known serious complication of radiotherapy administered to the head and neck region for the treatment of malignancies. The disease is a complex metabolic and tissue homeostatic deficiency created by radiation-induced tissue injury which produces devitalisation and devascularisation of bone.

The condition is painful, severely debilitating and frequently refractory to treatment. Patients usually state that it is a much worse condition than their original malignancy which required the radiotherapy. Complications of wound healing and spontaneous breakdown of tissue in irradiated areas are frequently observed. It is probably the most problematic wound in oral and maxillofacial surgery (Marx and Johnson, 1988).

Chapter 2 reviews the use and effects of radiotherapy in the head and neck region. Osteoradionecrosis is not a new disease, nor is it limited to the jaws. It has been recognised since the early 1900s, shortly after the introduction of therapeutic irradiation. The earliest reports of bone necrosis secondary to radiation damage appeared in the 1920s. Regaud, as cited by Mounsey et al (1993),

first provided a clinical discussion of ORN in 1922, and the pathology was further described by Ewing (1926b) under the name 'radiation osteitis'. Since that time various other terms have been used, including 'osteonecrosis due to radiation', 'radio-osteomyelitis', 'radio-osteonecrosis', 'radiation osteodysplasia', 'radiation osteitis', 'radiation necrosis' and 'osteoradioatrophy' (Pappas, 1969; Guttenberg, 1974). Later the terms 'aseptic osteoradionecrosis' and 'septic osteoradionecrosis' of the mandible were introduced to differentiate noninfected necrotic bone from infected necrotic bone (Guttenberg, 1974; Dolezal et al, 1982).

Osteoradionecrosis is not restricted to the facial bones. It has been described in a number of areas such as the pelvis, sternum, clavicle, and femoral heads (Stampfli, 1947; Bedwinek et al, 1976; Heimbach, 1988; Jansma et al, 1992; Granick et al, 1993). Osteoradionecrosis of any bone involves a concomitant nonhealing wound of both soft tissue and bone.

Osteoradionecrosis of the jaws is not only the most common site in the head and neck region but it has dramatic impacts on a patient's quality of life. This is due to the presence of teeth in the jaws, and the functional and cosmetic importance of the jaws.

Chapter 3 examines past and present theories of the pathogenesis, and controversies in the predisposing factors of ORN. The issue of the role of infection in the pathogenesis of ORN is still a major dilemma today.

Conservative and surgical methods have been used for the management of ORN, not always with successful results (Balogh et al 1989). Hyperbaric oxygen (HBO) has gained widespread use in the treatment of irradiated wounds, particularly ORN of the mandible. It has been used at the Royal Adelaide Hospital since 1987. Chapter 4 reviews the genesis of HBO therapy, its indications, and rationale in the management and prevention of ORN.

The mode of treatment of ORN has also changed dramatically. The acceptance of new theories and the publication of successful treatment modalities has influenced the choice of treatment utilised today. A literature review of the various treatment methods will be discussed in Chapter 5.

A large number of uncontrolled clinical studies, including Farmer et al 1978, Tobey & Kelly 1979, and Mounsey et al 1993, suggesting the efficacy of HBO, have been done; however these have failed to provide a clear summary of the extent of the benefits. Other than the investigations by Marx et al (1985), there are no well documented, prospective randomized studies evaluating the effectiveness of HBO. Many clinicians would agree that any wound treated with meticulous wound care, debridement, and bacterial control will improve to a certain degree. The added benefit of HBO, although widely accepted, has not been properly quantitated.

Ideally, an ORN animal model should be created to quantify and confirm the effects of HBO on this disease process. A review of the literature relevant to previous ORN animal studies is presented in

Chapter 6. There are no lower vertebrate ORN animal models because of ethical difficulties with the experimental use of animals. It has been stated, with some authority, that the dosages required and time taken to generate ORN in lower vertebrate animals is not achievable. (Marx, personal communication)

On the basis of the literature review and clinical experience with this dreadful disease, several aims were established using material from the Oral and Maxillofacial Surgery Unit, the University of Adelaide, and the Royal Adelaide Hospital.

The objectives of this study were to:

1. Evaluate the effectiveness of HBO in the management of ORN of the facial bones.

   This includes determination of:

   (i) Optimum dosages of HBO.

   (ii) The inter-relationship between HBO and surgical resection and grafting.

   (iii) The place of dental treatment in initiating osteoradionecrosis and in subsequent return to normal function.

2. Evaluate the effectiveness of HBO in preventing the development of ORN.

3. Replicate Marx's clinical findings on HBO.

4. Create an ORN animal model.

5. Determine the optimum radiotherapy dose required, and time taken, to create ORN in an animal model.

The materials and methods for the clinical evaluation of HBO in this study are detailed in Chapter 7. The materials and methods for the animal experiment are presented in Chapter 8.

The overall results of the clinical study are presented in Chapter 9 and of the animal study in Chapter 10. The findings of the two studies are discussed in subsequent chapters which parallel the results. The clinical study outcome is discussed in Chapter 11 and the animal study in Chapter 12. The overall conclusions are presented in Chapter 13.

II

REVIEW OF THE LITERATURE

CHAPTER 2

RADIOTHERAPY TREATMENT TO THE HEAD AND NECK

The management and cure of cancer of the head and neck carries morbidity regardless of the disease process or treatment modality employed. Generally the effects of surgery are obvious even to the most casual observer; however, those of irradiation evolve over time, manifesting themselves years or sometimes decades after the cure of the tumour. This chapter reviews the common applications of radiotherapy to the head and neck, and the sequential complications both in the short and long term.

Ionizing radiation is composed of photons that have been generated either electrically (x-rays) or from unstable nuclei of radioactive substances called isotopes, e.g. radium, cobalt (gamma-rays). The resultant photons from either process are fundamentally indistinguishable once they have left their source. The particular energy of a beam depends on its source. Particulate radiation is radiation produced by particles such as electrons, protons, alpha-particles and neutrons. These are most often charged species that are capable of ionizing any tissues they traverse at high velocity. They also tend to cause a relatively greater biologic effect than x- and gamma-rays (Catterall, 1986; McGregor,1986; Bernstein, 1993; Janjan, 1993; Goldwein & Meadows 1993).

Several forms of ionizing radiation have been used in the treatment of malignancy (Rubin & Doku, 1976). Essentially there are two main external irradiation modalities for the treatment of deep-seated malignant lesions: orthovoltage and supervoltage (megavoltage). Orthovoltage radiation uses low-voltage x-rays, ranging from 150 to 400 kV, with the skin surface receiving the maximal tissue dose (Pappas, 1969). The absorbed dose at this energy level is dependent on the atomic number of the tissue being irradiated. Bone has an atomic number approximately twice that of either muscle or adipose tissue. This means that orthovoltage has greater damaging effects on bone than on soft tissue (Mansfield et al 1981). Consequently, orthovoltage is infrequently used today.

Supervoltage radiation produces between 500kV and 8 million electron volts (meV), and megavoltage is greater than 8 meV (Mansfield et al 1981). Supervoltage can be generated from electrostatic generators, linear accelerators, betatrons and cobalt 60 units. Cobalt 60 has an energy level of 1.2 meV, falling within the range of supervoltage radiation. At this voltage, different tissues tend to absorb approximately the same amount of energy. This has been referred to as the 'sparing' effect of cobalt 60 and is a major factor in its widespread use today. Utilising supervoltage, 15 meV or more can be directed at the destruction of cancer cells, while minimising patient morbidity. In particular, it has been observed that when supervoltage radiation is used, there is a decrease in the dose to the bone and periosteum, with an attendant decrease in damage to their blood supply (Guttenberg, 1974). This is especially important in reducing the incidence of ORN. Furthermore, this modality of radiation is more sparing of the oropharyngeal mucous

membranes, thereby lessening the chance of ulceration of the soft tissues.

It must be pointed out, however, that despite the superiority of supervoltage over orthovoltage sources, radiation still produces untoward effects in tissues.

The biologically significant effect produced by ionizing radiation in tissues was originally measured as the radiation absorbed dose (rad). The newer SI unit of absorbed dose is the **gray** (Gy) where 1 gray is equal to 100 centiGray (cGy) or 100 rad (1 Gy = 100 rad). The exposure to the skin from a single chest radiograph is approximately 0.03 cGy, and a typical therapeutic dose which is used to treat a child with cancer ranges between 1000 and 5000 cGy (Goldwein & Meadows, 1993).

2.1 Therapeutic Radiation in Head and Neck

In the head and neck, therapeutic radiation is utilised most commonly in the treatment of squamous cell carcinomas and lymphomas. It tends to be more effective on less well differentiated lesions (Vermund et al, 1974; Regezi & Sciubba 1993).

The radiation level needed to kill malignant cells ranges from 40 to 80 Gy. In order to make it tolerable to patients, radiation is fractionated into daily doses of approximately 2 Gy. This allows delivery over a 4 to 7 week period of a total tumour dose of 40 to 50 Gy for lymphomas, and 55 to 80 Gy for squamous cell

carcinomas and sarcomas (Coleman, 1993; Regezi & Sciubba, 1993; McGrath et al 1995).

2.2 Effects of Radiotherapy

Even with the best modern techniques, in addition to the desired antitumour effects, the therapeutic levels of radiation used in the treatment of cancer produce irreversible changes in the normal tissues overlying and adjacent to the tumour. Like tumour cells, these normal cells are highly radiosensitive and radiation leads to varying degrees of cellular damage (Warren, 1943).

The major biological effect of irradiation on tissues in general is produced by ionization. The energy source, whether cobalt 60, linear accelerator, or other high energy form, causes release of photons that ultimately strike biologically important molecules within the tissues being irradiated, producing ionization effects. Ionization energy causes expulsion of an electron from an atom, producing a positive ion. The expelled electron (beta particle) attaches to another atom nearby, creating a negative ion. The net result is an ion pair. With gamma rays as the energy source, the resultant beta particle has enough energy to produce more than one ion pair before being absorbed. The unstable molecules generated can also produce secondary biochemical reactions that alter enzyme functions within tissues. Radiosensitivity will vary from tissue to tissue. The effect on cells is generally greater when mitotic activity of a cell group is high, when the mitotic process is prolonged, and when differentiation or function is not highly established (Regezi & Sciubba 1993).

The clinical relevance of the toxicity of radiotherapy is obvious. The clinician must recognise its importance in the various settings in which it is employed. When ionizing radiation is the definitive therapy higher doses are likely to be necessary, and the risk of toxicity is greater. This, however, may be dependent on the histology. Generally, definitive therapy for squamous cell carcinoma at its various sites in the head and neck will require doses of 55 to 80 Gy delivered to the primary site and the neck. Definitive therapy of lymphomas or rhabdomyosarcoma, diseases more common during youth, may require significantly lower doses, but these are usually delivered to sites that may impair growth of soft tissues or bone in the child. Furthermore, many of the complications of radiotherapy have a long latency period, and radiation during childhood even at lower doses may ultimately result in a higher incidence of problems than that delivered to adults (Spanos et al, 1976; Coleman 1993).

2.3 Pathological Tissue Effects

In evaluating the potential for difficulty in the irradiated patient it must be clear that, although the head and neck are anatomical areas that share certain functions, their components are basically very different tissues with very different responses to radiotherapy. Skin, muscle, bone, cartilage, mucosa, and blood vessels all manifest the basic radiotherapeutic insult in different ways. With this in mind, any approach to a problem must consider all of them.

The basic injurious effect of radiation can be grossly characterised as acute or chronic. Acute effects are the reflection of cell death secondary to inability to repair DNA damage in dividing cells, or to actual organelle damage caused by the combination of ionizing radiation and intracellular free radical production. Mucositis, second-degree skin burns, or moist desquamation, epilation, and loss of salivary function are all acute effects of radiation on cell systems with relatively rapid turnover. Muscle fibrosis, skin atrophy, brain necrosis, neuropathy, stricture of the oesophagus, retinopathy, cataract formation, radiation myelitis, hypo-pituitarism, hypothyroidism, and lymphatic obstruction are all long-term sequelae of cell death in less rapidly proliferating systems. They are the consequences of either the direct effect of radiotherapy or subsequent ischaemia induced by the obliteration of the microvasculature of each tissue that results from radiotherapy (Rubin & Casarett, 1968; Baker, 1982; Miller & Rudolph, 1990). In addition to the direct acute and chronic side effects of irradiation, the changes also render the tissue less resistant to infection or other traumatic events. Moreover, adjuvant radiotherapy or surgery performed on a previously irradiated patient may result in cumulative damage (Coleman 1993).

Stem cells in the basal layer of epithelium are also affected, which causes loss of these cells. This leads to mucosal ulceration because the normal physiological loss of cells in superficial layers by wear and tear cannot be replaced. As part of the repair process ulceration becomes replaced by granulation tissue which leads to

fibrosis. Progressive scarring and vascular compromise render oral mucosa susceptible to even minor trauma.

It was recognised from the early 1920s that the endothelial cell is one important cell type which is susceptible to therapeutic irradiation. Ewing, in 1926, ascribed the effect of irradiation on bone to interference with its nutrition as a result of obliteration of the vascular supply from the periosteum, the nutrient artery, capsular arteries and the bone marrow. Long-term effects on the organ system in which it resides can be profound. Endothelial cell changes include swelling, degeneration, and necrosis. This results in bulging of endothelial cells, causing narrowing of the lumen. There is also thickening of the intimal lining of blood vessels.

The end result is a progressive obliterative endarteritis, leading ultimately to circulatory impedance and occlusion. The histopathology of irradiated tissue shows hyalinisation, endarteritis, and thrombosis of small vessels (Rubin & Casarett, 1968; McGregor et al 1995). Subsequently the common underlying problem with this condition is poor perfusion. This decreases the delivery of oxygen, leukocytes and other immune substances, and inhibits removal of carbon dioxide and toxic metabolic waste products. Consequently there is parenchymal damage, resulting in decreased function (Regezi & Sciuba 1993).

The susceptibility of different cell types to radiation injury was noted by Desjardins (1932) in the early 1930s. He concluded that the severity of injury to the connective tissue cells, muscle cells, bone cells, and nerve cells depends indirectly on the injury of the

endothelial cells of the blood vessels and the associated ischaemia. Rohrer et al (1979) studied the effect of high-dose, fractionated megavoltage radiation on rhesus monkey mandibles. They observed a general reduction in number and calibre of blood vessels in the periodontium, periosteum, haversian bone and marrow. Similar histological changes have been seen in human specimens, which correlate with the clinical findings (Pappas, 1969; Marx, 1983).

Within 6 to 18 months following radiation, progressive sclerosis of the vessels in the irradiated area begins gradually to render the affected tissue ischaemic, and this progression continues for the rest of the patient's life (Kindwall 1992). This best explains the problems we face when operating on irradiated tissue.

With irradiation of salivary glands, the time dose relationship relative to salivary function is well known (Beumer et al 1979, Larson 1993). Clinical and experimental findings indicate that radiation in low dose can cause acute salivary flow rate diminution by rapidly destroying serous acinar cells within salivary glands. These cells are most severely affected and lost initially, while mucous cells, being more resistant than serous cells, are affected later. Mucous cells, in turn, are affected earlier and more acutely than ductal elements, which tend to persist longer than all other glandular epithelial cells. Minor salivary glands suffer similar changes to the major glands; however the severity is less (Jacob, 1993). During radiotherapy, and for a few months post treatment, some recovery of glandular function may be evident. The process of degeneration proceeds slowly, secondary to alteration of fine

vasculature and fibrosis of interstitial tissues. The fibrosis eventually leads to marked degeneration of the acinar secretory elements, with severe xerostomia being the clinical result (Frank et al 1965; Harwood et al 1973; Savage et al, 1985).

The direct effects of irradiation include the destruction of osteocytes, osteoblasts and haemopoietic marrow tissue. Bone is more susceptible to necrosis than is the adjacent soft tissue because of its physical properties. It absorbs more energy during x-radiation than do other tissues. The secondary radiation produced in bone also adds to the total energy absorbed (Gratzek et al, 1945; Mainous et al 1973).

Gowgiel, in 1960, irradiated the maxilla and mandible of an experimental group of monkeys. He concluded that ORN resulted primarily from the direct effect of irradiation on osteocytes; that necrosis always began in the interdental papilla of the mandibular molar; and that radiation produced significant thickening of the walls of arteries and arterioles, while veins and capillaries were not affected. Work by Furstman (1970) on the effects of irradiation demonstrated the impairment of condylar growth in rats subjected to total body radiation. He noted changes in the cartilaginous layers of the condyle, the calcifying matrix, and the osteoblastic and osteoclastic activity, as well as in the vascular elements.

The parenchymal fibroblast is essential for a satisfactory response to any injury. It is the key to wound repair. In the experimental animal, gradual depletion of parenchymal cells can be observed

following radiation exposure. Parallel findings in chronic radiation ulcerative wounds have also been described (Fisher 1993).

2.4 Clinical Effects of Radiotherapy

Patients may survive for years free of cancer but suffer severely from one or more of the complications of irradiation which are well documented in the literature (Colby, 1942; Gardham, 1939; Borsanyi et al, 1961; Bedwinek et al, 1976; Beumer et al, 1972; Dreizen et al, 1976; Engelmeier & King, 1983; Epstein et al, 1987; Fleming, 1990; Hart & Mainous, 1976; Macdonald, 1986). In the head and neck region the potential complications of radiation therapy are numerous and may result in oral sequelae such as, xerostomia, mucositis, fibrosis, trismus and dermatitis. Also alterations in taste, altered oral flora counts, periodontal ligament changes, photosensitivity, radiation caries, soft tissue necrosis and ORN (del Regato,1939; Wildermuth & Cantril, 1953; Rahn & Drane, 1967; Dreizen et al, 1976; Engelmeier & King, 1983; Epstein et al, 1987; Fleming, 1990; Westermark et al,1990). All these complications may cause primary or secondary pain, which results in poor nutrition and weight loss.

Of patients exposed to 60 Gy or more, most develop severe xerostomia. Xerostomia is the most common complication of radiotherapy to the head and neck region. It is frequently the patient's chief complaint during the post-radiation period. Xerostomia is defined as dryness of the mouth due to salivary gland dysfunction (Dorland's 1982). There are many causes of xerostomia including autoimmune disease (such as Sjogren's

syndrome), medications with anticholinergic effect, negative fluid balance, polyuria states, anaemia, selected nutritional or hormonal deficiencies, emotional and anxiety states, and therapeutic radiation involving the salivary glands (Regezi & Sciuba 1993).

Permanent damage to salivary gland tissue situated in the beam path may produce significant levels of xerostomia. The degree of xerostomia associated with radiation varies with the dose and location of the fields. Usually its onset is pronounced and rapid, and may not always be reversible. Not only does the volume of saliva fall drastically but there are also qualitative changes in viscosity, decrease in pH, immunoglobulin concentration and electrolytes. From this comes a significant shift in the oral microflora, with an increase in the proportion of cariogenic bacteria. The result is the potential for rapidly progressive dental caries, in addition to an increased incidence and severity of periodontal disease. The alteration in the physical nature of salivary fluid, including greater viscosity and reduced flow rate, may produce difficulties in deglutition. Patients usually complain of a burning mouth, masticatory difficulties and dysphagia. Unfortunately, other than the frequent use of water or artificial saliva, restitution of salivary gland function is usually not possible. Some recovery is often seen especially at lower radiation levels. There is currently no effective therapeutic measure that can be used to help patients with this problem. The drug pilocarpine and other sialogogues may be of some benefit to some patients during and following radiation therapy, provided some secreting glandular tissue remains (Jacob, 1993).

Extraorally, epidermatitis will develop within the field of radiation, which usually shows as a burn of the skin with concomitant suppression of facial hair growth (Marciani & Plezia, 1974; Marumick & Leveque, 1989; Marx ,1983a).

Fibrosis of the normal soft tissues that fall within the field of radiation is one of the insidious complications of radiation therapy. This reaction is not immediately apparent, but occurs progressively following radiation treatment. Fibrosis in muscle tissue and subcutaneous tissues can contract, thus limiting the ability to open the mouth. Again the severity of trismus is dependent on the dose, the radiation source and the number of fields radiated. Fibrosis of salivary glands as well as atrophy of glandular parenchyma may also occur, resulting in further decrease in salivary flow.

Of the numerous potential complications, soft tissue necrosis and ORN are the most serious pathological processes, and occur as a late complication due to ischaemia from a progressive obliterative endarteritis (Heimbach, 1988; Marx & Johnson, 1987). Tissue hypoxia imposes vulnerability to infection, hence the necrotising process may be enhanced by trauma and infection. Following irradiation, the risk of ORN continues indefinitely. The compromised circulation in the aged patient may further accelerate it. Xerostomia further increases the risk of necrosis.

Even though all sources of radiation do not affect bone within the field to the same degree, all irradiated bone loses its ability to remodel and ward off infection. Together with the compromise in

the blood supply, it leads to a decrease in osteoblastic and osteoclastic activity (Marx & Johnson, 1987).

CHAPTER 3

OSTEORADIONECROSIS

3.1 Definition of Osteoradionecrosis

The diagnosis of ORN is based upon clinical signs and symptoms.

The condition demonstrates a varied clinical and radiographic presentation and, because no laboratory tests exist, a simple useful working definition of ORN is that of Marx and Johnson (1987):

"An exposure of nonviable irradiated bone, which fails to heal without intervention"

3.2 Clinical Presentation of Mandibular Osteoradionecrosis

Clinically and radiographically, ORN shows a wide spectrum of presentations.

The first sign of mandibular ORN may be a small area of exposed bone, sometimes accompanied by complaints of pain. Occasionally pain alone may be the first symptom. Once ORN has developed, patients are troubled by deep-boring pain.

In the clinical presentation it may show as a tooth extraction socket which has failed to heal for months, or a small area of spontaneous bone exposure over an edentulous mandible, or a continuous complete exposure of alveolar bone, extending bilaterally across the mandibular midline. As it progresses, intraoral or extraoral fistulae may develop, often with a malodorous constant drainage. There may be wide areas of cutaneous exposure of non-viable bone, and pathologic fractures may occur in advanced cases, leading to impaired function and disturbance of the aesthetic appearance of the face (McIndoe, 1947; La Dow, 1950; Mainous and Hart, 1975; Meyer, 1970; Marx, 1983; Epstein, 1987; Ioannides et al, 1994). This is further accompanied by late sequestration and sometimes permanent deformity (Bragg et al, 1970; Hart & Mainous, 1976; Fleming 1990). Suppuration is not commonly observed with this condition; however when it is present, it is usually due to secondary infection.

The exposure of bone may be associated with bad taste, halitosis, local tenderness and paraesthesia. Severe trismus may develop when large areas of the posterior part of the mandible are involved, thus causing pterygoid muscle spasm and fibrosis. Pain on movement of the jaw frequently prevents adequate nutritional intake and the general clinical condition of the patient progressively deteriorates.

An important component that is quite often overlooked is the significant loss of overlying soft tissue, reiterating the fact that ORN not only represents true bone necrosis, but is also a disease of soft tissue. In really severe cases there is skin loss, together with the

associated muscle and salivary gland tissue. In some reported cases massive soft tissue loss includes part of the ear, and exposure of the mandible from the temporomandibular joint to the midline. Thus the soft tissue, as well as bone, must be part of any treatment plan (Marx, 1984).

3.3 Radiological Presentation

Imaging may assist in the diagnosis. Radiologically this condition also presents in a wide variation of forms, ranging from normal bony morphology, to localised areas of osteolysis, to pathologic fractures and to massive osteolysis (Pappas, 1969). Ill-defined areas of radiolucency with sequestra are pathognomonic in a patient with a history of radiation therapy. Mottled areas of osteolysis are usually late changes. Early radiographic diagnosis of ORN is not possible, except with scintigraphy (Miles, 1992).

Other radiographic findings may include irregular bony resorption and visible tooth extraction sockets which persist twelve months following extraction. Also irregular radiopacities may be seen due to sequestrum formation and pathological fracture. It has generally been agreed that radiography is not helpful in diagnosing early necrosis, and that when changes finally occur, they may be variable (Niebel & Neenan, 1957; Chambers et al, 1958; Guttenberg 1974).

There is no correlation between the radiographic picture and the clinical extent or severity of the disease. In some cases, for example, a close to normal radiographic picture may be associated

with large areas of exposed non-viable bone which has not lost mineral content or undergone resorption. On the other hand, cases which appear clinically as small areas of exposed bone may only be the tip of the iceberg, and in fact radiologically can show larger areas of non-viable bone that will continue to become exposed over time (Marx and Johnson, 1988).

Generally x-rays show past osseous changes and do not necessarily reflect the present state. Plain radiography only demonstrates severe bone damage when more than 30% of bone crystal has been lost (Ardran, 1951). Thus radiographs can be misleading if interpreted alone without any clinical correlation.

3.4 Other Imaging Tests

Other imaging tests include Nuclear Medicine (Scintigraphy), Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI).

The sensitivity of scintigraphy, or radionuclide scanning, is well documented, and osseous changes in osteomyelitis and similarly in radionecrosis may be seen as early as 24 hours into the course of the inflammatory change (Parrish et al 1989). Phosphate compounds, usually labelled with technetium (^{99m}Tc), are used extensively. Scanning may also be done using gallium (^{67}Ga) and indium (^{111}In). Generally fifteen millicuries of ^{99m}Tc labelled phosphonate are given intravenously. Imaging is carried out following a wait of 1 to 2 hours, to allow the 'normal' bone activity to cease before the patient is placed under a gamma camera, which

detects individual scintillations. Diffuse patterns of radioactivity are observed on the subsequent films, which outline the areas of abnormal activity ('hot spots'). Nuclear Medicine scans can be beneficial in outlining the anteroposterior dimensions of the necrotic process. However they are nonspecific and are less useful than a plain x-ray which gives a better representation of osseous change. Also impaired blood supply (to carry the product) or areas of infarction can give negative scans (Hutchison et al 1990; Miles, 1992; O'Mara, 1992).

CT scanning is valuable in determining the extent of the ORN in the buccal or lingual cortex of the mandible, particularly if cortical perforation is present. CT findings might include increased signal intensity within the marrow cavity, due to the replacement of normal adipose tissue (with low attenuation properties) by oedema, or granulation tissue (higher attenuation) (Miles, 1992). It is invaluable, during the surgical treatment planning, in determining the amount and extent of osseous resection. In addition it is useful in screening for further recurrence of the original malignancy.

MRI is certainly more expensive, and slightly more difficult to interpret, than plain x-rays or CT scans. Broadly it is not indicated in routine evaluation of ORN. MRI would be indicated where CT imaging is unavailable, in patients who are allergic to iodine, or where CT images have been degraded by artefacts from dental amalgam. Such metallic artefacts are less likely with MRI. The intravenous contrast agents designed for MRI, such as gadolinium-

DTPA, are safer than the iodinated contrast agents used for CT (Holliday & Prendergast, 1992; van Ransburg & Nortje, 1992).

3.5 Staging of Osteoradionecrosis

Due to the heterogeneous presentation of ORN and its variable response to treatment, a system of classification based upon clinical and radiographic findings would facilitate treatment decisions, and allow classification for research purposes. Two main classification systems have been proposed. The staging system used at Wilford Hall (Marx 1983) was based upon the response of selected patients to treatment with HBO and aggressive surgical debridement. This will be described later in this section (3.5).

Epstein et al (1987) proposed a system of classification which reflect the progress of the condition. It correlates the severity of clinical findings, symptoms and treatments:

Stage I encompasses asymptomatic disease which has healed or resolved. Pathologic fracture may have occurred (Stage Ib), but the patient will have been reconstructed to provide continuity of the jaw.

Stage II is asymptomatic or controlled symptomatic osteo-radionecrosis which is chronic (> three months) and persistent, but not progressive. That is, the lesion is not tender, remains stable in size, and neurologic symptoms of paraesthesia and anaesthesia, if present, are not getting worse. The patient is either pain free or the discomfort is

well controlled. Patients may have a pathologic fracture (Stage IIb) and compromised jaw function; however, the symptoms are stable.

Stage III is progressive active ORN manifesting signs and symptoms of continuing disease. The objective of treatment is resolution of the necrotic lesion and reversion to Stage I disease.

A summary of Epstein et al's classification is presented in Table 3.1.

The staging and techniques described below draw heavily on the work of Robert E. Marx while researching at Wilford Hall Medical Centre of the US Air Force in San Antonio, Texas. This staging system for ORN of the mandible defines how hyperbaric therapy is used in combination with surgery. To date his protocol has produced the best published results and is currently used in many centres around the world, with minor variations (Marx and Ames, 1982; Marx ,1983; Kindwall, 1993).

Staging is critical as it is an indication of the severity of the disease process, and also dictates the type of surgical and HBO management.

Table 3.1 Epstein et al's (1987) clinical classification of osteoradionecrosis.

CLINICAL CLASSIFICATION and TREATMENT OF OSTEORADIONECROSIS			
Stage	Description	Symptoms	Treatment
I	Resolved, healed	None	Follow-up, prevention of recurrence
I a	No pathologic fracture		
I b	Pathologic fracture		Reconstructed
I I	Chronic, persistent non-progressive	None, or controlled	Local wound care Antiseptics/antibiotics, analgesics, HBO (if indicated) Marx protocol
I I a	No pathologic fracture		
I I b	Pathologic fracture	Jaw dysfunction	
I I I	Active, progressive	Progressive	Local wound care Antiseptics/antibiotics, analgesics, HBO Marx protocol
I I I a	No pathologic fracture		
I I I b	Pathologic fracture	Jaw dysfunction	

The Marx-Wilford Hall USAF Medical Centre Protocol for ORN consists of three stages.

Stage I - is defined as showing only a small area of exposed bone, which may range from a pinpoint to 2 or 3 mm, with three exceptions representing advanced disease: orocutaneous fistulae, pathologic fracture, or radiographic evidence of bone resorption to the inferior border. Radiographs in these cases reveal the mandible to be essentially healthy, without mottling or radiolucency that extends deep into the body of the bone. In other words, the mandible should not appear to be seriously involved on x-ray.

Treatment of Stage I

Since the lesions are more complicated than soft tissue injury and involve bone, Stage I lesions are treated with 30 HBO dives at 2.4 ATA for 90 minutes, 5 to 6 days a week. This is to make certain that the maximal HBO effect has been produced. No surgery or debridement is carried out during treatment, other than irrigations or removal of mobile sequestered bone fragments. In tissues that are responding, bone will soften, granulation tissue will appear, and inflammation should subside. Patients are then given an additional 10 to 40 dives until mucosal closure is achieved. If the wound completely heals without further treatment, the patient is designated a 'Stage I responder' and the treatment is then complete. If there is no clinical improvement by 30 HBO exposures, as evidenced by extended or continued exposure of

bone, absence of mucosal proliferation, or the presence of inflammation, the patient is advanced to Stage II.

Thus, in summary, Stage I patients respond to HBO treatment and do not require surgical intervention.

Stage II patients are Stage I non-responders to HBO treatment, or who have more alveolar bone exposed. Generally, a lesion of around 1 cm diameter is about the minimum size for a Stage II.

Treatment recommendation for Stage II

Stage II patients have all had 30 hyperbaric treatments and become candidates for surgical debridement. These patients require surgical intervention in the form of a transoral alveolar sequestrectomy or cortical plate removal of the lingual or buccal cortex alone, to bleeding bone. Stage II surgery implies that the inferior border of the mandible remains intact. It has been recommended that saline-cooled saws be used, rather than heat-generating burs (Kindwall 1993). Also, soft-tissue reflection should be kept to a minimum to preserve blood supply. Soft tissue closure should be done in two or three layers using the periosteum first, followed by muscle or fat or submucosal connective tissue, then mucosa. Following debridement, the patient receives a further ten HBO dives. If healing is complete, treatment stops and the patient is referred to as a 'Stage II responder'. If the wound fails to heal and dehisces, the patient is advanced to Stage III.

Stage III patients are those who have extensive bone involvement or those who have failed to respond to Stage II HBO treatment.

This includes : pathologic fracture ,
orocutaneous fistulae, and
radiological evidence of bone involvement
through the entire mandible to the lower border.

Treatment recommendation for Stage III

There is too great a mass of overtly dead bone such that HBO alone with minimal debridement cannot resolve the problem. The patients do not respond to anything less than jaw resection plus HBO. All these patients receive 30 hyperbaric treatments if they have not already been through Stage I or II treatment. They then undergo a transoral resection of all of the involved portion of the mandible. At that time, any remaining necrotic soft tissue is also excised.

The osseous resection should be carried back to bleeding bone as a sign of viability. Similarly, soft tissue margins are also determined by the presence of bleeding at incision. Following resection the mandible is stabilised, preferably with external fixation. Soft-tissue deficits can be addressed, and myocutaneous flaps or free tissue transfer of soft tissue can be carried out to reconstruct any soft-tissue deficits. The patient then receives 10 more hyperbaric treatments, completing the 30/10 protocol.

3.6 Temporal Bone Osteoradionecrosis

Irradiation to the temporal area could similarly cause injury to all of the major tissues of the region. These tissues include the external soft tissue, the temporal bone itself, and the structures encased within the bone: the middle ear and the neurosensory organs of the inner ear. Irradiation treatments to this area have been given for a wide variety of both benign and malignant conditions. The most frequent neoplasms treated with radiation therapy include malignant neoplasms of the temporal bone and, most commonly, squamous cell carcinoma of the mastoid mucosa of the middle ear. Radiotherapy treatments to tumours of adjacent regions also include the temporal bone within the field. The lesions may include tumours arising in the intracranial cavity, parotid gland, external ear, orbit, nasopharynx, and the maxilla (Glass et al, 1984; Wurster et al 1982; Lee et al, 1988; Inokuchi et al, 1990).

Fortunately, severe radiation injury to the temporal bone is a rare complication of external beam therapy. Furthermore, when radiation injury occurs the complications may not present until many months or years after treatment. When they occur, however, they may be quite extensive and devastating (Nagorsky 1993).

The pathogenesis is the same as in the mandible, with therapeutic doses of irradiation inducing an obliterative endarteritis and periarteritis in the vessels supplying bone (Ewing 1926). This results in an avascular, aseptic necrosis with bone loss. The histologic changes are very similar. They include empty lacunae, secondary to death of osteocytes, preponderance of osteolysis,

connective tissue infiltration around spicules of dead bone, decrease or total absence of new bone formation, and the loss of bone marrow (Schuknecht & Karmody 1966).

Interestingly, the onset of temporal ORN may be delayed for many years. In the series presented by Ramsden et al (1975), the latency period extended up to 23 years, with an average interval until presentation of 7.5 years following radiation. Other series have suggested latency periods as long as 35 years, with mean time to presentation as long as 20 years (Guida et al, 1990; O'Neill et al, 1979; Thornley et al, 1979; Wurster et al, 1982). The duration of the latent period depends on total radiation dose absorbed by the tissue and the degree of vasculitis. Delayed osteitis, after moderate radiation doses, may not become clinically apparent for decades. Ewing, in his general statement, attributed the long latent period to low metabolic rate and slow turnover of bone as compared to other tissues.

Several local factors contribute to the temporal bone's susceptibility to ORN. It is a superficial compact bone with a thin layer of overlying soft tissue. This is especially true in the external auditory canal, the site of the less severe but more frequent localised ORN. The temporal bone has a poor blood supply and also is in direct communication, via the eustachian tube, with the potentially infecting organisms of the nasopharynx. Furthermore, superficial skin breakdown of the external auditory canal is common following radiotherapy, and provides a route of entry for the normal floor of the canal to invade the tympanic ring (Nagorsky 1993).

Radiation-induced injury to the temporal bone is largely a clinical diagnosis. Any patient with a history of radiation therapy to this region or surrounding structures is at risk. Furthermore, a high index of suspicion should be maintained in any patient with otologic symptoms. Patients with localised disease typically present with mild otalgia and purulent aural drainage. Clinical examination reveals evidence of infection, or granulation tissue, within the external canal. Patients with diffuse disease typically present with deep-boring pain and copious purulent otorrhea. The possibility of recurrence of the original pathology must be ruled out in these cases.

Radiographic assessment of the patients generally reveals osteolysis of the temporal bone architecture. CT scans, MRI, and radiolabelled imaging studies are useful in determining the extent of the radionecrosis and destruction. Complications of diffuse ORN include significant infection or abscess of the local and adjacent structures. This includes intracranial complications, as well as erosion into the inner ear structures or the facial nerve. Further extension of the infection through the anterior aspects of the temporal bone may result in invasion of the temporomandibular joint and parotid gland. Such cases require extensive surgical debridement and definitive control of the primary radionecrosis as well as the resulting infection. With central nervous system involvement, it can be extremely difficult to manage.

If the disease is limited to the ear canal and tympanic ring, then treatment generally involves aggressive local management. This

includes meticulous cleansing of the external acoustic canal, and removal of any necrotic material. Bone sequestra are allowed to separate on their own prior to removal. Also topical antibiotic drops have been recommended to help in the cleansing of the necrotic tissue. Advanced disease requires surgical debridement. As in mandibular disease, all necrotic tissue is removed until vascularised, healthy appearing bleeding bone is encountered. Hyperbaric oxygen has been used as an adjuvant to conventional therapy and has gained popularity in recent years (Nagorsky 1993).

The use of vascularised regional or distant flaps also aids in long-term control of temporal bone ORN. Regional myocutaneous flaps, including the latissimus dorsi or trapezius muscles, can reach most areas of the temporal bone, providing healthy vascularised tissue for reconstruction. As with any irradiated tissue, the suitability of the tissue bed prior to reconstruction must be considered, and can be enhanced with hyperbaric oxygen.

3.7 Incidence of Osteoradionecrosis

The incidence of ORN varies considerably from centre to centre where irradiation for oral cancer has been studied. It is quoted in the range of 2% to 20% by Bedwinek et al (1976), Coffin (1983), Morton (1986), Marx & Johnson (1987), Berger et al (1990) and Harris (1992). This variation is probably determined by technique-related morbidity and the veracity of the audit. Daly and Drane reported the incidence of spontaneous tissue breakdown following radiotherapy, unassociated with any specific trauma to

be 39%. Marx (1983) reports a 35% incidence of spontaneous breakdown, and states that it appears to be related to high radiation doses and possibly implant sources. Marx and Johnson in 1987 reported a 39% incidence of spontaneous ORN in a pool of 536 patients.

RESULTS OF PUBLISHED ORN INCIDENCE STUDIES

Year	Authors	No of Pts	ORN	%	Years Studied	Site of Cancer
1938	Watson & Scarborough	1819	235	12.9	1930-1937	Oral Exclude lip
1962	MacComb	251	93	37.0	1952-1959	Oral
1963	MacDougall et al	364	18	5.0	1940-1959	Oral
1966	Grant & Fletcher	176	66	37.5	1954-1962	Tonsil
1971	Rankow & Weissman	176	12	6.3	1965-1968	Oral
1972	Beumer et al	278	10	3.6	1961-1969	Oral Exclude lip
1972	Daly et al	304	66	21.7	1966-1971	Oral/pharynx
1972	ang	262	15	5.8	1959-1968	Tonsil
1974	Cheng & Wang	76	13	17.1	1959-1968	Tonsil
1974	Marciani & Plezia	220	23	10.5	1951-1973	Oral
1976	Bedwinek et al	381	54	14.2	1966-1971	Oral/pharynx
1980	Murray et al	104	16	15.4	1971-1975	Floor of mouth retromolar
1981	Morrish	100	22	22.0	1971-1977	Oral

1983	Coffin	2853	22	0.7	1970-1981	Oral, neck, sinuses, salivary glands
1986	Marciani & Ownby	109	3	2.8	1976-1984	Oral/pharynx
1987	Schweiger	324	6	1.8	1979-1983	Oral/pharynx
1989	Widmark et al	431	19	4.4	1974-1979	Oral/pharynx, salivary glands, ear, nose + accessory tissue

The incidence of ORN has been declining over the past three decades as improved methods of irradiation and standards for dental evaluation and management have emerged (Dolezal et al, 1982; Epstein et al, 1987; Balogh, 1989).

3.7.1 Factors Influencing Incidence of Osteoradionecrosis

Several factors relating to the radiotherapy, the tumour, and the dental status are thought to influence the incidence of this condition (Rankow & Weissman, 1971; Solomon et al, 1968; Murray et al., 1980a; Morrish, 1981; Morton, 1986). The older orthovoltage therapy techniques resulted in a higher energy absorption by bone than the surrounding soft tissues. With the arrival of megavoltage therapy, the energy deposited in bone is much reduced (Meyer et al,1962). However, not all studies reported a decrease in the incidence of ORN (Coffin, 1964; Rankow & Weissman, 1971). Certainly the total radiotherapy dosage given affects the incidence of ORN (Grant & Fletcher, 1966; Rankow & Weissman, 1971;

Bedwinek et al., 1976; Murray et al., 1980a; Morrish et al., 1981). Several studies have shown that the risk of ORN increases if the total dose of radiation is more than 65 Gy (Morrish et al., 1981). Ewing (1926) highlighted the concept of fractionating the dose to reduce damage. It has also been mentioned that time-dose fractionation characteristics play a role in the development of acute and intermediate effects of radiotherapy (Bloomer & Hellman, 1975). Some surveys showed that the use of interstitial implants led to a higher incidence of ORN (Beumer et al., 1972; Murray et al ., 1980a).

It is generally well accepted that the incidence of osteo-radionecrosis is higher in patients with tumours located close to bone, such as the floor of the mouth (Watson & Scarborough,1938; MacComb, 1962; Bedwinek et al., 1976; Murray et al., 1980a). In some surveys, the tumour size (T stage) was seen as a factor influencing the incidence of ORN (MacComb,1962; Grant&Fletcher, 1966; Rankow & Weissman, 1971). Others, however, feel that size has no effect (Murray et al., 1980a; Morrish etal., 1981). Surgery in the irradiated field is another factor that has been shown to increase the incidence of ORN (Rankow & Weissman, 1971; Daly et al., 1972).

Another general observation, and also shown by Murray (1980b), is a relationship between the presence of dental disease in dentate patients, and the incidence of ORN. Many surveys have noted an increased incidence of ORN in dentate patients (Beumer et al, 1972; Murray et al, 1980a; Morrish et al, 1981), and that the incidence

falls when a good programme of dental care is instituted (Daly et al, 1972; Murray et al, 1980a).

3.7.2 Tooth Extractions

There is no unanimity of opinion regarding the management of teeth and their supporting structures in the irradiated patient. There is no doubt tooth extraction is an aetiological factor in the development of ORN, but there is still uncertainty as to the optimum timing of the extractions and, indeed, to the techniques of extraction. In the pre-antibiotic era, Watson and Scarborough (1938) favoured pre-irradiation dental clearance. Daland (1949) said that there were no exceptions to teeth being extracted before irradiation. Niebel and Neenan (1957) advocated removal of all teeth in the path of irradiation before initiation of radiotherapy. Francisco (1966) recommended that all diseased teeth in the path of planned radiation be removed before radiotherapy. Rankow and Weissman (1971) suggested dental clearance plus alveoloplasty, 10-14 days prior to radiotherapy. Meyer (1970) advocates pre-irradiation extractions, together with alveolectomy, and feels it is a reason for his fairly low incidence of ORN (5.3%).

Contrary to earlier recommendations, Beumer et al (1972), Daly et al (1972), and Bedwinek et al (1976), all showed a higher incidence of ORN with pre-irradiation extractions. Conversely, Morrish et al (1981) felt pre-irradiation extractions did not lead to an increased incidence of ORN. Beumer et al (1983) recommend that 7-10 days healing is advisable, but where the radiation dose is going to exceed 6500 rads, 14-21 days should be allowed. Grant and

Fletcher (1966) and Morrish et al (1981), feel that post-irradiation extractions are more likely to cause ORN than pre-irradiation extractions, while MacComb (1962) felt that there was no difference. Surprisingly, latter work by Daly et al (1972) showed a lower incidence of ORN following post-irradiation extractions than that following pre-irradiation extractions.

The consensus on extraction technique both pre- and post-irradiation is somewhat divided. In broad terms, a conservative approach with atraumatic, non-surgical removal of teeth is advocated, and this was further emphasised by Coffin (1964, 1983). Others feel that alveolectomy and removal of any sharp bone, with primary closure of the soft tissues over the socket, is preferable (Beumer et al, 1972; Horiot et al,1981). The use of antibiotic prophylaxis for post-irradiation extractions is advisable, although there is no scientific data supporting its use. The issue of the role of infection in the aetiology of ORN will be discussed later in Chapter 5.2.

In most studies the incidence of ORN in edentulous patients is lower than in dentate patients (Murray et al, 1980a; Morrish, 1981). Morton & Simpson (1986) stated that ORN in edentulous patients, which is not related to previous extractions, is often of a minor nature.

3.8 Why the Mandible is More Susceptible than the Maxilla

In the head and neck region the mandible is most frequently affected, whereas ORN involving the maxilla is rare. It has been suggested by Myer that the mandible is more frequently affected because it is more often in the field of radiation, and also receives a higher dose of radiation. Others (Engelmeier et al, 1983; Galler et al, 1992) have suggested that the mandible possesses a reduced blood supply as compared to other skeletal bones, which predisposes its bone and adjacent soft tissues to the destructive effects of this necrotic process. Experimentally, Gowgiel in 1960 showed that when a whole skull was irradiated the mandible was still more frequently affected by ORN. Gowgiel felt that the more dense compact configuration of the mandibular bone led to greater scattering of radiation, with consequently increased radiation to mandibular osteocytes. It has also been suggested that the better blood supply to the maxilla protects it from ORN (Rubin & Doku, 1976).

Previously clinicians felt that the inferior alveolar artery had a primary role in nourishing the mandible, but Bell et al (1970) demonstrated that there is also a sufficient blood supply from the surrounding soft tissues, even if the inferior alveolar artery were obstructed.

The normal mandible receives its blood supply from three types of vessels (Sanger et al, 1993). The major nutrient vessel is the

inferior alveolar artery, which is a branch of the maxillary artery. The second major source of vessels are the attachments of the muscles of mastication. These occupy approximately two thirds of the mandible and are particularly prominent in the ascending ramus and the angle. Anteriorly, a third type of vessel, the direct perforator, arising from vessels that supply the salivary glands or from the vessels that supply the skin, is also found. Work in animals by Hellem and Ostrup (1981) suggest that the blood supply to the body of the mandible under normal conditions comes almost entirely from the inferior alveolar artery. However, when this source is obstructed, only the anterior portion of the mandible has a fairly quick switch to a peripheral blood supply from the periosteum. The posterior mandibular alveolus, however, does not benefit from this kind of collateral blood supply.

There are age-related vascular changes that are important to consider. Studies by Bradley (1972) have indicated that, with time, the inferior dental artery gradually fails as the major blood supply because of arterial disease and possibly atrophy of more distal bone segments. He demonstrated an apparent decreasing capacity of the inferior alveolar vessels that occurs with aging. It was his belief that the blood supply, predominantly centrifugal (blood flowing from endosteal vessels outwards) in youth, acquires a centripetal (blood flow from periosteum) distribution later, based primarily on the muscular and accessory perforating vessels. The changes are particularly prominent in senile, edentulous mandibles and in older individuals in whom the extraosseous plexus of vessels formed by the facial, buccal, and lingual arteries predominates. This ultimately results in the mandible being in an

'endartery' situation, and could well be one of the main anatomical reasons why the mandible is more susceptible than the maxilla.

It is probable that a combination of these factors is responsible for the higher prevalence of ORN in the mandible than in the maxilla.

3.9 Aetiology and Pathophysiology of ORN

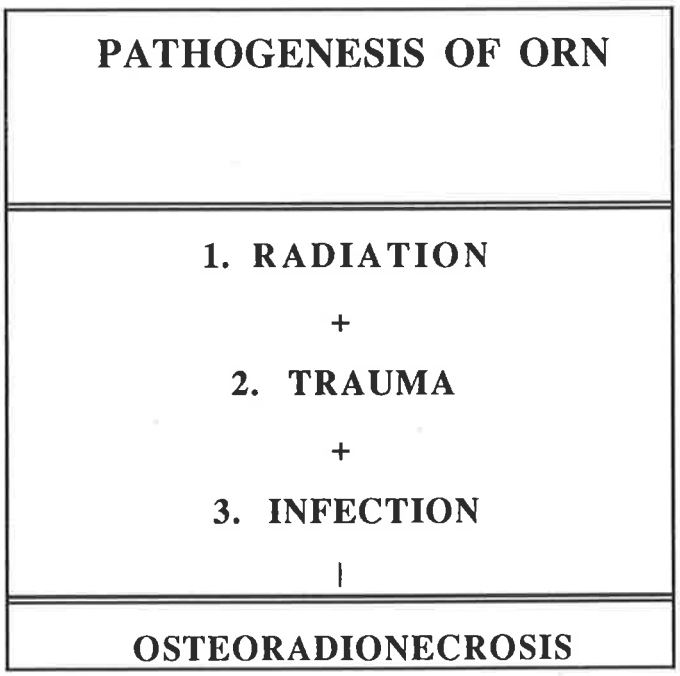
The underlying cause of ORN has never been unequivocally proven and the exact pathogenesis of ORN is not known. The main controversy is over the relative importance of the death of the osteocytes and osteoblasts, and the role of damage to the vasculature. Gowgiel (1960) believes that ORN results primarily from the direct effect of radiation to the osteocytes. Despite the above controversy, the direct effects of radiation on the bone and the contiguous tissues is the initial factor that reduces vascularity and results in reduced vitality and impairment of reparative and regenerative capacity. Such tissues are also less resistant to infection. Then there are secondary factors, such as physical trauma, surgical manipulation, and infection that stress the healing capacity. Multiple factors are therefore involved in the pathogenesis of ORN in addition to radiotherapy.

3.10 Old Concept of Pathogenesis of ORN

Some early work by Watson and Scarborough in 1938 and Kanthak in 1941 suggested that radiation damage was followed by trauma, and subsequent infection, to produce ORN (Watson& Scarborough, 1938). Thus traditionally the pathogenesis of ORN was accepted for

a long time as a triad of radiation, trauma and infection, which was further supported by Meyer in 1970 (Figure 3.1). Meyer described the role of trauma to be a portal of entry for oral bacterial flora into the underlying bone, leading to osteomyelitis. Furthermore, he said that infection progresses relatively rapidly in the irradiated bone, which has lost its resistance to bacteria, and that radiation osteomyelitis sets in and spreads through bone which cannot wall off the infection.

Figure 3.1 Old concept of pathogenesis of osteoradionecrosis



Sources of trauma that have been listed as causes of ORN are dental extractions before, during and after radiation treatment; cancer surgery, followed by radiation treatment; biopsies; dental treatment; wearing of denture prostheses; and sharp food particles (Cutler, 1951; Cook, 1952, 1966 & 1963; Hart & Mainous, 1976, Fleming 1990, Galler et al 1992). It has also been suggested that

mastication and parafunctional habits can cause trauma to the bone and overlying mucosa and hence are possible aetiologic factors in the development of ORN (Prabhu et al, 1992).

3.10.1 Current Concept of Pathogenesis of ORN

Marx (1983a) elegantly challenged the traditional infective pathogenesis theory of the triad sequence and presented a new concept in the pathophysiology of ORN. He showed that ORN is not a primary infection of irradiated bone, and that micro-organisms appear to act more as surface contaminants than as infective agents. Marx believes that ORN is a nonbacterial process and any micro-organism seen is periosseous in origin and/or location.

Marx (1983b) showed, through histological studies, that on the tissue level radiation causes endothelial death, hyalinization and thrombosis of vessels. Thus the microvascular circulation diminishes and the degree of fibrosis increases with time in irradiated tissue.

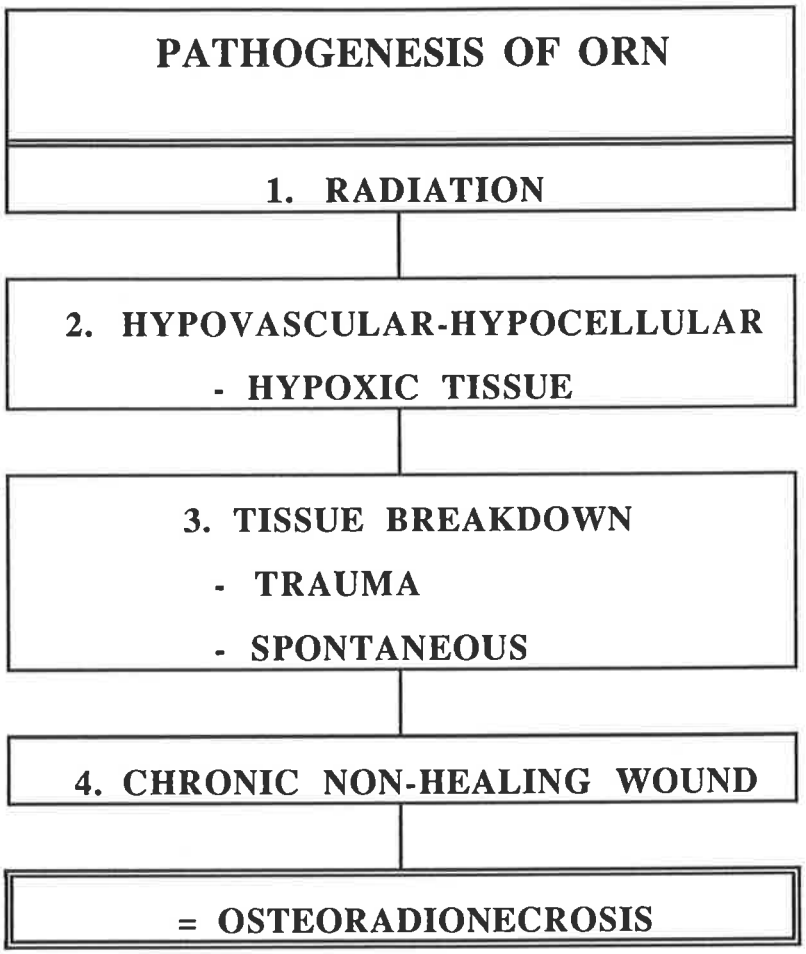
The risk of ORN therefore also increases with time (Marx & Johnson, 1987). The studies revealed that the periosteum becomes fibrotic and osteoblasts and osteocytes become necrotic, with fibrosis of the marrow spaces. Furthermore, the mucosa and skin also become fibrotic, with reduced cellularity and vascularity of the connective tissue. At the organ level the result is a composite tissue which is hypovascular, hypocellular, and hypoxic compared with non-irradiated tissue, and Marx refers to this as the 'THREE H' principle of irradiated tissue.

Normal healthy tissues undergo cellular turnover where old cells are replaced by new cells. Likewise bone undergoes resorption and remodelling with loss of osteocytes. New bone is laid down by osteoblasts. Similarly, structural collagen undergoes a normal daily lysis with replacement by newly synthesised collagen. In the hypoxic, hypocellular and hypovascular irradiated tissue, the ability to replace normal collagen loss or normal cellular loss is severely compromised (Marx 1983b). These changes adversely affect the healing capacity of irradiated tissue. Thus bone can become nonviable, unrelated to micro-organisms, but related more to the original radiation damage.

It can be seen that the role of trauma in the initiation of ORN is a single quantum of collagen lysis and induced cellular death. This produces a wound with a nutritional and basic elements of tissue repair requirement that are beyond the capabilities of the local tissue to provide (Marx 1983b). The greater metabolic demand required may exceed the healing capacity of irradiated tissue and produce radionecrosis. It, therefore, acts as a secondary factor and increases the risk of ORN because the irradiated tissues are unable to cope with the injury. In hypoxic injured tissues, macrophages are not stimulated to reorganise the wound, and fibroblasts fail to lay down new collagen, resulting in chronic nonhealing wounds (Mounsey et al 1993).

A summary of Marx's current concept of the pathogenesis of ORN is presented in Figure 3.2.

Figure 3.2 **Current concept of pathogenesis of osteoradionecrosis.**



Tissue necrosis occurs when the rate of tissue breakdown exceeds the rate of healing. It is the end stage of tissue injury induced by irradiation. With this principle, once a wound is created in irradiated tissue, the chances of effective healing would be very low considering the greatly increased demands for oxygen, energy and nutrition in a tissue that could not maintain itself at its former level of metabolic demand.

Thus we can conclude that ORN is a problem of wound healing rather than of infection. This is supported by the observation and

documentation of radiation-induced aseptic necrosis in anatomical sites, such as femoral head, clavicle, and lumber spine, without the introduction of bacterial flora (Marx 1984). In the head and neck, the bones have a thin mucosal covering between them and the bacterially contaminated nasal and oral cavity.

The pathological process explained above applies to the composite of both soft and hard tissue. Based on these newer concepts of the pathophysiology of ORN, it becomes readily apparent that HBO, which induces angiogenesis, may have some benefit (Mansfield, 1981; Marx & Ames, 1982; Marx, 1984). This will be discussed in Chapter 4.

3.11 Role of Infection

Although the changes of endarteritis obliterans and hypocellularity are well recognised, the role of infection has confused the understanding of both pathogenesis and management. These concepts have been challenged as a result of findings that a large proportion of osteoradionecrotic lesions are aseptic (Bedwinek et al, 1976; Marx, 1984).

The role of sepsis is still controversial. Many of the gross cases of ORN reported appear to have been infected (Rankow & Weissman, 1971; Saunders et al, 1978; Parulekar & Paonessa, 1980; Dolezal et al, 1982). Although it was initially felt to play a major role, most clinicians have seen cases of gross necrosis with no evidence of infection. In Meyer's series (1970) he reported that there was suppuration at some time in all his cases. Meyer (1970) failed to

demonstrate, through cultures or tissue sections, such a spread of osteomyelitis and micro-organisms throughout the bone. He also failed to show septic destruction in such avascular tissue, which cannot mount an inflammatory response or wall off micro-organisms. Furthermore, this sepsis theory could not explain the occurrence of ORN in other sterile anatomical sites as previously discussed.

3.12 Spontaneous Osteoradionecrosis

Spontaneous ORN has been documented in the literature as a valid entity and is related to higher radiation doses. It is produced when mucosal breakdown results from the tissue's inability to keep up with the cellular turnover and collagen synthesis.

In a large series reviewing ORN of the mandible, Marx and Johnson (1987) noted two distinct patterns of this disease. Approximately 60% of all cases fell into a post-traumatic group, the majority of which were associated with extraction of teeth. However approximately 40% of ORN were spontaneous in onset. There were significant differences in the two groups. The spontaneous cases appeared between 6 and 24 months after irradiation and fell dramatically after 2 $^{1}/_{2}$ years. The trauma-induced lesions showed a bimodal distribution, with the first peak at 3 months after radiation injury, and were generally related to a surgical site, such as tooth extraction or mandibulotomy. A second peak was noted beginning at 2 years and peaking at 5 years, with additional new cases seen after that. The persistent addition of new cases in

the traumatic group is evidence for the irreversible and cumulative effects of radiation.

Previously it was thought that the difference between spontaneous ORN and trauma-induced ORN was only the traumatic event. The study by Marx and Johnson in 1987 instead showed that they were two different entities, with each having an entirely different time course and radiation pathosis. They believe that in spontaneous ORN there is a greater outright cellular kill of tissue elements. The initial recovery and attempts at repair cannot meet the demand for replacement of cellular and structural elements rendered nonviable by the radiation. In such cases, tissues break down as they pass through the hyperaemia and inflammation stages, past hypovascularity and fibrosis, and directly into necrosis, usually within the first two years. Thus in this type of ORN the radiobiologic tissue damage causes necrosis to develop directly, rather than after initial tissue recovery.

In contrast, with trauma induced ORN the tissue recovers to a less than normal homeostatic level, then becomes necrotic only after secondary wounding occurs (Marx et al, 1985). Marx and Johnson feel that trauma-induced ORN represents more of a mixture of cell death and cell injury. There is a small amount of outright normal cellular kill and a greater amount of nonlethal cellular injury to normal cells. Thus these tissues cannot maintain normal homeostasis and are susceptible to any form of trauma. The lessened healing capacity may result in ORN.

Although the above pathogenesis of spontaneous ORN explains the time course noted in their study (Marx & Johnson, 1987), it fails to explain the delayed onset of temporal ORN as reported by several authors. In the series presented by Ramsden et al (1975), the latency period extended up to 23 years, with an average interval until presentation of 7.5 years following radiation. Other series have suggested latency periods as long as 35 years, with mean time to presentation as long as 20 years (O'Neill et al, 1979; Thornley et al, 1979; Wurster et al, 1982).

CHAPTER 4

HYPERBARIC OXYGEN

4.1 Definition of Hyperbaric Oxygen

"Hyperbaric oxygen (HBO) therapy is the intermittent inhalation of 100 per cent oxygen at a pressure greater than that at sea level."

(Cianco and Sato 1994)

4.2 Background

Hyperbaric medicine had its beginnings in 1939, when Albert Behnke of the US Navy reported success treating decompression sickness with oxygen at 2.8 atmospheres absolute (ATA). At that time this method was not adopted Navy-wide because of fear about the fire hazard, and it was not until 1967 that HBO therapy of bends was officially accepted. (Myers et al, 1982; Kindwall, 1992)

Today, HBO therapy is a well established technology that is being used in the treatment of many conditions. The indications for HBO therapy are summarised in Table 4.1 (Fattore & Strauss, 1987; Sippel et al; Kindwall, 1992, Wood & Liggins, 1996).

Table 4.1 **Indications for HBO therapy**
(Modified from Wood & Liggins 1996).

INDICATIONS FOR HBO
1. Radiation necrosis of bone and soft tissues
2. Problematic nonhealing hypoxic wounds
3. Chronic refractory osteomyelitis
4. Compromised skin grafts and flaps
5. Traumatic ischaemia and crush injuries
6. Refractory soft tissue infections
7. Diabetic ulcers
8. Clostridial cellulitis
9. Clostridial myonecrosis (Gas gangrene)
10. Necrotizing fasciitis
11. Carbonmonoxide and cyanide poisoning
12. Vascular gas or air embolism
13. Decompression sickness
14. Acute smoke inhalation
15. Chronic sclerosing osteomyelitis

Hyperbaric medicine is concerned primarily with the physiologic and therapeutic applications of oxygen at pressures greater than one atmosphere absolute (ATA) (Fattore & Strauss 1987). The delivery of HBO therapy is attained by having the patient breathe 100% oxygen through a tight fitting mask, hood, or endotracheal tube, in a recompression chamber with an environment of compressed air ranging from 2.0 to 2.8 atmospheres absolute.

Generally all treatment regimes with HBO are similar and are measured by the number of 'dives' in the chamber. A 'dive' consists of breathing 100% pure oxygen at 2-2.4 atm of pressure. The 'dive' lasts approximately 90-120 mins per day, including compression and decompression. Treatment of ORN usually involves 1 dive a day, 5 or 6 times a week until the required number of 'dives' is completed.

4.3 Hyperbaric Chamber Types

Hyperbaric chambers are of two general types:

(1) The multiplace unit, which holds two or more patients simultaneously; and

(2) The monoplace chamber, which treats only one patient at a time.

Both types of chamber are suitable for treating ORN. Also both types of chamber can reach the required pressure of 2.4 atmospheres absolute (ATA), although most monoplace chambers are limited to a maximum pressure of 3 ATA. There are advantages and disadvantages to each type of unit.

The multiplace chamber is pressurised with compressed air, and the patient receives oxygen via a tight-fitting oro-nasal mask, tightly sealed head tent, or endotracheal tube (Figures 4.1 and 4.2). Most of these chambers are large enough to accommodate several

Figure 4.1 **Subjects receive 100% oxygen by mask in compressed air hyperbaric chamber.**
Medical attendants breathe chamber air and are decompressed according to oxygen decompression procedures.
(Courtesy of Royal Adelaide Hospital HBU)

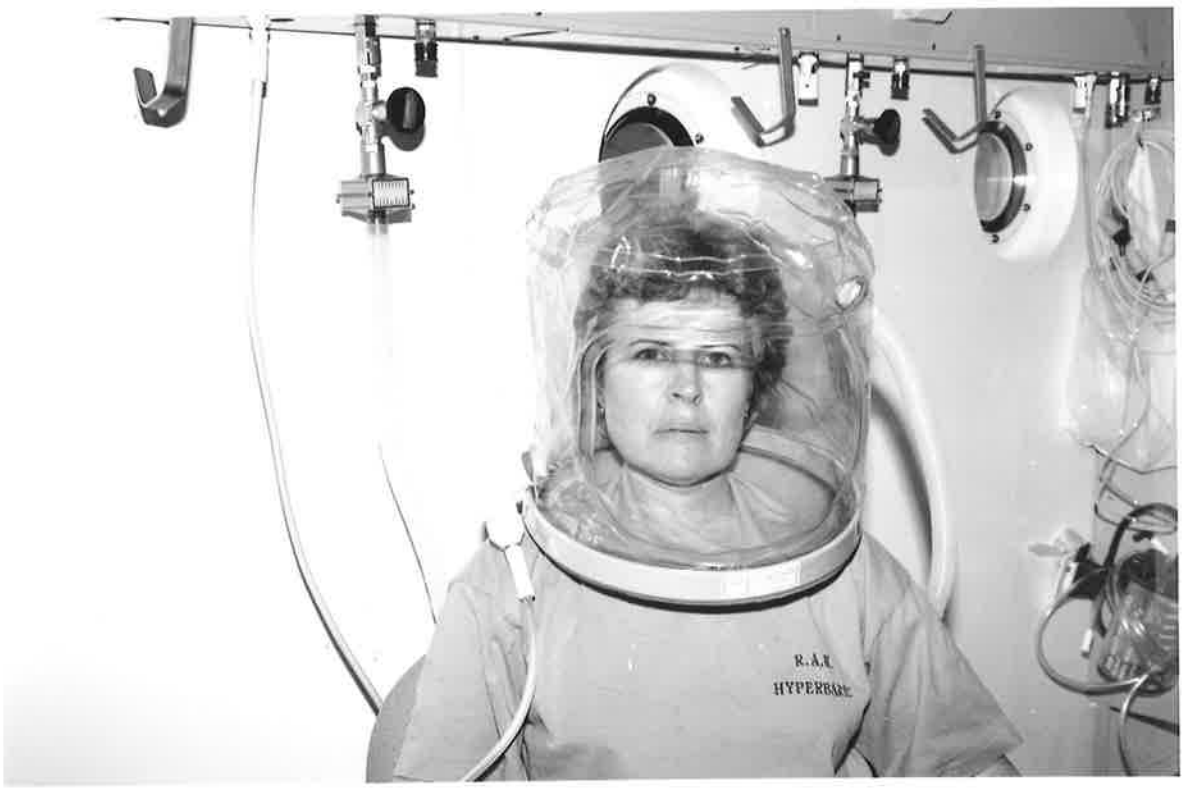


Figure 4.2 **Oxygen administered with head tent (hood) in compressed air multiplace hyperbaric chamber** - for patients who cannot wear mask. (Courtesy of Royal Adelaide Hospital HBU)

patients and attendants at once, and may have an airlock device that allows movement into and out of the chamber which remains at depth. In the United States and Australia the presence of an inside attendant to be with the patients is always required. The inside attendant breathes air at pressure and thus risks the possibility of decompression sickness, although this is rare and usually obviated by very conservative decompression tables (Kindwall 1993). The patients are at no risk of decompression sickness as they breathe oxygen.

Oxygen is toxic under pressure, and to avoid this, 'air breaks' are usually given to decrease the chance of central nervous system oxygen toxicity or grand mal seizure. Other advantages of multiplace chambers include the ability to deliver hands-on care and suction during treatment. With the newer, bigger multiplace chambers, claustrophobia is less of a problem. However they are more expensive to install.

Monoplace chambers are also available which consist of a cylinder accommodating a single patient in an environment of compressed oxygen. Thus the chamber is pressurised with pure oxygen, and the patient breathes the chamber atmosphere, which obviates the need for a mask or hood. The advantages of the monoplace chambers are that they are cheaper to install and do not require bulky compressors in a separate room. Also patients with facial external fixations, surgical wounds, or other appliances about the face, do not have a problem with a mask or hood because none is required. However, they have some limitations, including claustrophobia and inaccessibility of the patient to the physician,

and are potential fire hazards, which make them less than ideal (Fattore & Strauss 1987). Claustrophobia is a much greater problem in monoplace chambers, occurring in 10% to 20% of the patients (Kindwall 1993). This can be overcome with reassurance and pretreatment sedation.

4.4 Mechanism of Action of HBO

Hyperbaric oxygen has a variety of effects in addition to the mechanical compression to reduce the size of gas bubbles associated with air and gas embolism. Besides this, the most important component of HBO therapy is increasing the amount of oxygen dissolved in plasma and tissues. Putting a patient in the hyperbaric chamber has no other known physiologic effect.

The theoretic rationales of periodic elevation of PO_2 by Hyperbaric oxygen are multiple. Hunt & Pai in 1972 reported that HBO enhances the killing ability of leukocytes. Mader et al (1980) reported enhanced neutrophil mediated bacterial killing in response to HBO in an osteomyelitis model. It is toxic for aerobic and anaerobic bacteria. For fungi its effect is static rather than cidal (Hamblen, 1968; McAllister et al,1963). It inhibits toxin formation by certain anaerobes, increases the flexibility of red cells, reduces tissue oedema, preserves intracellular adenosine triphosphate (ATP), and maintains tissue oxygenation in the absence of haemoglobin. In addition, it stimulates fibroblast growth, increases collagen formation, promotes more rapid growth of capillaries (Knighton et al 1981) and terminates lipid peroxidation (Kindwall 1992).

Zhao et al (1992) carried out a series of experiments using an ischaemic rabbit dermal ulcer model, utilising HBO to overcome the effects of hypoxia, and found a very modest but significant effect of HBO in accelerating healing. Furthermore, they found that the combination of transforming growth factor-beta (TGF-beta) or platelet-derived growth factor (PDGF) and HBO totally reversed the profound ischaemic healing deficit and restored healing to normal.

4.5 Morbidity Associated with HBO

Hyperbaric oxygen is one of the most benign treatments given in hospitals today. Overall, complications of administering HBO are few and permanent sequelae are rarely reported.

The following is a summary of HBO complications and side effects arranged in order of frequency.

1. Barotrauma of the ear

The most common complication of HBO therapy is barotrauma or ear squeeze. Sanger et al (1993) report that 2% to 5% of patients will experience difficulty with increased middle ear pressure and require myringotomy. It is inherently more difficult to inflate the middle ear because the inner ends of the eustachian tubes, located in the nasopharynx, have slit-like openings. These openings tend to close tighter if they are not opened actively. If the patient has descended more than about one metre without clearing the ears, it will be impossible to voluntarily open the tubes through swallowing, yawning or engaging in the Valsalva manoeuvre.

Sometimes the chamber will have to be brought up slightly to facilitate ear clearing. Ear barotrauma was classified by Wallace Teed (as cited in Hyperbaric Medicine Practice 1995), a United States Navy Submarine Medical Officer during World War II, into four types based on the appearance of the drum:

Teed I - Erythema or injection of the handle of the malleus

Teed II - Erythema or injection of the entire drum.

Teed III - Haemorrhage into the substance of the tympanic membrane itself.
(Broadly, these haemorrhages appear as bright red patches on the drum.)

Teed IV - Deep blue/black appearance of the drum indicating blood filling the middle ear. The ear drum may or may not be ruptured.

2. Sinus squeeze

This is the second most common HBO complication and usually occurs in patients with upper respiratory tract infections or allergic rhinitis. It is due to blockage of the openings to the various sinuses in the head, caused by an overgrowth of tissue, oedema or mucus. It can easily be confused with a toothache associated with a maxillary tooth. Broadly, a course of steroid nasal spray, antihistamines and decongestant nasal spray just before the dive allows treatment to continue.

Frontal sinus squeeze can cause extremely severe pain, which is rarely tolerable if not relieved by decongestants or very slow

compression. Pain associated with a sphenoid sinus squeeze is projected to the occiput or the vertex of the skull (Kindwall 1995).

3. Ocular effects

It has been observed that during the course of multiple hyperbaric treatments (20 treatments or more), some patients may complain of a temporary difficulty in focusing sharply on distant objects as they develop myopia that is usually reversible. These changes are believed to result from an alteration in the shape of the lens, however, the reason for these changes remain obscure. In some individuals, refractive error may not completely revert to its pretreatment level, although this is rare. Generally, older people tend to be affected much more frequently than younger people. It is recommended that new glasses for myopia should not be prescribed for at least 8 weeks following cessation of HBO treatment (Davis et al 1988).

On the other hand, HBO treatment tends to improve presbyopia. Patients may present proclaiming their pleasure at not needing to use reading glasses anymore. Such patients need to be advised that the improvement is only temporary and their vision should return to its pretreatment level within 6 weeks of cessation of HBO therapy (Kindwall 1995).

4. Claustrophobia

Davis et al (1988) report that approximately 1 out of every 50 patients shows some form of confinement anxiety in the multiplace

chamber. However it is rare for this to be severe enough to require sedation. The presence of an attendant inside the chamber is beneficial and is a major preventive factor. The attendant distracts claustrophobic patients in conversation and encourages them to read during treatment, or plays cards with them. It is important to assure the patient of full control at all times and that treatment can be terminated upon any feeling of anxiety. Any patient's wish to leave the chamber must be accommodated immediately to avoid producing a panic. Later, treatment may be tried again with appropriate presedation.

Monoplace chambers can cause a lot of anxiety for patients, and approximately 1 patient in 10 will have claustrophobia severe enough to make treatment difficult or impossible (Davis et al, 1988; Kindwall, 1995).

The more seriously ill the patient is, the less the chance of developing claustrophobia.

5. Pulmonary oxygen toxicity and other respiratory complications

These are often cited as major concerns. Hyperbaric oxygen-induced toxicity seizures occur in less than 0.5% of patients. Oxygen can produce pulmonary toxicity at one atmosphere, but 24 hours of continuous oxygen breathing are usually required before early signs appear. Clinical signs of oxygen toxicity include substernal chest pain, cough and decrease in vital capacity. At 2 ATA these changes appear within six hours. However, continuous

HBO exposures rarely exceed two hours. At treatment depths of 2.0-2.4 ATA with intermittent oxygen and air schedules, pulmonary symptoms are not seen (Davis 1988).

Pneumothorax and an emphysematous bleb can occur; however, they are rare. They are a risk in patients with pulmonary bullae, and hence highlight the importance of prehyperbaric patient assessment and screening.

6. Central nervous system oxygen toxicity

This is rare and manifests clinically as grand mal seizures. Davis et al (1988) report the incidence of oxygen convulsions to be 1.3 per 10,000 patient treatments, at a pressure of 2.4 ATA.

7. Toothache

Sometimes patients may complain of toothache during compression or decompression. Frequently this is caused by a dental restoration that has an air space trapped under the filling. The changes in pressure cause movement in the dentinal tubules which is transmitted to the pulp causing pain. If the ache becomes unbearable then it may necessitate replacement of the restoration (Kindwall 1995).

8. Numb fingers

It is rare, but some patients will complain of numbness tingling in the ulnar distribution of their fingers, usually after receiving more

than 20 HBO dives. The cause for this is obscure and unknown. Management consists of reassurance, as the paraesthesia will disappear 4 to 6 weeks following cessation of HBO therapy. (Kindwall 1995)

4.6 Effects of HBO on Cancer

For years it was initially feared that occult or recurrent tumours which had outgrown their blood supply might be stimulated by exposure to HBO. Ten percent of the patients with radionecrosis, who were referred to the University of Miami had residual oral cancer along with their radionecrosis (Marx 1995). There was a genuine concern about HBO's potential to accelerate cancer development or tumour growth rate.

The accepted concept was that additional oxygen availability would enhance tumour cell replication, and this was supported by the fact that bulky tumours develop radioresistant, and often necrotic, centres due to hypoxia (Marx & Johnson, 1988). It was felt that any improvement with HBO in the ischaemia associated with a malignancy was potentially detrimental. However, in the management of increasing numbers of patients with radionecrosis who presumably had their malignancy eradicated, some patients with residual tumour were inadvertently treated. In these patients, it was commonly observed that most of the osteoradionecrotic areas improved dramatically, except for the area which was subsequently found to contain tumour. Hence in that sense, it was almost a diagnostic test.

Generally, failure of a well circumscribed area to heal with HBO is an indication for biopsy. The inadvertently treated patients did not seem to exhibit a more aggressive growth of the tumour. Subsequent animal experiments have shown that HBO does not stimulate the growth of tumours (Johnson et al, 1967; Feder et al, 1968; McMillan et al, 1989; Nemiroff, 1988; Granstrom et al, 1990; Nemiroff, 1991; Sklizovic et al, 1993). At least two studies suggest that HBO may have a slight suppressive effect (Ehler et al, 1991; Marx & Johnson, 1988).

4.7 HBO in the Treatment of Osteoradionecrosis

The concept of ORN as a superficially contaminated area of exposed ischaemic bone has enabled a complete re-evaluation of treatment. Based on the newer concepts of the pathophysiology of osteo-radionecrosis, it became apparent that HBO may have some beneficial effects, hence it has been advocated in the treatment of ORN. HBO therapy is the most recent advance in the management of ORN.

Statistics from the University of Miami clinics indicate that, before the advent of HBO treatment, the cure rate for ORN of the mandible was only 8% (Marx & Johnson 1988). The use of HBO in the management of mandibular ORN has been described by Mainous et al (1973), Mainous and Boyne (1974), Mainous and Hart (1975), Hart and Mainous (1976), Farmer et al (1978), Davies et al (1979), Mansfield et al (1981) and Laman et al (1992). Experiments with rats (Heimbach 1988) and clinical studies (Marx 1983b), have

shown HBO to improve tissue angiogenesis and collagen synthesis in wound healing.

Many authors have reported successful use of HBO as an adjunct to surgical and antibiotic therapy in the treatment of ORN of the mandible (Bond et al, 1967; Davis et al, 1979; Farmer et al, 1978; Hart & Mainous, 1976; Mainous & Hart, 1975; Mainsfield et al, 1981; Van Merkesteyn et al , 1981; Marx, 1982, 1983, 1987).

Marx (1983a) believes that in ORN the basic lesion is a chronic non-healing wound, and thus irradiated tissues have a reduced ability to deal with trauma. This is generally noted by all surgeons operating in irradiated sites. Although HBO does not produce an increased rate of healing in well perfused wounds, it has been shown experimentally to have a favourable effect on the rate of healing of ischaemic wounds (Kivisaari & Niinikoski, 1975; Niinikoski, 1977; LaVan & Hunt, 1990). Work by Ketchum et al, (1970) showed HBO to stimulate angiogenesis in experimental burns.

Studies carried out at the hyperbaric unit at the US Air Force School of Aerospace Medicine demonstrate that the PO_2 in the irradiated area will rise to approximately 80% of normal after 18 to 30 treatments (Marx 1984). It plateaus at this level, but this is sufficient to make surgery and grafting in the radiated area possible. The tissues can often go on to heal spontaneously. Furthermore it has been shown that there is also increased fibroblastic proliferation and collagen formation when PO_2 is intermittently raised to 20-30 mm Hg (Silver, 1969; Hunt & Pai,

1972). Silver (1969) showed that the tissue PO_2 is raised above these levels during hyperbaric dives. Attempts to use HBO alone were generally unsuccessful, although some patients did heal.

Marx (1983) has pointed out that HBO is an adjunct to aggressive management of osteoradionecrotic bone. When it is used as an adjunct, increased collagen formation and neovascularization will help in healing. In advanced cases, removal of the bone must be the primary treatment for the control of the process.

Hart and Mainous (1976) showed that HBO relieves the often crippling pain that accompanies ORN, and promotes wound healing and skin grafting. Pain relief is believed to be due to the increase in circulation and the resultant dilution of noci-chemical mediators

Collagen formation is severely impaired at PO_2 concentrations below 30mm Hg. Fibroblasts can only produce collagen when tissue PO_2 reaches 30mm Hg (Niinikoski & Hunt, 1972; Lidner, 1977; Fattore & Strauss 1987). It is only after sufficient collagen has been formed that capillary buds then invade the collagenous matrix, facilitating rapid capillary ingrowth. Without this collagenous support, capillary growth is retarded (Kindwall 1992).

The major benefits of HBO, as stated by Marx & Johnson (1988), appear to be:

1. Reversal of the hypocellular-hypovascular-hypoxic tissue bed thus improving the host tissue's ability to support and maintain viable bone.

2. Inducement of angiogenesis - HBO increases the vascularity in the tissues injured by radiation and thus tissue viability and healing capacity is increased, reducing the risk for spontaneous or trauma induced ORN.

Improvement in radionecrosis with HBO (Marx 1984) occurs in three phases:

1. Lag phase
2. Exponential rise phase, and
3. Plateau phase

The transcutaneous oxygen values in the irradiated field during HBO treatment are illustrated in Figure 4.3.

1. The first or **lag phase** represents the first six to eight HBO exposures and does not involve measurable angiogenesis. It is a phase of collagen synthesis and capillary budding. Tissue oxygen tensions are consistently 30-50% of non-irradiated tissue until about the eighth day.

2. The second phase is called the **exponential rise phase** and is one of rapid revascularisation. In this phase, which occurs between the eighth to eighteenth HBO exposure, tissue oxygen tensions increase from about 30% of controls to a maximum of 82% of non-irradiated tissue. There is an organised collagen network.

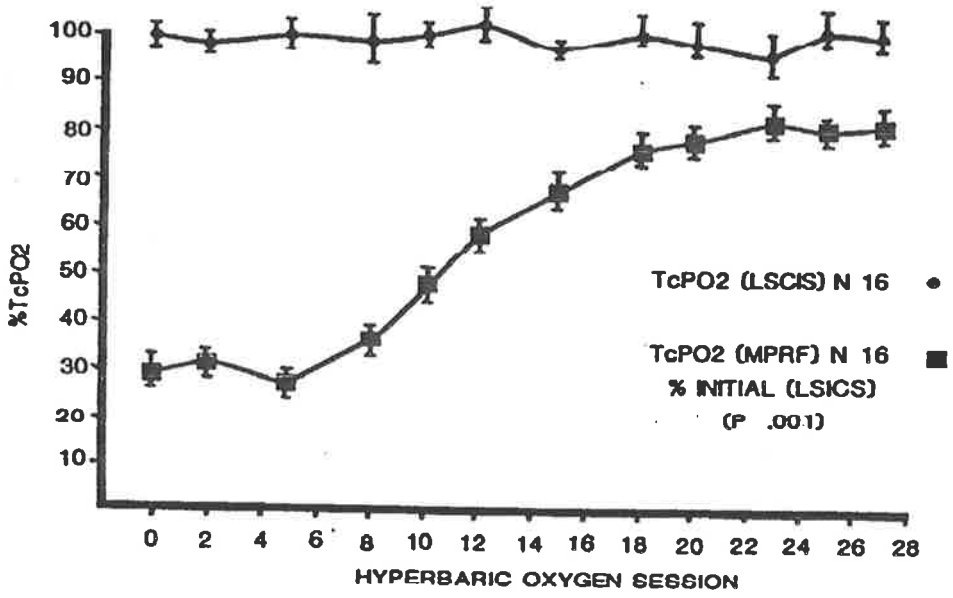


Figure 4.3 **Curve illustrating vascular density (measured by transcutaneous oxygen values) of irradiated tissue as a function of hyperbaric oxygen sessions.**

$TcPO_2$ = Transcutaneous oxygen tension values; LSICS = Left second intercostal space; MPRF = Mid-point of the Radiated Field. (From Marx, 1984)

The accelerated rise in tissue oxygen values during this phase is due to capillary budding and perfusion of previously hypovascular tissue. Its steep slope reflects revascularising wounds which rapidly proliferate vessels into its central hypoxic core from peripheral established vessels.

3. The third phase is referred to as the **plateau phase** and is reached after maximum angiogenesis. The tissue oxygen tension in this phase levelled off at 82% of controls between the eighteenth and twenty-third session, and did not improve with the additional HBO treatment. The flattening of the graph represents the maximum gain in capillary density attainable by HBO. There is correction of tissue hypoxia and elimination of lactate and hydrogen ions which are the known initiators of healing. Oxygen tensions are 80-85% of non-irradiated tissue.

Hyperbaric oxygen does not hypervascularise already well vascularised and well perfused tissue. This is illustrated by the straight line values seen at the control site and shows that HBO does not influence unaffected tissue (Figure 4.3). The control site, in relation to this graph, is the left second intercostal space (LSICS), which is used as a reference outside the radiation field (Marx 1984).

Generally most authors also use intensive local measures, antibiotics, and, where indicated, surgery such as sequestrectomy. Marx's (1984) comprehensive protocol involving the use of HBO has been presented in Section 3.5. With this protocol, patients failing

to respond within a limited time to simple HBO therapy move on to simple surgery, and then to resection and bone grafting. So far this protocol appears to produce the best results, with cure rates now over 90%. These results are obtained only when HBO is used before surgery and when the described surgical techniques and grafting procedures are followed closely. However, in a report of four cases, Mainous et al in 1973 found surgery unnecessary and reported spontaneous resorption of sequestra.

The use of a combined HBO and reconstructive surgery approach will be discussed in Chapter 5, under surgical treatment of ORN.

HBO therapy has also been used in the management of post-irradiation soft tissue necrosis (Greenwood & Gilcrist, 1973; Davis et al, 1979).

Both the adjunctive oxygen and surgery are a formidable undertaking for patients who have already received prolonged and difficult treatment for their neoplasm, even without considering the resources required.

Marx, Johnson and Kline (1985) analysed the cost effectiveness of treating patients with a protocol of HBO. The total cost parameters of ORN treatment were calculated from a review of 175 patients. The figures used were normalised to prevailing cost and fee schedules in US dollars as of July 1, 1984. Their analysis illustrated the tremendous expense associated with treating ORN by any method.

Without either HBO or surgery, the average 1-year cost of treating ORN is $28,500. The extended average cost is $62,000 because of the need to continuously treat an unresolved disease. They also found that there were hidden costs that were not readily apparent, and that only 8% of patients resolved their disease. The other 92% of the patients went to other practitioners or other institutions and accumulated additional ORN-related costs, not reflected in these figures. In addition, there were the social costs of pain, analgesic dependence, job absenteeism and time separated from families. With their combined HBO with surgery protocol (which yielded a 100% resolution of disease), the average total cost amounted to as much as $30,000. However, the average 1-year cost of ORN prevention was significantly less at $8,000. Considering it reduced the incidence of ORN from about 30% to about 5.5%, this HBO protocol is certainly cost effective.

In summary, when ORN is diagnosed, the health care system must anticipate a tremendous expense. Furthermore, the patient and relatives must face the concern of a potentially painful and debilitating disease, which requires an investment of time and expense inherent in preventive techniques. This includes the up-front delivery of HBO (Marx et al 1985).

CHAPTER 5

TREATMENT AND PREVENTION OF OSTEORADIONECROSIS

"Osteoradionecrosis of the jaws has frustrated the best preventive and treatment measures by the specialities of radiation oncology, oral and maxillofacial surgery, and hyperbaric medicine.''
(Marx & Johnson, 1988).

5.1 Management of Osteoradionecrosis

Various treatment modalities have been used to arrest or reverse ORN. These include local wound care, antibiotic coverage, surgical procedures and the administration of HBO. Several different treatment protocols have been suggested for ORN and cure rates using these treatments range from 33% to 100% (Marx & Ames, 1982; Epstein et al, 1987; Marciani & Ownby, 1986; Robinson et al, 1971; Marx, 1983). Treatment involves either a nonsurgical or surgical approach, with many advocating a combined approach. Either way the primary goal is the control of the necrotic process, pain and any superimposed infection.

Any consideration of the management of ORN would be incomplete without reference to prevention of this destructive disease.

5.2 Non Surgical Treatment

The conservative approach, in broad terms, includes counselling in oral hygiene, appropriate pain medication, use of antibiotics, local irrigation, local debridement, use of HBO and removal of small bone sequestra as needed. This approach can be categorised as follows:

1. Change in life style

Changes, such as giving up alcohol and smoking, avoiding hot, cold, spicy or rough foods and giving up wearing dentures, are advised (Rankow & Weissman, 1971). As short term measures to help a very small area of necrosis, these steps may be useful in avoiding further trauma to the tissues. However, in the long term management of someone with ORN, compliance with these instructions is often poor, and can only be considered as an adjunct to other therapy. The patients are usually chronic smokers and some are alcoholics, hence getting them to give up these habits and follow preventive measures is often difficult.

2. Topical treatment

Local measures have their merits, especially the maintenance of good oral hygiene. Patients are advised to pay special attention to oral hygiene in order to prevent secondary infection of the exposed area. The goal is to decrease the incidence of further dental disease which will tend to exacerbate the condition. Usually all dentate patients with ORN are encouraged to see their dentist regularly on a 3 to 6 months basis.

Various types of mouthwash have been advocated, including regular gentle irrigation of the area. In some centres patients are given 10 ml syringes to help in irrigation. Various common mouthwashes used range from salt and sodium bicarbonate (Rankow & Weissman, 1971), zinc peroxide and hydrogen peroxide (Francisco 1966), to antiseptics such as chlorhexidine (Coffin, 1983). However it has been claimed, with some evidence, that chlorhexidine at concentrations greater than 0.2%, when used for sites not directly associated with the teeth, delays, rather than promotes, healing (Bassetti & Kallengerger, 1980). It is a fact that chlorhexidine has cytotoxic properties and this effect may be due to disorientation of the lipoprotein membrane and of the cytoplasmic membranes. Also, fibroblasts are much more sensitive than epithelial cells (Bassetti & Kallengerger, 1980).

The use of packs over exposed bone has been popular in the past. MacComb (1962) used zinc peroxide mixed with carboxyl-methylcellulose in hydrogen peroxide, and also mentions the use of 5% neomycin solution or acriflavin as alternatives. Morton and Simpson (1986) found packs useful, especially for covering small areas of exposed bone and delicate granulation tissue, following separation of a sequestrum. He recommended its use for keeping necrotic bone cavities clean in patients who are not ready for definitive management. The use of packs is usually a short term measure. Morton & Simpson found Bismuth & Iodoform paste (BIPP) on ribbon gauze very satisfactory, as it remained fairly soft and stayed quite clean. This can either be packed or sutured into bony cavities.

Analgesics or narcotics have been used in many instances. The only drawback is that in many patients pain is present for long periods. Prolonged use of these drugs results in untoward effects of them either losing their potency at the therapeutic level, or producing addiction. Analgesics cannot be withheld from these patients and some patients do require chronic pain management.

3. Systemic Antibiotics

Many clinicians consider ORN to be a chronic infective osteo-myelitis of irradiated bone with mixed oral micro-organisms, including actinomyces and candida (Happonen et al, 1983; Harris, 1992). Hence these patients were treated with long term antibiotics, with or without minor surgical procedures to induce healing or mucosal cover. Such management is often unsuccessful, varying from 25-46%, and the ultimate need for resection is high (Harris 1992).

The role of antibiotics is doubtful. Some clinicians use antibiotics to control episodes of secondary infection. In many clinics no clear distinction is made between septic and aseptic ORN. Rankow and Weissman (1971) treat all patients with a three week course of a broad spectrum antibiotic such as tetracycline. Rubin and Doku (1976) give penicillin (500mg) and continue for as long as necessary. Coffin (1983) uses tetracycline without sensitivity testing. His regime includes 250mg 6-hourly for 1 week, then 8-hourly for 2 weeks, and continues with 12-hourly doses until healing occurrs. This can take more than a year.

Parulekar and Paonessa (1980) divide ORN into aseptic and septic cases. The latter are treated with high dose intravenous penicillin which is changed if the results of culture and sensitivity tests indicate resistance. Marx (1983a), on evaluation of material from 26 consecutive cases of ORN found that no organisms were present in the deep tissues, but 75% of cases had surface organisms with candida species and streptococci predominating. Others have found the most predominantly cultured organisms to include Staph. aureus and albus, haemolyticus and viridans, Pneumococcus, Pseudomonas and E. Coli (Mansfield et al., 1981).

Like Marx (1983a), Morton and Simpson (1986) felt that as not all cases of ORN are infected, the use of long term antibiotics was therefore not indicated. They feared the possibility of the development of resistant strains of micro-organisms which should be avoided. However a number of ORN cases are infected, which, if inadequately controlled, can become rapidly progressive and destructive and difficult to treat. It was felt that the amount of necrotic tissue present, and the diminished vascular supply of the surrounding tissue, makes delivery of high antibiotic levels in the affected tissue difficult to achieve.

It has been suggested by Ibsen & Urist (1964) that tetracycline would be suitable for use in ORN because of its attraction to bone, especially where new bone has been formed. However, tetracycline is bound in bone and the insoluble salt is probably inactive. It has been claimed that when the tetracycline complex is

resorbed it is likely that the local drug level is not increased to bacteriologically active levels (Ibsen & Urist, 1964).

Morton and Simpson (1986) usually give penicillin initially but change according to the culture and sensitivity results, including culture for anaerobes. They also add metronidazole to counteract the anaerobes in these patients.

Systemic antibiotics are best reserved for signs of active infection. They are not well delivered to the poorly vascularised tissues.

4. Ultrasound Therapy

Ultrasound therapy has been tried by some (Young & Dyson, 1990; Harris 1992) as a simple means of promoting neovascularity and neocellularity in ischaemic tissues. Harris (1992) has shown that treatment of 21 patients with ultrasound plus metronidazole, produced healing without surgery in 48% (10) of cases. The dosage of ultrasound is high but these results are impressive.

Ultrasound, together with other physical modalities of generating energy such as pulsed high frequency electromagnetic stimulation, have been employed to facilitate healing in intractable conditions, varying from ischaemic varicose ulcers to fracture non union (Dyson, 1982; Dyson et al, 1976; Pilla et al, 1990; Harris, 1992).

At this stage very little is known of the cellular mechanisms underlying the therapeutic action of ultrasound. Harvey et al (1975), as cited by Harris (1992), have shown that therapeutic

levels of ultrasound stimulate protein synthesis in fibroblasts. It is speculated that the ultrasound pressure wave may mechanically deform connective tissue cell membranes, altering their ionic permeability, and so activate the intracellular second messenger adenylate cyclase (Harris 1992).

5. Electromagnetic stimulation

Electromagnetic stimulation (EMS) is a well-established, but controversial, method used in orthopaedics for the treatment of non-union, pathologic fracture with or without osteomyelitis and avascular necrosis (Barak et al 1988). EMS treatment involves generating an electromagnetic field which is believed to stimulate vascular proliferation into bony tissue. This is achieved by producing electrical waves through electrodes. The process increases calcium uptake and promotes osteogenesis (Kort et al, 1982; Sutcliffe & Goldberg, 1982). Barak et al (1988) described a case of ORN successfully treated with electro-magnetic stimulation for 12 hours a day for 9 months.

Treatment with EMS has the advantage of being non-invasive and a less complicated technique, with a minimal chance of morbidity. It permits the treatment to be carried out on an ambulatory basis. Furthermore, it is very simple, inexpensive, and there are no known complications (Barak et al 1988). However the prolonged treatment duration is a major setback, and there are no major studies in the literature reporting its use on ORN.

6. Hyperbaric Oxygen

This has been discussed in Chapter 4.

5.3 Surgical Approach

The conservative approach objective is to arrest the destructive process of ORN and epithelialisation of the underlying bone. However, in moderate to severe ORN surgical intervention may be necessary to halt the process by removal of all the affected bone. The extent of surgical intervention depends on the individual case. However, preservation of function and avoidance of disfigurement are important goals in the treatment plan.

Osteoradionecrosis decreases the quality of life, hence treatment should be directed toward restoring both the mandible and a healthy intraoral environment, to prevent further episodes of the disease. From both a functional and cosmetic standpoint, surgical management can be effective in achieving satisfactory rehabilitation goals.

The key to success is adequate resection (Obwegeser & Sailor, 1978; Robinson, 1975). Much of the failure to control osteo-radionecrosis in earlier series was due to inadequate debridement, and a failure to recognise the extent of the disease process (Marx 1983).

The surgical approaches recommended in the management of ORN vary from simple sequestrectomy, to alveolectomy, to hemi-mandibulectomy, or even total mandibulectomy, depending on the

degree of necrosis. The criteria for surgery have been discussed by many authors (Daland, 1941; Hunt & Breit, 1948; Obwegesser & Sailer, 1978; Sailer, 1973; Baker, 1983; Beumer et al, 1984; Marx, 1984; Epstein et al, 1987; Kindwall, 1993).

Generally a surgical approach is considered if an area of ORN fails to respond to simple conservative measures, or in cases of extensive involvement. Resection of radionecrotic bone may be done either intra- or extraorally (Freestone et al, 1973). Marchetta et al. (1967) were concerned about, and drew attention to, the morbidity associated with the extraoral approach to resection, and recommended an intraoral approach. In some patients treatment may involve simple excision of the sequestrum or sequestrectomy with saucerization. Minimal debridement and sequestrectomies do not remove all dead or hypovascular bone. It may actually result in extension of disease as more bone is devitalised. (Sanger et al 1993)

Radical resection of the mandible may have to be resorted to in other instances. Rankow and Weissman (1971) describe a technique for intraoral hemimandibulectomy. Morton and Simpson (1986) felt that if a resection were to be carried out involving the posterior horizontal ramus and reconstruction of the defect was not planned, then removal of the mandible to a higher level, or even disarticulation of the condyle, should be performed. This was due to a tendency for the distal fragment to be displaced superiorly and medially causing pain, discomfort and even ulceration, in the tuberosity region of the maxilla.

The presence of intraoral fistulas usually requires some debridement of unhealthy mucosa, and the thickened mucosa may not advance well. In such cases, closure by a flap may be indicated (Ivy,1949). Local soft tissue flaps can be used. The tongue remains a good source of local tissue, despite irradiation, although many other regional or free flaps are available (Zarem et al 1983).

It has been noted that while surgery aims to remove necrotic tissue, unless measures are taken to improve vascularity, successful healing may not be achieved. Hahn and Corgill (1967) recommended drilling holes from non-vital to vital bone, to allow ingress of healing granulation tissue. This was in the hope that the circulation would cause an osteoclastic and osteoblastic reaction and form new bone.

With the current concept of its pathophysiology, most authors feel that unless radical resection is planned, the surgery should be designed to create as little trauma to bone as possible. It has been recommended by some (Rankow & Weissman, 1971; Dolezal et al, 1982) that sequestrectomies should be delayed until the necrotic bone can be lifted off with ease, so as not to damage the delicate granulation tissue in the bed. Marx (1983b) proposed transoral alveolar sequestrectomy with primary mucosal closure as part of his combined HBO therapy and surgery protocol.

Morton and Simpson (1986) found formal mucosal closure after sequestrectomy difficult in most cases, and attributed this to the friable nature of the tissues. It is also felt that raising local flaps to perform closure risks damage to the flap and the underlying bone.

Raising the periosteum to create local flaps certainly runs the risk of devascularising bone which, in these patients is dependent predominantly on this centripetal blood supply (Bradley, 1972).

Debridement and primary closure, or closure with a muscle or myocutaneous flap, may give dramatic relief of pain and eliminate fistulas. In some patients, this may mark the reconstructive endpoint. In selected patients, resection of the necrotic bone with preservation of the inferior cortex of the mandible is possible. In these cases mandibular continuity is maintained, although risk of subsequent fracture is high.

Unfortunately, in most patients, large bone resections such as hemimandibulectomies cause loss of mandibular continuity, with secondary collapse of the remaining mandibular segments and varying degrees of soft-tissue contracture, if the mandible is not reconstructed (Cordeiro & Hidalgo, 1995)

To achieve a good aesthetic and functional result some consideration must be given to reconstruction, although this is not an absolute essential in all cases (Luce, 1995; Wells et al, 1995). One option is the use of a metal reconstruction plate to span the defect without bony reconstruction. This approach has been successfully applied to immediate reconstruction, following resection, of large tumours with a poor prognosis (Klotch et al 1990). If either plate fracture occurs or the patient survives and is cured, then secondary reconstruction with a vascularised bone graft is the treatment of choice. However, a significant incidence of plate exposure in irradiated patients is noted. This is particularly

true of anterior defects. For almost all patients, bony reconstruction is desirable, particularly if dental rehabilitation is contemplated. Morton and Simpson (1986) advocated the application of intermaxillary fixation for a period post-operatively in patients undergoing partial resections to reduce the tendency of the mandible to deviate.

The surgeon has many options for reconstruction. Several reconstruction techniques are available and should be evaluated when considering resections. The choice depends on the training and experience of the surgeon. Success was defined (Kindwall 1993) as meeting the following six criteria:

1. Continuity of the entire mandible and mucous membranes;
2. Sufficient alveolar bone height to support prostheses;
3. Sufficient osseous bulk to support the stresses of mastication;
4. Maintenance of bone in the long term;
5. Elimination of soft-tissue deficiencies; and
6. Restoration of normal mandibular form.

Whatever technique is contemplated, the objective is to fulfil the above six criteria for success. Of particular importance in oral rehabilitation are criteria 2, 3 and 4, which are too often ignored. These features are important in allowing good dental prosthetic reconstruction and stability, and consequently improved masticatory function. They are too often ignored by operators who fail to consider, or lack, oral prosthetic rehabilitation experience.

If the oral cavity is healed, thus eliminating the potential for contamination by secretions, bone grafting via an extraoral approach is feasible and recommended (Marciani et al,1976; Baker, 1983; Lukash et al, 1984; Marx, 1983; Marx & Ames, 1982). Obwegesser and Sailer in 1978 described their experience with intraoral resection and immediate reconstruction with iliac crest or rib bone grafts. They found that in only 2 of their 10 cases was healing completely free of complication due to the friable and poor quality of the soft tissues. Success rates for nonvascularised bone grafts in irradiated beds are low.

Adams and Szal (1979) reported a 50% success rate, and Obwegesser and Sailer noted complete loss of the graft in 30% of the patients, and partial loss in an additional 50% of patients. The difficulty with this technique, as pointed out by Marx (1982, 1984), is that these operators failed to address the basic pathophysiology of these irradiated tissues, which is now possible through the use of HBO therapy. Bone grafts placed in a hypocellular bed will undergo an unacceptably high rate of resorption and/or delayed infection. For this reason, HBO therapy as an adjunct prior to, and following, bone grafting has improved success rates significantly (Feldmeier et al, 1981). Sufficient time prior to bone grafting is needed to complete at least 20 dives at 2.0 atmospheres to induce neoangiogenesis.

With Marx's (1983b) combined HBO-surgery protocol, grafting was delayed for 10 weeks following the resection, whilst the patient received further HBO. In bone reconstruction, Marx and Ames (1982) have combined the use of cancellous bone graft with

banked allogeneic or cadaver bone, which in normal vascularised tissue does induce bone formation. The cadaver mandible is burred out and filled with cancellous bone from the patient, which is then placed through an extraoral incision. An additional 20 to 30 HBO treatments are given.

Advantages include a decreased donor site morbidity, because the use of cadaver mandible eliminates the need for a large bone graft. Sufficient cancellous bone can be obtained through relatively small incision and osteotomy in the iliac bone. Usually a good contour of the reconstructed mandible is achieved and future dental rehabilitation is possible. The procedure is short and does not require microvascular skills.

Disadvantages with this method include the theoretic risk of viral transmission with cadaver bone, the need to delay reconstruction to complete the HBO treatments, and expense of treatments.

Healing of the graft is slow and occurs by creeping substitution, after which time remodelling to stress further strengthens the bone. Certainly during the procedure special care must be taken not to perforate into the oral cavity, because any contamination may result in infection and loss of the nonvascularised graft. Thus, in combining increased tissue oxygen levels with bone thought to contain inducing proteins, HBO acts as an adjunct to bone formation and repair.

Free bone grafts have been used in the past to reconstruct resected areas of the mandible affected by ORN, with variable success;

however, with HBO therapy, their success rate appears greatly improved. The improved results with HBO therapy are comparable to, or better than, vascularised compound flaps, and both techniques address the basic underlying problem of reduced vascularity and reduced tissue viability.

Morton and Simpson (1986) described the use of pedicled bilateral nasolabial flaps, to provide a thick vascular cover for the anterior mandible affected by ORN resulting in a pathological fracture. This showed good callus formation a year later. Dolezal et al (1982) described a technique involving the use of a deltopectoral flap to give vascularised soft tissue coverage, followed a few weeks later by the placement of a free bone graft in the mandibular defect.

The development and refinement of microvascular techniques have allowed the utilisation of free vascularised osteocutaneous flaps incorporating bone. These flaps bring with them their own blood supply, thus maintaining bone viability, increasing total vascularity in the recipient bed, and forming new collateral channels in the irradiated tissues. This permits a one stage reconstruction and revascularisation of the bone and soft tissues.

Flaps are of two types: pedicled or microvascular. Pedicled flaps may be brought in locally or from a distance, but they maintain their original blood supply. Pedicled flaps, which carry bone, include the trapezius osteomyocutaneous flap (Conley, 1972; Dermergasso et al, 1979; Panje, 1985; Panje & Cutling, 1980; Perlman et al, 1983; Oishi & Luce, 1995), the pectoralis osteomyocutaneous flap (Ariyan, 1980; Conley, 1972), and the

sternocleidomastoid flap using a portion of the medial clavicle. Also the temporalis muscle, with a portion of calvarium, has been used for mandibular reconstruction.

The pedicled flaps generally rely on circulation via a muscle to provide blood supply to the bone through periosteal perforators. The trapezius, sternocleidomastoid, and pectoralis major myo-cutaneous flaps are excellent sources for reconstruction of soft tissue defects in the head and neck. However, the blood supply to the bone in these flaps is indirect via the perforators, and is not as vigorous as that in microvascular free flaps. Ariyan (1980) demonstrated viability with bone labelling in the rib when combined with the pectoralis major muscle. Some clinical drawbacks with pedicled osteomyocutaneous flaps include frequent nonunions and occasional total necrosis of the bone or late resorption, making it less than ideal for mandibular reconstruction.

Sternocleidomastoid flaps, which can incorporate the medial portion of the clavicle, have limited use. They may not be available for use in patients who have had modified neck dissections. All of these flaps are limited in their arc of rotation. They are ideal for short, relatively straight segments of bone reconstruction. Their main advantage is that they bring bone, with dependable vascularity, from outside the irradiated field. However, a major disadvantage of the pedicled osteomyocutaneous flaps is that the amount of bone transferred is usually insufficient to support a denture or osseointegrated implants (Sanger et al 1993).

Microvascular free flaps are increasingly being used for the reconstruction of composite defects in the head and neck (Rosen et al, 1979). These flaps have significant advantages over bone grafting or pedicled osseomuscular flaps. In free flaps, the blood supply to the bones usually involves direct perforator or nutrient vessels, hence the vascularity of the bone is rich, and multiple osteotomies can be made in the bone without adversely affecting bone survival. Also the thickness and height of bone transferred is usually sufficient to support either dentures or osseointegrated implants. Morton and Simpson (1986) have reconstructed a number of patients using microvascular techniques with groin flaps, and have reported excellent cosmetic and functional results.

Each microvascular flap has its own strengths and weaknesses. Historically, the rib was the most commonly used in the early days of microvascular surgery (Ostrup & Fredrickson, 1974; Ostrup, 1975). However it has since been surpassed by other flaps because it provides inadequate bone width and height for implants or dentures. Furthermore it cannot be osteotomized easily. The radial forearm flap has been described as means of reconstruction (Song et al, 1982; Soutar et al, 1983; Soutar & Widdowson, 1986). It can provide 8 to 10 cm of thin, cortical bone. However, for extensive radionecrotic defects this bone is inadequate for dental rehabilitation. Also limited osteotomies may be made. The metatarsal flap has been described (Duncan et al 1985, Macleod 1982) but it has limited application in oral rehabilitation because of its short bone length.

The three major free flaps used in mandibular reconstruction are the iliac crest, scapular, and fibular osseous or osteocutaneous flaps.

The iliac crest is based on the deep circumflex iliac artery and is excellent for defects up to the size of a hemimandible (Coleman & Wooden, 1990; Taylor et al, 1979). During reconstruction the ipsilateral crest is usually taken, since it has a natural curve, and minimal shaping and osteotomies are required. Furthermore the rich cancellous bone supply is excellent for osseointegrated implants (Riediger, 1988; Sanger et al, 1988). The main disadvantage is the bulk of the skin paddle. Urken et al (1989) described a procedure involving using a paddle of internal oblique muscle, based on the ascending branch of the deep circumflex iliac vessels, to provide thin, adherent oral lining to aid in dental reconstruction.

The scapular flap incorporates the lateral border of the scapula and is supported by the circumflex scapular vessels (Coleman & Wooden, 1990; dos Santos, 1984; Nassif et al, 1982; Swartz et al, 1986). It has the unique advantage that multiple fasciocutaneous skin paddles can be taken with the flap if necessary. Other modifications include the use of the serratus, with or without rib, based on this vascular tree. A long vascular pedicle is available, and its overall reliability is excellent. Generally up to 12 cm of bone can be harvested. This flap has a rich periosteal blood supply to the bone, and osteotomies can be safely performed. Osseointegrated implants have been successfully inserted into scapular bone (Swartz et al1986). However the thickness of bone

for osseointegration is variable between patients and the location along the lateral border of the scapula, hence it is not always present.

The fibular flap is supplied by the peroneal artery and its perforators and venae comitantes. It provides the longest segment of bone, up to 25 cm (Coleman & Wooden, 1990; Hildago, 1990; Sanger et al, 1990; Taylor, et al1975), and the bone can undergo multiple osteotomies without endangering viability. Although the bone length has been claimed to be ideal for angle-to-angle mandibular reconstruction, it lacks curvature and arch form for dentures. The fibula width and depth may not be adequate for osseointegrated implants. Furthermore it is highly cortical in nature, which makes insertion of osseointegrated implants somewhat more difficult than with iliac crest bone.

For reconstructing large osteoradionecrotic defects, microvascular free flaps have become the treatment of choice. A significant advantage is the ability to transfer a composite flap, in which oral lining is restored, at the same time healthy vascularised bone is reconstructed. Because the blood supply to the bone is so good, the junction between the remaining mandible and the vascularised graft heals much like a fracture, and does not depend on creeping substitution (Sanger et al 1993). With combined plate fixation of these flaps, bone strength is excellent immediately, and early mobilisation of the mandible is possible. Furthermore micro-vascular free flaps are clearly superior for composite defects in which oral contamination may lead to the loss of nonvascularised or pedicled flaps. However, these flaps are not without drawbacks.

The skin available with the scapular, iliac crest or fibular flaps is often thick and bulky. Also, in the cases of the scapula and iliac crest, it can be quite fatty. This is not ideal for intraoral reconstruction, and needs to be revised prior to any dental prosthetic rehabilitation. Intraoral hair may also be a problem. For this reason, a skin graft placed directly on muscle may be superior to a skin paddle (Urken et al 1989).

The radial forearm and metatarsal free flaps provide thin, pliable skin that is ideal for intraoral reconstruction, but unfortunately the bone available with these flaps is not as good as with the other microvascular free flaps. Further disadvantages of free flap reconstruction include added operative time, and the donor site morbidity may be greater than that of osteomuscular pedicled flaps or nonvascularised bone grafts. The disadvantage in operative time may be outweighed by the fact that multiple procedures for reconstruction are less likely if oral lining and reconstruction is accomplished in a single operation (Sanger et al,1993).

Microvascular flaps may fail due to thrombosis. In spite of high levels of irradiation, major arteries adequate for anastomoses are usually present. However, atherosclerosis may be a problem in either the donor or recipient site. For this reason preoperative arteriography is essential in patients who have been heavily irradiated. Particular attention should be paid to absent or surgically ligated vessels, coexisting atherosclerosis, or radiation induced fibrosis, which narrows vessels.

Another significant finding that indicates a vessel may be unsatisfactory for microvascular repair is a corkscrew appearance to the vessel shortly after branching off from the external carotid artery. In such a vessel, the intima tends to pull away from the vessel wall, making it difficult to anastomose. It is recommended that angiograms of both carotid systems be obtained (Sanger et al 1993). Often the opposite neck is used for vascular access. In patients who have undergone surgery and irradiation, there are generally more branches of the external carotid present on the contralateral neck, and less fibrosis and difficulty getting to them. Also a better quality of vessel is obtained.

Arteriograms are also useful for selecting vessels for the recipient arterial anastomoses. However, it is claimed (Sanger et al 1993) that direct inspection may reveal large areas of atherosclerotic plaque not seen on the arteriogram, and in general these are far fewer close to the origin of the vessel. It is for this reason they recommend either end-to-end anastomoses of the major vessels as they arise from the external carotid, or end-to-side anastomoses to the external carotid.

In mandibular reconstruction, an extraoral approach is generally favoured to avoid contamination of the wound from oral secretions. However, this is not always possible as sometimes, with microvascular free flaps, oral lining replacement is done simultaneously if necessary. With submandibular approaches it is suggested (Sanger et al 1993) that a generous flap be raised in the

subplatysmal plane, which provides maximal vascularity to the skin flap.

In chronic cases of ORN with fistulas there may be induration and contraction of the neck skin, which makes closure of soft tissue defects very difficult. For this reason a cutaneous paddle is added to the flap in the neck. Also, when assessing the remaining mandible, any moth-eaten or irregular bone is resected. With the use of reconstruction plates, periosteal stripping should be kept to a minimum.

Sanger et al reported experiencing, on one or two occasions, progression of ORN in the nonreconstructed area at the site where periosteal stripping was extended to place fixation plates. It is now recommended that the mandible should be exposed and plated directly over the periosteum as well as bone. It is suggested that miniplates may be useful in this regard, because they can be applied with minimal periosteal trauma. Certainly extraoral fixators continue to play a part in the management of ORN, especially in those cases in which the lesion is resected and healing of the intraoral fistula is allowed to occur prior to definitive reconstruction. However, loosening and pin tract infection are more common than in nonirradiated patients (Sanger et al 1993).

Since many patients with ORN quite often have multiple medical problems, Sanger et al (1993) recommend using two operative teams when using free flaps. One team prepares the mandible and neck while the other harvests the flap.

5.4 Osteoradionecrosis Prevention

The best treatment of ORN is prevention. Certainly the morbidity associated with ORN is well documented. The enormous treatment and social costs (Marx, Johnson & Kline 1985) involved justify the notion 'prevention is better than cure'.

5.4.1 Pre-Irradiation Dental Management

Osteoradionecrosis may occur spontaneously or secondary to dental disease (Sanger et al 1993, Marx 1983,1984). Extraction of teeth in the irradiated jaw accounts for 89% of all trauma induced cases of mandibular ORN (Kindwall 1992).

The most successful methods for prevention of ORN are measures taken prior to irradiation (Sanger et al 1993). Preventive strategies must include a thorough dental examination and prophylaxis. The close evaluation of the oral cavity and radiographs of the jaws and teeth allows an accurate assessment of the dentition and bone status. Sanger et al (1993) suggested that prior to commencing radiotherapy, all restorative and periodontal treatment should have been completed. Endodontic therapy does not appear to increase the risk of ORN. Periodontally diseased teeth with furcation, periapical involvement or grossly decayed teeth should be extracted prior to radiation therapy.

It is now felt that extractions should be performed 2 to 3 weeks prior to radiation therapy, and should involve atraumatic

extraction techniques, which include alveolectomy with primary closure when possible (Rominger et al, 1962; Greenspan 1993).

In both dentulous and edentulous patients, emphasis is placed on maintaining good oral hygiene prior to, during and post radiotherapy. In the majority of cases, basic oral hygiene instruction is a must, because these patients have never practiced good oral hygiene. These patients are also encouraged to stop smoking. Fluoride treatments, in the form of 0.4% stannous fluoride gel, 1.0% sodium fluoride, or 1.0% acidulated fluorophosphate gel, have been used to improve residual teeth. While the patients are having radiotherapy, it is recommended that they receive fluoride treatment, maintain excellent oral care, and where indicated antifungal and/or antiseptic mouthwashes (Carl et al 1972; Haber-Cohen & Debiski, 1990; Regezi et al, 1976).

5.4.2 Post-Irradiation Hyperbaric Oxygen Prophylaxis for Osteoradionecrosis Prevention

Marx and Johnson (1988) report that approximately 35% of ORN occurs spontaneously where soft tissue breaks down over nonviable bone, and 65% is initiated by some form of trauma, such as tooth extraction, biopsies, dental prostheses, etc., which creates a nonhealing wound with exposed nonviable bone. The irradiated patient quite frequently presents a dilemma to the clinician: 'One risks ORN initiation by leaving dental and periodontal disease untreated, and one also risks ORN initiation by interventions that wound such compromised tissue' (Marx & Johnson 1988).

As with preirradiation cases, atraumatic surgical techniques should be implemented involving minimal dissection and reflection of the mucosa. There should be minimal trauma to bone and any sharp edges should be eliminated prior to primary closure (Rahn et al, 1968; Sanger et al 1993).

In spite of meticulous surgical techniques and antibiotic therapy, ORN still occurs with an alarming frequency in post-radiotherapy extraction patients. HBO given to irradiated patients prior to dental extractions may prevent or decrease the incidence of ORN. Marx et al (1985) proposed prophylactic pre-surgical HBO consisting of 20 preoperative dives of 90 minutes each at 2.4 atmospheres absolute. Following extractions and/or surgery, a further 10 HBO treatments are administered. With this combination of HBO and good surgical technique, Marx et al (1985) reported an incidence of ORN of 5.4% as compared with the antibiotic group of 29.9%.

As for bone grafting, sufficient time to induce neovascularization and obtain the benefits must be present, and hyperbaric treatment must be done as part of a coordinated prophylactic protocol. Certainly the cost-effectiveness of such an exercise should be borne in mind, since it is much cheaper than to treat someone who has ORN (Marx et al 1985).

CHAPTER 6

ANIMAL STUDIES

Most animal studies have been on investigation of radiation damage to the mandible and surrounding tissues. Several investigators (Chambers et al, 1958; Gowgiel, 1960; Myer et al, 1962; Rohrer, 1979; Granstrom et al, 1982), have studied the aetiology and pathogenesis of ORN using animal models. There was a lot of controversy over the relative importance of the death of the osteocytes and osteoblasts, and the role of damage to the vasculature.

Gowgiel (1960), in his experiment with rhesus monkeys, concluded that ORN results primarily from the direct effect of radiation on the osteocytes. Ruben and Casarett (1968), as cited by Rohrer et al (1979), believed that the principal factor in radiation damage to the cells in mature bone is vascular damage. This uncertainty appears to have been clarified by Rohrer et al (1979). They investigated the effect of high dose cobalt-60 irradiation on rhesus monkey mandibles to determine the changes in the mandible that would predispose the patient to ORN. A tumouricidal dose of 4,500 rads in 10 fractions, equivalent to 7,000 rads in 35 fractions, of cobalt-60 radiation was delivered through bilateral ports to the mandibles of rhesus monkeys. Not only did they observe clinical

changes similar to those seen in humans, they also observed significant microscopic changes in the mandible.

These changes included loss of osteocytes from bone, changes in the periosteum, changes in the periodontal ligament, changes in the marrow, and obliterative endarteritis of many of the blood vessels. In essence this study confirmed that a combination of injury to bone cells and surrounding tissue and vascular damage predisposes the patient to ORN. It is well appreciated that late radiation effects may have a significant impact on the healing of irradiated tissue, yet most animal studies have focused on the acute effects of radiation on wound healing. The evaluation of long term chronic effects certainly requires more time, patience and further costs. Obtaining ethical approval for such studies would also be difficult.

Animal studies have also been used to investigate the incidence of ORN in relation to irradiation doses. Experimentally, Chambers et al (1958) used orthovoltage to irradiate the mandibles of two groups of adult mongrel dogs. Group 1 was composed of 7 dogs. There was no preirradiation extraction in this group. Total irradiation ranged from 3,000 to 8,000 roentgens. Osteo-radionecrosis developed in every instance where the quantity of irradiation was 5,000 R or more. Group 2 consisted of 14 dogs in which the right posterior teeth had been removed before irradiation. Osteoradionecrosis occurred in 12 of 13 dentulous areas to which 4,000 R or more were delivered. Osteoradionecrosis developed in only 3 of the 13 dogs in the areas made edentulous.

Ng et al (1959) used adult mongrel dogs treated with orthovoltage to determine at what dose levels ORN could be produced. The first experiment used 8 dentulous dogs and the total amount of irradiation ranged from 3,000 to 8,000 R. Osteoradionecrosis developed in 4 dogs. A second experiment was designed to study the effect of preirradiation extraction of teeth. Fourteen dogs were used. Osteoradionecrosis developed in 12 of 14 hemi-mandibles in which teeth were not extracted. Osteoradionecrosis developed in only 3 of 14 hemimandibles made edentulous before irradiation. Ng and his associates concluded that removal of teeth before irradiation of the mandible significantly decreased the incidence of ORN.

HBO therapy has developed, both experimentally and clinically, and appears to be of therapeutic value in tissue healing. Tissue healing is oxygen-dependent, and HBO exerts its beneficial effect via this oxygen dependence. HBO has been reported to increase energy production, collagen synthesis, capillary growth, and osteoblast-osteoclast activity (Shaw & Basset, 1967; Hunt et al, 1969; Penttinen, 1972;Nilsson et al, 1987; 1988, 1989; Nilsson, 1989).

Zhao et al (1992) carried out a series of experiments using an ischaemic rabbit dermal ulcer model utilising HBO to overcome the effects of hypoxia, and found a very modest but significant effect of HBO in accelerating healing. Furthermore they found that the combination of transforming growth factor-beta (TGF-beta) or platelet-derived growth factor (PDGF) and HBO, totally reversed the profound ischaemic healing deficit and restored healing to normal. However, despite extensive studies, many aspects and details of

HBO effects on tissue healing remain obscure. Certainly both quantitative and qualitative investigations could be expected to provide additional information regarding the effectiveness of HBO.

In the light of ethical considerations and because of the inability to design reliable, controlled human studies, it would seem that a simple and reproducible animal experimental model might provide a basis for further studies. Many animal systems have been developed to evaluate radiation-impaired wound healing; however, to date, no lower vertebrate ORN animal model exists. It is quite evident from the literature that most studies have used higher vertebrates. However these larger animals are expensive, limiting experimental numbers, and require far more resources to maintain. Also with the current animal ethical climate and in particular the painful nature of this disease process, investigators are facing increasing opposition to the experimental use of larger animals. It would seem appropriate that a lower vertebrate animal model would be ideal. With increasing University research funding cuts, it would not only be cheaper but easier to maintain, require less resources, and allow the use of appropriate experimental numbers.

III

MATERIALS AND METHOD

CHAPTER 7

CLINICAL STUDY EVALUATING THE EFFECT OF HYPERBARIC OXYGEN ON THE TREATMENT AND PREVENTION OF OSTEORADIONECROSIS

Hyperbaric oxygen therapy has been used at the Royal Adelaide Hospital since 1987 for the treatment and prevention of ORN. This study is a review of patients who have been treated with HBO for ORN and ORN prevention by the Oral and Maxillofacial Surgery Unit at the Royal Adelaide and Adelaide Dental Hospitals.

7.1 Materials and Methods

7.1.1 Materials

7.1.1.1 Selection of patients

The population pool included all patients treated at the Royal Adelaide Hospital Hyperbaric Unit, and Oral and Maxillofacial Surgery Unit, for ORN or ORN prevention of the facial bones from 1987 to February 1996. The study included both a retrospective and a prospective evaluation.

Records were retrieved from the Oral and Maxillofacial Surgery Unit, the University of Adelaide, and the Hyperbaric Unit of the

Royal Adelaide Hospital for all patients who were treated for either ORN or ORN prevention between 1987 and December 1991. These patients formed the retrospective review group.

From 1992 to February 1996 all patients presenting to the Oral and Maxillofacial Surgery Unit with ORN or a history of irradiation to the head and neck region and requiring oral surgical procedures, were included in the prospective study.

The Caucasian patient sample was drawn from the metropolitan area of Adelaide. Coincidentally there were no Asians or Aborigines in the sample. Socioeconomic bias influenced the sample, as patients were only eligible for treatment if they held health care cards (unemployed, sickness benefits, pensioners).

7.1.1.2 Criteria for inclusion in the trial

To have been selected for review, patients had to fulfil the following criteria:

Patients must have had:

(1) A proven diagnosis of head and neck cancer.
(2) Treatment that included therapeutic doses of radiation to the head including either or both jaws and the major salivary glands.
(3) Hyperbaric oxygen treatment.
(The only exceptions were patients in the control group who did not receive HBO treatment.)

Patient's consent was obtained prior to reviewing medical records.

Ethics committee approval (Approval number H/06/92) was obtained to retrospectively review patient casenotes, radiographs, dental records, radiotherapy and surgical records.

7.1.1.3 Retrospective review

Histories of 26 patients treated at the R.A.H. Hyperbaric Unit for ORN and ORN prevention of the facial bones from 1987 to 1991 were reviewed to determine their presenting features and subsequent management.

7.1.1.4 Prospective review

A prospective study was commenced in 1992 as a continuation of the retrospective review. Broadly any patient with ORN or requiring prophylactic HBO for ORN prevention was prospectively reviewed. Patients were evaluated on presentation then referred for hyperbaric consultation and management. On completion of their hyperbaric and dental or surgical treatment, the essential data were then recorded. Besides the routine post-operative follow-up reviews, patients were reviewed on a six monthly recall for monitoring of their oral status and function.

Variables recorded were the same as for retrospective cases and the same record sheets were used.

7.1.2 Population Pool

During the period 1987 to February 1996, a total of 55 patients was referred to the Royal Adelaide Hospital Hyperbaric Unit for HBO treatment, either for ORN or ORN prevention, to their facial bones using the Unit's protocol.

Their histories were reviewed for the study. Eighteen of the patients had ORN and 37 required prophylactic HBO prior to oral surgical procedures.

The patients were divided into three groups:

1. Osteoradionecrosis Group

   This group included all patients with ORN for at least three months with no improvement in spite of adequate conservative therapy.

   In this study the diagnosis of ORN was determined by identifying persistent exposure of bone for 3 months or longer in irradiated regions of the jaws which failed to heal with conservative measures.

2. Hyperbaric Oxygen Prophylaxis Group for ORN

   Patients with a history of having received therapeutic doses (40 to 70 Gy) of radiotherapy to the head and neck for

treatment of malignancy and who required dental extractions or other oral surgery were included.

These patients received prophylactic HBO treatment pre- and post-surgically for prevention of ORN. They were closely monitored and followed up for any signs of ORN.

3. Control Group

This group included two lots of patients who effectively did not receive any therapeutic HBO. One group comprised those who were worked up for prophylactic HBO treatment pre-operatively but had contraindications for HBO therapy, so did not receive any HBO. The second group comprised those who commenced HBO therapy and had to abandon it very early as a result of complications (less than 5 HBO dives).

Certainly this is not a true control group but in view of the refractory nature of this disease, ethically one cannot withhold treatment from patients who are experiencing a lot of pain and discomfort.

7.1.3 Treatment Protocol

Patients received HBO treatment or dives in a multi-place chamber at the Royal Adelaide Hospital Hyperbaric Unit.

Each dive consisted of:

(1) 100% oxygen breathed via a face mask or plastic hood;
(2) Chamber compression either to 2.0 or 2.4 atmospheres absolute pressure (ATA);
(3) Oxygen exposure for 90 minutes, once per day, six days per week.

The Royal Adelaide Hospital HBO ORN prevention and treatment protocol is based on, and is, a variation of the Marx-Wilford Hall USAF Medical Centre Protocol. It consists of three treatment regimes depending on the stage of ORN.

STAGE I OSTEORADIONECROSIS

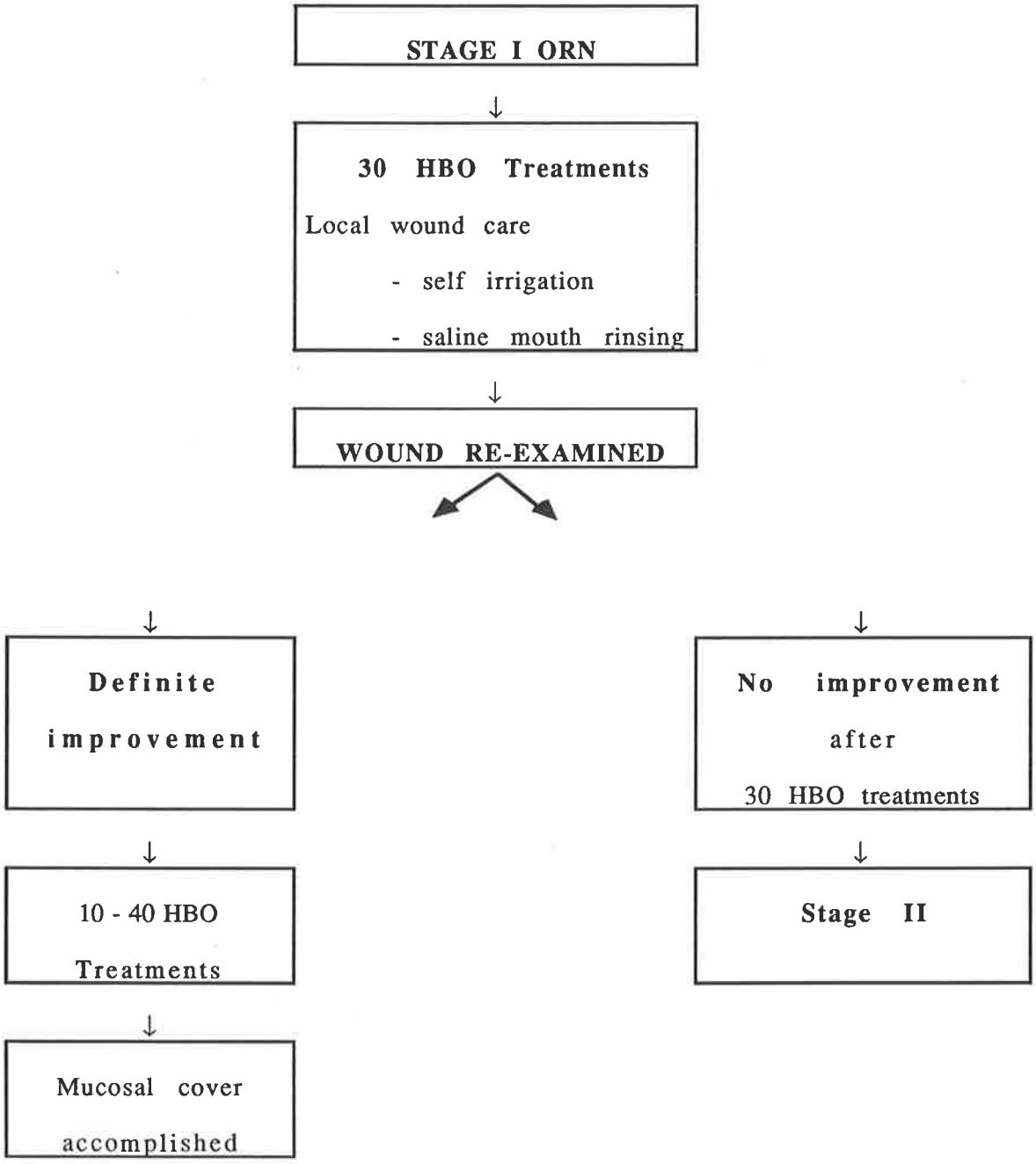
Stage I cases are those with only a small area of exposed osteoradionecrotic bone, with three exceptions representing advanced disease: orocutaneous fistulae, pathologic fracture, or radiographic evidence of bone resorption to inferior border. In other words, the mandible should not appear to be seriously involved on x-ray.

The protocol involves HBO treatment only and no surgical intervention. The patient receives 30 dives and wound care, including self irrigation or mouth rinsing using saline, after which the wound is re-examined. If the wound shows definitive signs of clinical improvement, such as resorption or spontaneous sequestration of exposed non-viable bone, a decrease in the amount of exposed bone, softening of the exposed bone,

granulation tissue beginning to cover the exposed bone, and absence of inflammation, the patient has a further ten to forty dives until mucosal cover is fully accomplished. If there is no clinical sign of improvement by 30 dives, as evidenced by continued or extended exposure of bone, absence of mucosal proliferation or presence of inflammation, the patient is considered a nonresponder to Stage I and is now considered a Stage II.

A summary of Stage I treatment protocol is presented in Figure 7.1.

Figure 7.1 Stage I Hyperbaric Oxygen treatment protocol



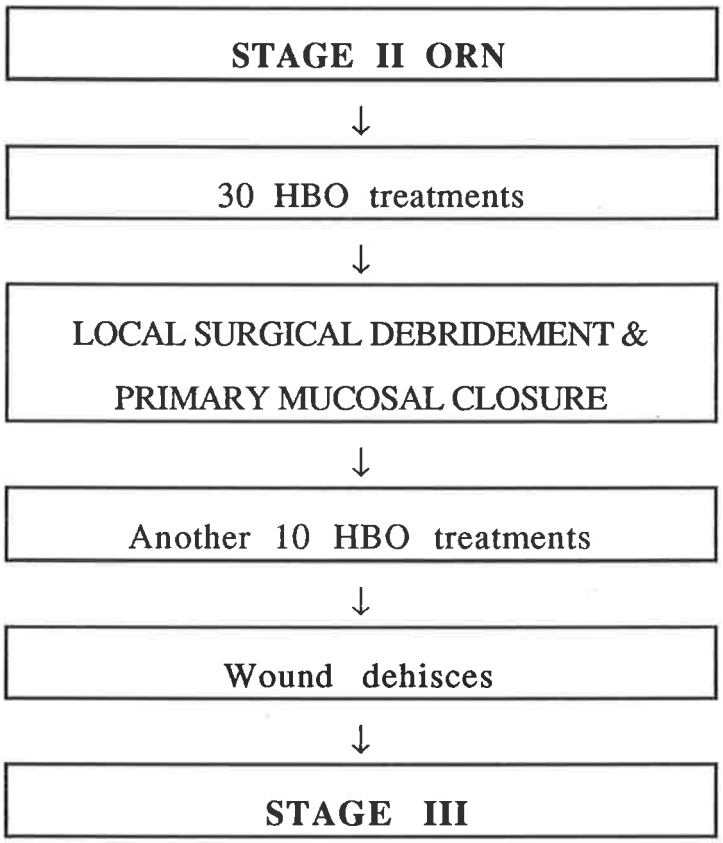
STAGE II OSTEORADIONECROSIS

Stage II occurs when there is failure of Stage I to HBO treatment, or where more alveolar bone is exposed.

Management involves hyperbaric treatment first followed by surgery then further post-surgical hyperbaric treatment. The site of radionecrosis involvement is usually only cortical or superficial bone and surgery involves a transoral alveolar sequestrectomy down to a base of bleeding bone with a primary mucosal closure. Minimal periosteal reflection is carried out for labial access and lingual periosteum is allowed to remain completely attached until the specimen is delivered, and only that which is attached to the specimen is reflected. Labial and lingual mucoperiosteal flaps are closed over a base of bleeding bone. Patients continue with a further ten HBO dives after surgery. If the wound dehisces, leaving exposed bone, the patient is identified as a non responder to Stage II and is advanced to Stage III.

A summary of Stage II Hyperbaric Oxygen - Surgery (Sequestrectomy) treatment protocol is presented Figure 7.2.

Figure 7.2 Stage II Hyperbaric Oxygen-Surgery treatment protocol

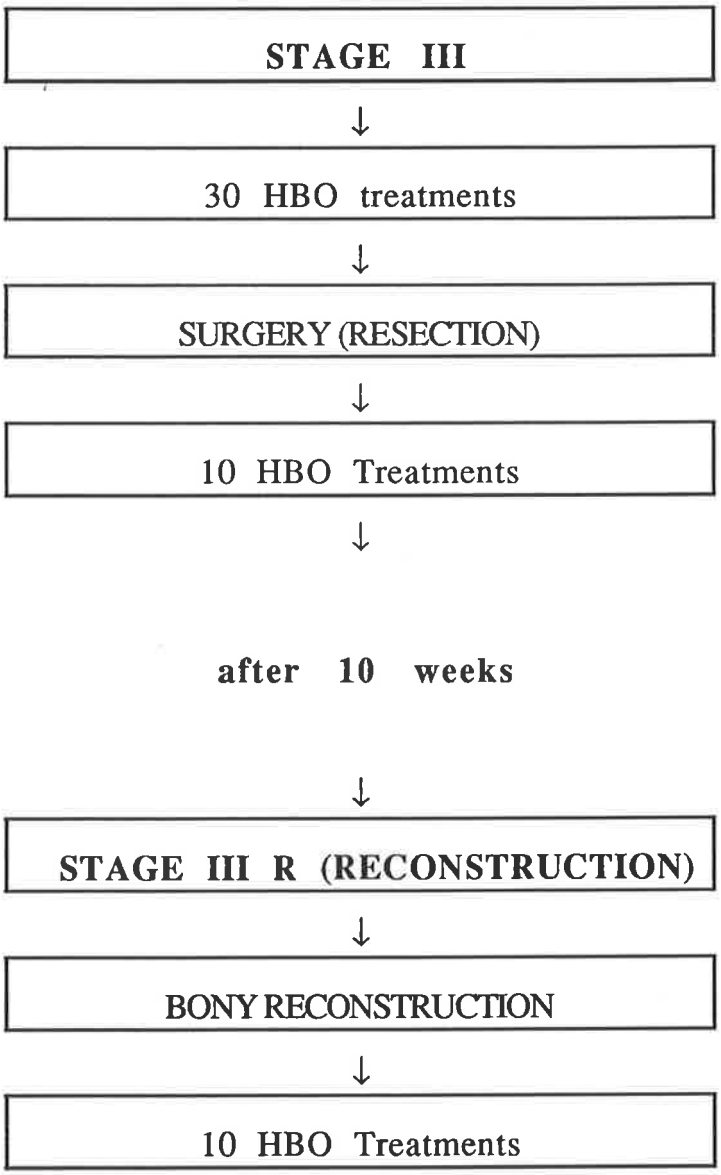


STAGE III OSTEORADIONECROSIS

Stage III individuals are patients with extensive areas of ORN where there is too great a mass of overtly dead bone to respond to anything less than jaw resection. The initial presentation of these patients includes either a pathologic fracture, orocutaneous fistula, or radiographic evidence of resorption to the inferior border. In Stage III, after an initial minimum course of 30 HBO dives, the patient undergoes a transoral partial jaw resection, the margins of which are determined at the time of surgery by the presence of bleeding bone. The mandibular segments are stabilised with either intermaxillary fixation or external skeletal pin fixation. Also if there is any oral dehiscence or orocutaneous fistula, deepithelialization and primary closure are done. The operation is in a compromised tissue environment, with a high potential for wound infection; perioperative prophylactic antibiotics are administered mainly to minimise this risk. Following surgical resection patients receive a further 10 HBO dives, and are given 10 weeks to allow for healthy mucosal closure, before they are advanced to Stage III-R (Reconstruction Stage).

In Stage III-R, 10 weeks after resection, the patient undergoes a bone graft reconstruction using a strictly transcutaneous approach, without oral contamination. Then 10 more HBO dives are given, and jaw fixation is maintained for 8 weeks. A summary of Stage III Hyperbaric Oxygen-Surgery (Resection) treatment protocol is presented in Figure 7.3.

Figure 7.3 Stage III Hyperbaric Oxygen-Surgery protocol

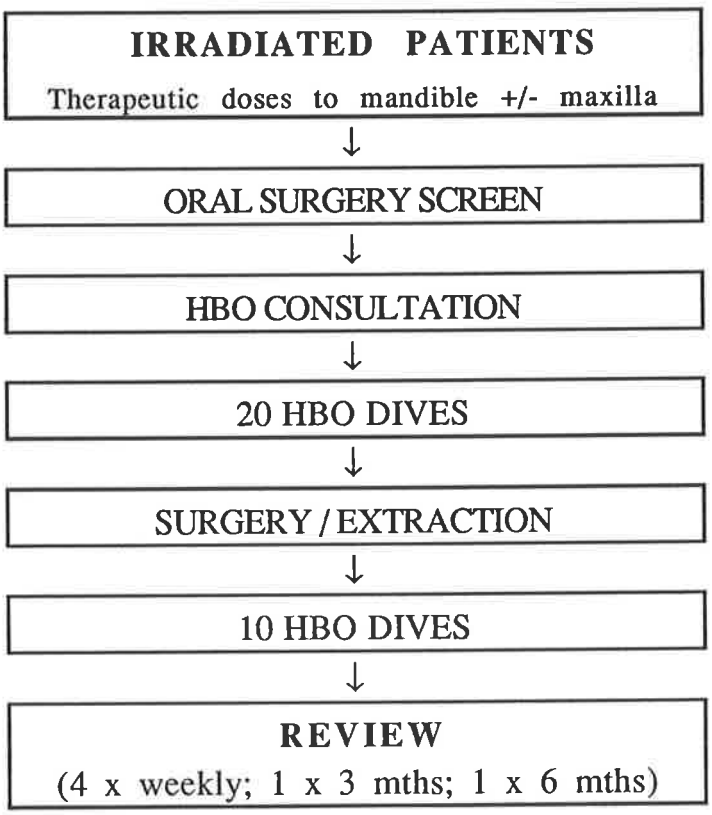


Hyperbaric Oxygen Prophylaxis Protocol for the Prevention of Osteoradionecrosis

Patients with a history of having received therapeutic doses of irradiation to the head and neck region for treatment of malignancy, and requiring dental extractions or oral surgery, received prophylactic HBO treatment pre and post-surgically for prevention of ORN. Patients received twenty sessions of HBO preoperatively and ten sessions postoperatively.

A summary of the HBO prophylaxis protocol is presented in Figure 7.4.

Figure 7.4: Hyperbaric Oxygen prophylactic protocol



7.2 Method

7.2.1 Data Collection

Data collection on all patients was divided into four sections which included:

(1) Pre-Hyperbaric Treatment History

Data included:

(a) Malignancy - date of, type, site and stage, and mode of treatment.
(b) Radiotherapy - date, dose, and whether mandible was in the primary beam.
(c) Preirradiation dental evaluation - dental status in both jaws whether dentate or edentulous, timing of tooth extraction and timing of prosthodontic treatment in relation to radiotherapy.
(d) ORN diagnosis - variables recorded at time of presentation with ORN included the date of onset, time interval from radiotherapy to ORN, initiating factors for radionecrosis, presence and severity of mucosal dehiscence, bone infection, pathologic fracture, and radiological appearance of facial bones.

The diagnosis of ORN was determined by identifying bone exposed three months or longer in irradiated regions of the facial bones and staged according to the

Marx-Wilford Hall USAF Medical Centre Protocol. (Table 7.1)

Table 7.1 Stages of Osteoradionecrosis

STAGE	I	Small area of bone involvement
	II	Failure of Stage I HBO treatment or More mandibular bone exposed
	III	Extensive bone involvement Pathologic fracture Orocutaneous fistula X-ray evidence of osteolysis to lower border of mandible Failure of Stage II

(e) Prehyperbaric Oral status evaluation - at the time of presentation for hyperbaric treatment, the dental state and oral function including presence of pain, analgesic requirement daily, food chewing ability, mouth opening and nature of saliva were recorded.

(2) Management of ORN / ORN Prevention

Variables recorded relating to management of ORN or ORN prevention included:

(a) Hyperbaric treatment duration, date commenced and date ceased, number of treatments, dive characteristics and duration, and presence or absence of hyperbaric complications.

(b) Type and description of surgery for ORN or type of dental/surgical treatment carried out which required prophylactic hyperbaric treatment.

(c) Antibiotics used alone or with surgery, the type, dose, route and the duration of antibiotics.

(3) Examination Post-Hyperbaric

At the time of examination, the following variables were recorded:

(a) Malignancy: duration from first presentation up to now, current state and current treatment of malignancy.

(b) Presence or absence of ORN and duration of first hyperbaric treatment to time of examination.

(c) Examination findings including the presence and degree of severity of mucosal dehiscence, skin dehiscence, bone infection, pathologic fracture, radiological appearance of the facial bones in comparison to prehyperbaric x-rays, dental state, type and use of prostheses.

Furthermore oral function was also evaluated including severity and frequency of pain, analgesic requirements, food chewing ability and saliva composition.

(4) Patient Questionnaire

At the time of examination, each patient was given a questionnaire regarding his or her opinion of the hyperbaric treatment. The patients were assessed as to whether they felt HBO changed how they felt generally, altered their eating ability, speech, jaw opening, mouth dryness and pain level.

Questions were included about their experience of the chamber; whether they would have the same hyperbaric treatment again, and whether they would recommend hyperbaric treatment to others with a similar problem. They were also invited to make any other comments on their experience.

7.2.2 Record Sheets

Record sheets were used to record the variables for each patient and categorised under four sections described above. These are in **Appendix 1.**

(1) Presentation - Prehyperbaric treatment history
(2) Management of ORN / ORN prevention including hyperbaric treatment, surgery, dental treatment, and antibiotics.
(3) Examination findings - Post hyperbaric
(4) Patient questionnaire

7.2.3 Sequence

Following patient informed consent to be in the study, casenotes were reviewed and record sheets (1) and (2) above were completed by members of the Hyperbaric Unit and Oral and Maxillofacial Surgery Unit. Further consultation and checking of data was carried out by members of both Units.

On completion of the initial retrospective data gathering, patients were examined at the Oral and Maxillofacial Surgery Department for evaluation of their oral and facial status, current oral function and progress. X-rays were reviewed and where necessary further x-rays were taken. Record sheets (3) and (4) were filled in during this outpatient examination.

The patients' participation in this study did not alter their current course of treatment, however any pathology detected on examination was treated accordingly. The data gathered were coded and computerised for descriptive statistics and presentation of results.

7.2.4 Six - Monthly Evaluation

Patients in the study were reviewed on a six monthly basis to monitor their progress. During this review they were checked for any signs of ORN, recurrence of malignancy, oral status and function, and radiological evaluation for evidence of disease in the irradiated region. Any complaints or disease process diagnosed

during this review were addressed by appropriate treatment or referral.

7.2.5 Statistical Analysis

The data gathered were coded and computerised for descriptive statistics and presentation of results.

The variables in the groups were assessed by the mean value, standard error and standard deviation using Stat View SE + Graphics 1.04. (Abacus Concepts Inc., 1988) The Student's t-test for unpaired values was used to determine the significance of differences for each group's response.

$\bar{x}$ Mean $\quad \frac{\Sigma x}{N}$

se Standard error of the mean $\quad \frac{s}{\sqrt{N}}$

r Correlation coefficient $\quad \frac{\Sigma (x-\bar{x})(y-\bar{y})}{\Sigma (x-x)^2 (y-y)^2}$

t Student's unpaired t-test

$$\frac{(\bar{x}_1 - \bar{x}_2)}{\sqrt{\frac{\left[\Sigma(x_1)^2 - \frac{\Sigma(x_1)^2}{N_1}\right] + \left[\Sigma(x_2)^2 - \frac{\Sigma(x_2)^2}{N_2}\right]}{2} * \left[\frac{N_1 + N_2}{N_1 N_2}\right]}}$$

$N_1 + N_2 - 2$

where N = number of determinations

s = standard deviation

x,y = observed scores

$\bar{x}_1$ = mean of the group 1 observations

$\bar{x}_2$ = mean of the group 2 observations

CHAPTER 8

ANIMAL EXPERIMENT TO CREATE AN OSTEORADIONECROSIS ANIMAL MODEL

8.1 Materials and Methods

This study was conducted in accordance with appropriate ethical guidelines as set down by the Animal Ethics Committee, The University of Adelaide (Approval number S/023/94).

Eleven (n=11) 10 week old male Sprague-Dawley rats, weighing 224 - 246g, comprised the experimental group. The animals were maintained in wire cages and held in a room with 12-hour light/day cycles with an ambient temperature of 21 degrees Celsius. The animals were allowed free access to water and standard laboratory pellets.

A span of irradiation doses below and above Marx's radiated rabbit model study (1990) dealing with radiation tissue damage was used.

An equivalent to Marx's actual dose of 17 fractions of 3.2 Gy per fraction would be 6 fractions of 6.00 Gy per fraction. This was calculated using an alpha beta ratio for human bone from Overgaard (1988) (Wigg, personal communication, 1994).

The eleven rats were grouped into 1 control animal and 5 pairs, with each pair receiving 4, 5, 6, 7, and 8 fractions of 6.00 Gy per fraction respectively, to give a span of doses below and above Marx's method. The control received no irradiation.

The 6.0 Gys were given as 2 fractions per week to a total of 4, 5, 6, 7, 8 fractions respectively.

The total cumulative radiotherapy dose received by each pair is shown in Table 8.1.

Table 8.1 Rat irradiation dosages.

RAT RADIOTHERAPY DOSAGES			
GROUP	**RAT NO.**	**No. of fractions (6.0Gy per fraction)**	**Total radiotherapy dose (Gy)**
C	CONTROL	none	0
1	I + II	4 x fractions	24 Gy
2	III	5 x fractions	30 Gy
3	IV +V	6 x fractions	36 Gy
4	VI + VII	7 x fractions	42 Gy
5	IX+X	8 x fractions	48 Gy

The facial region that was irradiated included the parotid and submandibular salivary glands as the posterior limit, the mandibular ramus and body including the mandibular artery with the anterior limit 1cm from the nose and the superior limit below the eye (Figure 8.1).

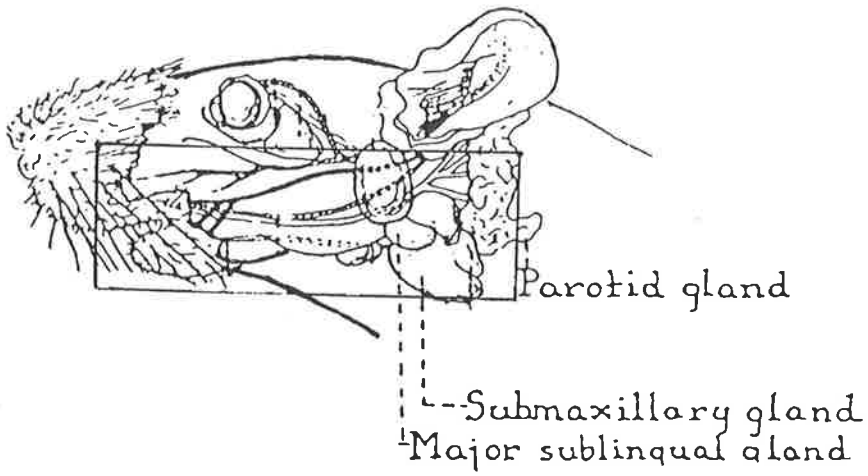


Figure 8.1 **Diagram illustrating the irradiation field on the rat mandible and surrounding tissues.** (Diagram modified from Farris and Griffith, 1949)

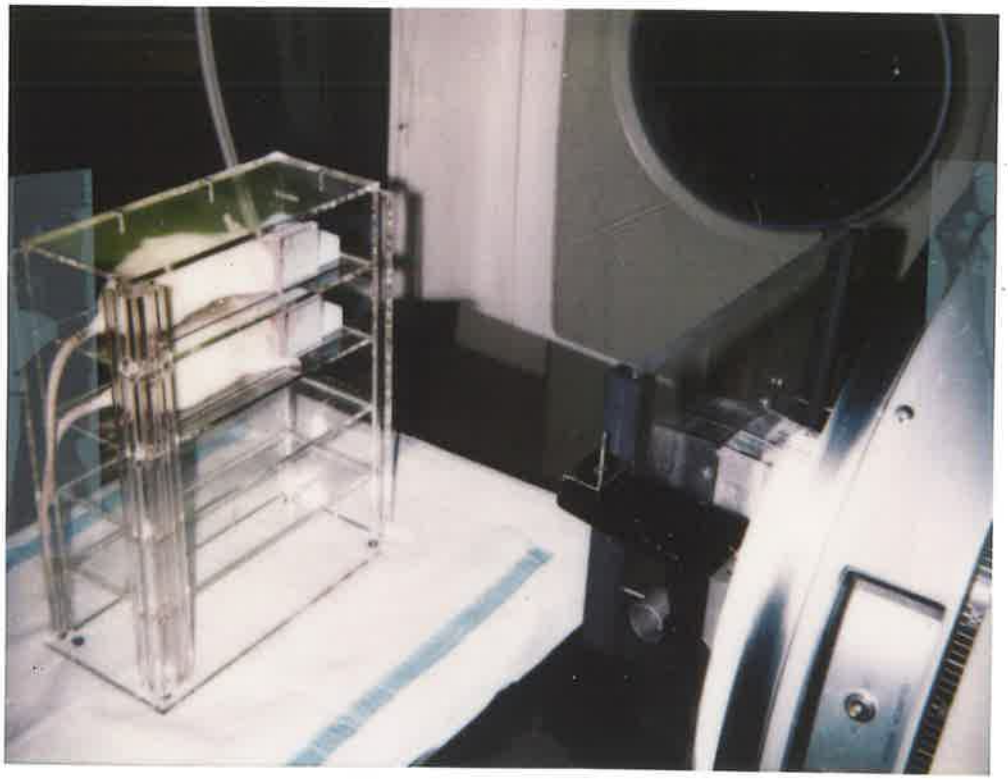


Figure 8.2 Photograph showing rats being irradiated.

Two rats were irradiated at a time placed prone on perspex plate and ramp. (Figure 8.2)

Each rat was anaesthestised using 0.1 ml Nembutal (Pentobarbitone sodium) intraperitoneal injection for immobilisation during irradiation of the mandible. This dose was calculated following the manufacturer's recommended dosage of 1 ml of the 6% solution (veterinary, 60 mg/ml) per 5 lb body weight.

The rats were monitored on a daily basis as per post-irradiation chart throughout the whole experiment. **(Appendix 2)**

Each pair of rats was allowed 6 months to develop hypovascular-hypocellular-hypoxic tissue as shown by time curves from Marx and Johnson (1987).

After 6 months a standard injury was created in the anterior alveolar region of the fully irradiated mandible.

For surgical anaesthesia, the rats were placed first in an ether chamber until they became drowsy and easily manageable. Then each rat was anaesthetised using 0.1 ml Nembutal intraperitoneal injection.

A 1cm incision was made along the alveolus in the edentulous area immediately posterior to the incisors. The mucosa was bisected and the mandible exposed. With a 2mm diameter round dental bur, a round hole was drilled 3mm through the outer cortex of the mandible.

The objective was to create a traumatic wound in an irradiated area simulating a surgical osseous injury. The wounds were not sutured and left to heal secondarily.

Care was taken during the operation to avoid aspiration of blood. This was done by meticulous gentle suction or by the use of cotton gauze swabs.

Immediate post-operative care included close monitoring of airway, the protrusion of the tongue to ensure a clear airway, and the placement of the head for unobstructed breathing and for drainage of blood by gravity.

Recovery from the anaesthetic was gradual and took an average of 2 hours to complete.

The wound was then reviewed for signs of healing or breakdown (osteoradionecrosis) over a further 6-month period.

At 12 months following commencement of irradiation each animal was sacrificed by intraperitoneal injections of 1.0 ml of the 6% Nembutal solution. This is 10 times the anaesthetic dose. Respiration would stop after an average of 5 - 10 minutes. At this point the rats were decapitated. The mandible was removed and fixed in 10% Formalin (10% Neutral Buffered Formalin) for 4 days. Fixation was at room temperature. The mandibles were then decalcified. Decalcification was monitored using x-ray end point determination. Radiographs were taken prior to decalcification and subsequent films were taken to check for absence of residual calcium in the bony tissues.

The rat mandible was sectioned at the mandibular symphysis following decalcification. The right half was used for histological assessment. It was subdivided into anterior, middle and posterior segments before subsequent processing and sectioning. The specimens were then washed for one day in running tap water, both to neutralise acid and to remove EDTA or salt precipitation on, or within, the tissue. Washing is necessary also, to neutralise the acid effects within the tissue itself, so that staining with Basophilic dyes, such as Haematoxylin, are not effected.

After decalcification the specimens were dehydrated and then embedded in wax. The anterior and posterior specimens of the mandible were used for evaluation. Ultrathin sections were cut with a microtome and mounted on slides (Figure 8.3). The anterior serial sections included the site of surgically induced trauma. All specimens were stained with haematoxylin and eosin. The staining procedure utilised is presented in **Appendix 3.**

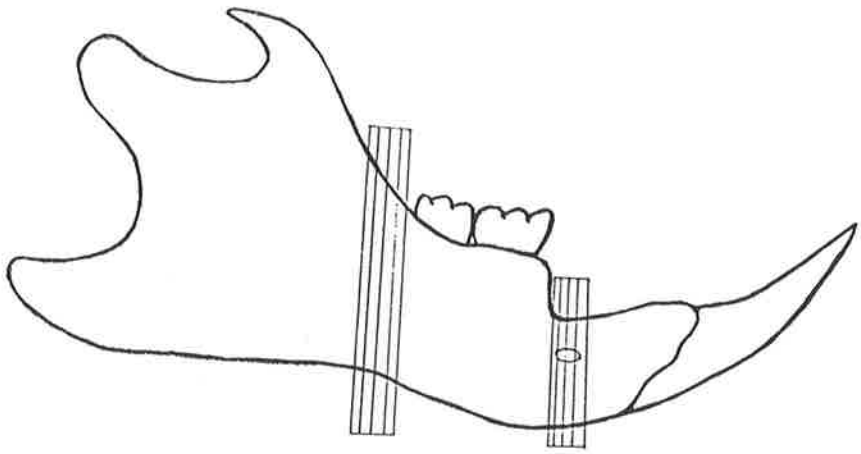


Figure 8.3 Right half of rat mandible illustrating site of anterior and posterior sections used for histological evaluation.

Histological evaluation was carried out looking for radiation tissue change or ORN The mandibular osseous tissue, vessels and surrounding soft tissue were evaluated for irradiation-induced changes and evidence of necrosis. Since multiple sections were examined from each specimen, the number of cells recorded was

the average observed from each specimen. The total cell count scores were based on the number of lacunae within a 1mm x 1mm square grid viewed under the light microscope using 100X magnification.

The inferior alveolar artery and its smaller branches were examined in each section for narrowing of the lumen. The extent of change relative to the internal elastic lamina was subjectively assessed as mild (up to 25% reduction in lumen), moderate (25 - 50% reduction in lumen) or severe (greater than 50% reduction in lumen). Multiple serial sections were examined from each specimen. The change recorded for the artery as a whole was the most advanced observed.

IV

RESULTS

CHAPTER 9

CLINICAL STUDY RESULTS

A total of 55 patients was referred to the Royal Adelaide Hospital Hyperbaric Unit for Hyperbaric Oxygen (HBO) treatment, either for ORN or for ORN prevention to their facial bones, from 1987 to February 1996. Out of this total, 18 patients had ORN and 37 patients had a history of irradiation to the head and neck region and required oral surgical procedures.

9.1 HBO Prophylaxis Group and Control Group Results

All 37 patients with a history of irradiation were referred to the RAH Hyperbaric Unit for prophylactic HBO therapy prior to surgical treatment or dental extractions. Of these, 30 received prophylactic HBO and in 7 cases HBO was contraindicated. These patients formed the control group (Table 9.1).

Table 9.1 Patient pool HBO Prophylaxis group and control group.

Patient Pool: HBO Prophylaxis & Control Groups		
37 patients - HISTORY OF IRRADIATION TO MANDIBLE		
ALL REFERRED FOR HBO		
OF THESE:	30	PROPHYLACTIC HBO PRESURGERY
	7	HBO CONTRAINDICATED - Control Group

Out of the 30 cases, 1 was excluded because of hyperbaric complications and 29 were included in the study. The patient who was excluded did not proceed to further surgical treatment.

9.1.2 Prophylactic HBO Control Group (n=7)

These were patients in whom HBO was contraindicated, or who developed HBO complications early requiring termination of HBO therapy. They formed the control group.

A summary of the contraindications is presented in Table 9.2. The control group patients included 3 (43%) who suffered from claustrophobia; 1 (14%) had tuberculosis during childhood leaving residual bullae in both apices of the lungs and thus was at risk of developing pulmonary barotrauma; 1 (14%) patient had spontaneously discharged a screw and pus, and was in severe pain, so HBO was not considered as urgent surgical treatment was indicated; 1 (14%) patient had 2 HBO dives and developed grade II barotrauma terminating his HBO treatment; and control patient number 7 (14%) had received prophylactic HBO therapy 6 months earlier prior to some dental extractions, however, this time he required a full dental clearance and did not have any further HBO therapy on recommendation from HBU consultants. Hence he was included in our control group.

Of the 20 males and 9 females in the prophylactic group, 21 (72%) were more than 50 years of age and there were 5 (18%) cases under 30 years of age. The mean age was 52 years. (Tables 9.3 & 9.4)

In the control group there were 6 (86%) males and 1 (14%) female. (Table 9.3 & 9.4) Six cases were more than 50 years of age, with a mean of 56 years.

A summary of patient data regarding tumour characteristics and surgical management and radiotherapy is presented in Tables 9.5-9.8. It is not the purpose of this report to try to identify aspects of tumour characteristics and/or radiotherapy which increase the risk

Table 9.2 Prophylactic HBO control group.

CONTROL GROUP	
Patient No:	**REASON FOR INCLUSION IN CONTROL GROUP**
1	Extreme claustrophobia
2	Extreme claustrophobia
3	Extreme claustrophobia
4	In pain, discharged mandibular screw + pus Required urgent surgical treatment
5	Childhood Tb with residual bullae At risk of developing pulmonary barotrauma
6	Grade II barotrauma after 2 HBO dives Ceased HBO treatment
7	Previous HBO therapy 6 months earlier for extractions. Recommended no further HBO required for dental clearance

Table 9.3 Age distribution of HBO prophylactic group and control group.

Group	No.	Age range (yrs)	Mean (yrs)	Std. Dev.	Age Distribution
HBO Prophylactic	29	20 - 73	52.586	15.5	< 30 yrs: 5 30-50yrs: 3 > 50 yrs: 21
Control	7	47 - 64	56.286	6.157	< 30 yrs: 0 30-50yrs: 1 > 50 yrs: 6

Table 9.4 Sex distribution of HBO prophylactic group and control group.

SEX	HBO PROPHYLACTIC GROUP	CONTROL GROUP
Male	20	6
Female	9	1
Total	29	7

of ORN, as these topics have been well-described in other reports (Epstein et al, 1987; Widmark et al, 1989). This report attempts to identify a group of patients with irradiated jaws and then tries to draw conclusions as to the prophylactic benefit of hyperbaric oxygen.

The type of malignancy is presented in Table 9.5. Squamous cell carcinoma was the predominant malignancy in both groups, accounting for 19 (66%) of the prophylactic cases and 6 (86%) of the control group. The remaining cases included 4 (14%) patients with lymphoma, 2 (7%) patients with mucoepidermoid carcinomas of the parotid,1 (3.4%) patient with adenoid cystic carcinoma, 1 (3.4%) patient with thyroid papillary carcinoma, 1 (3.4%) patient had chondrosarcoma of the mandible and a case each of meningioma (3.4%) and astrocytoma (14%).

The site of malignancy is presented in Table 9.6.

The sites of these lesions varied, but they were predominantly in the oral and pharyngeal regions. With the prophylactic group, 8 (28%) were in the pharynx, 14 (48%) were involved the oral region, 4 (14%) in the parotid, 1 (3%) involved the thyroid, and 1 (3%) was in the middle cranial fossa.

The control group lesions included 5 (70%) involving the oral region, 1 (14%) involving the larynx, and 1 (14%) involving the temporoparietal region

Table 9.5 Primary malignancy type requiring irradiation.

	HBO PROPHYLACTIC GROUP	CONTROL GROUP
MALIGNANCY TYPE	19 S.C.C.	6 S.C.C
	4 LYMPHOMAS	1 ASTROCYTOMA
	2 PAROTID TUMOURS	
	1 ADENOID CYSTIC CARCINOMA	
	1 THYROID PAPILLARY CARCINOMA	
	1 CHONDROSARCOMA	
	1 MENINGIOMA	
Total	29	7

Table 9.6 Site of malignancy.

	HBO PROPHYLACTIC GROUP		CONTROL GROUP
SITE	8	PHARYNX/LARYNX	3 TONSILLAR
	5	TONGUE- FLOOR OF MOUTH	1 TONGUE
	4	PAROTID REGION	1 SUBMANDIBULAR
	3	PALATE	1 LARYNX
	2	ANTERIOR MANDIBLE	1 TEMPOROPARIETAL
	2	RETROMOLAR REGION	
	2	TONSILLAR FOSSA	
	1	LOWER LIP + CHIN	
	1	THYROID	
	1	MIDDLE CRANIAL FOSSA	
TOTAL	29		7

The Head and Neck surgical treatment type is presented in Table 9.7.

Table 9.7 Surgical management of malignancy of HBO prophylactic patients and control group patients.

MALIGNANCY SURGICAL TREATMENT	HBO PROPHYLACTIC GROUP (n)	CONTROL GROUP (n)
NO SURGERY	6	0
LOCAL RESECTION	8	1
RADICAL RESECTION	15	6
TOTAL	29	7

Malignancies that required surgery have broadly been categorised into radical and local resection.

Radical surgery includes any major surgery such as a maxillectomy, laryngectomy, functional and radical neck dissection, with or without mandibular osteotomy, suprahyoid neck dissection in combination with mandibulectomies, or alveolectomies.

Local resections include local excision of tumours only with or without discontinuity of the organ involved or neck dissection.

The majority of patients had some form of surgical clearance of the tumour, with or without nodal resection. Fifteen (52%) patients in the prophylactic group had radical neck surgical treatment for

their malignancy, 8 (28%) patients had localised resection only, and 6 (21%) patients received irradiation treatment only and no surgery.

In the control group, 6 (86%) patients had radical neck surgery for their malignancy and 1 (14%) had local resection only.

The irradiation dose is presented in Table 9.8.

Table 9.8 Total cumulative radiotherapy dosages for HBO prophylactic group and control group.

TOTAL RADIOTHERAPY DOSE	HBO PROPHYLACTIC GROUP (n)	CONTROL GROUP (n)
30 - 50 Gy	4	
50 - 55 Gy	6	
60 - 66 Gy	14	3
Not known	5	4
Total	**29**	**7**

All patients received irradiation to the mandible. The cumulative dose of radiation to the mandible in both groups ranged from 30 to 66 grays (Gy). In the prophylactic group, 48% (14) of patients received irradiation in the range of 60 to 65 Gy, 21% (6) of patients received 50 to 55 Gy and 14% (4) of patients received less than 50 Gy. These latter 4 patients included 2 with squamous cell carcinomas involving the soft palate and retromolar region respectively, and 2 with lymphomas.

Of the control group, at least 3 (43%) cases received 60 to 64 Gy and we could not ascertain the irradiation doses in the remaining 4 cases (57%).

Radiotherapy dosages for 5 cases in the prophylactic group and 4 cases in the control group could not be obtained because some of these patients had irradiation some two to three decades ago, or they had received irradiation interstate.

The Hyperbaric Oxygen (HBO) management for the prophylactic group is presented in Table 9.9.

Out of the total of 29 patients, 25 (86%) patients received 20 pre-surgical HBO dives and 24 (83%) patients received at least 10 post-surgical HBO dives, as per the unit protocol.

There were 3 (10%) patients that developed HBO complications while having post-surgical treatment and terminated their HBO treatment prematurely, hence the 1 - 3 post-surgery HBO.

We have included 2 patients in the study who developed HBO complications following 8 and 9 presurgical dives respectively, since they already received the minimum dose required for irradiated tissue to respond. Collagen synthesis is stimulated in fibroblasts at the periphery of the irradiated field after 8 to 12 treatments which allows the initial phase of collagen synthesis and endothelial cell proliferation to take place (Marx 1984).

Table 9.9 Hyperbaric Oxygen management for prophylactic group.

HBO PROPHYLACTIC GROUP	
Patients (n)	**HBO Management**
2	Total 8-9 pre-surgery HBO only
3	Total 21-23 = 20 pre-surgery HBO 1-3 post-surgery HBO
21	Total 30 = 20 pre-surgery HBO 10 post-surgery HBO
1	Total 38 = 28 pre-surgery HBO 10 post-surgery HBO
1	Total 45 = 17 pre-surgery HBO 28 post-surgery HBO
1	Total 50 = 20 pre-surgery HBO 30 post-surgery HBO
Total 29	

One patient received 28 presurgical HBO dives because there was some concern about blood supply to her irradiated, reconstructed free osteomyocutaneous grafted mandible. She was worked up for insertion of 5 mandibular implants.

Note that in 3 patients the total HBO dive cycle of the Unit protocol was exceeded because clinical improvement appeared still to be taking place. One patient had a total of 50 dives, the usual 20 presurgical and 30 postsurgical, because he was very slow to heal postoperatively following removal of mandibular bone plates and insertion of 5 implants into his reconstructed free osteomyocutaneous grafted mandible. He was treated for three weeks postsurgically until the wounds had healed completely. This prolonged postoperative HBO treatment was due to poor clinical healing and concerns about blood supply to his mandible.

The surgical procedures carried out in these patients requiring prophylactic HBO therapy are presented in Table 9.10.

The majority, 76% (22) of cases, had dental extractions, alveoloplasties and primary closure of the wounds. 86% (19) of these cases received perioperative antibiotics. Postoperatively 95% (21) healed without any evidence of ORN. However 1 (4%) case developed ORN.

There was 1 (3%) case of resection of tumour recurrence, marginal mandibulectomy and extraction of remaining lower teeth; 1 (3%) case of removal of bone plates, extraction of two

Table 9.10 Oral surgical procedures requiring prophylactic HBO.

HBO PROPHYLACTIC GROUP			
Patients (n)	**Surgical Procedure**	**Perioperative Antibiotic**	**Outcome (Post-op)**
22	Extraction of teeth Md +/- Mx +primary closure	19 Yes	21 Healed 1 ORN
1	Marginal mandibulectomy, resection of tumour recurrence + extraction of lower teeth	Yes	Healed
1	Removal of bone plates + 2 molars - Insertion 5 x implants in mandible	Yes	Healed
1	Insertion 5 x maxillary implants + bone graft to maxillary alveolus	Yes	Healed
1	Removal of Mx Radicular cyst + extraction 3 Mx + 3 Md teeth	Yes	Healed
1	Insertion 2 x implants mandible	Yes	Healed
1	Cryofreeze R. Mandibular nerve for pain + removal of bone plates mandible	Yes	Healed
1	Insertion 5 implants into bone grafted mandible.	Yes	Healed
29		25 Yes	1 ORN 27 HEALED

mandibular molars and insertion of 5 mandibular implants; 1 (3%) case of removal of a large maxillary radicular cyst, and extraction of 3 posterior maxillary and mandibular teeth; 1 (3%) case of insertion of 2 mandibular implants; 1 case (3%) of bone graft and insertion of 5 implants to left maxilla; 1 case (3%) of cryofreeze of the right mandibular nerve for pain and removal of mandibular bone plates; and 1 (3%) case of insertion of 5 implants into bone grafted mandible. All these 7 (24%) cases received perioperative antibiotic cover and all healed well postoperatively without any evidence of ORN.

The antibiotic regimen used include Amoxycillin 1g or Penicillin G 1.2g intravenously preoperatively, followed by a 5 day oral course of Amoxycillin 500mg TID or Penicillin V 500mg QID respectively. Patients who were allergic to Penicillin received Cephalothin 1g intravenously preoperatively, followed by an oral course of Keflex 500mg QID for 5 days. The rationale for this was to provide coverage against potential pathogenic Gram positive micro-organisms in the oral cavity.

The surgical procedures carried out on patients in the control group is presented in Table 9.11.

Of the 7 cases, 4 (57%) had extraction of teeth and primary closure and these patients received perioperative antibiotics. Three of the cases healed and 1 (14%) developed ORN.

Table 9.11 Oral surgical procedures in Control Group.

CONTROL GROUP			
Patients (n)	**Surgical Procedure**	**Perioperative Antibiotic**	**Outcome (Post-op)**
4	Extraction of teeth + primary closure	4 Yes	3 Healed 1 ORN
1	Extraction of teeth Md+Mx + removal bone plates in mandible	1 Yes	Healed
1	Full dental clearance + removal of mandibular tori	1 Yes	Healed
1	Removal of exposed bone plate + excision of sinus tract	1 Yes	Healed
7		**7 Yes**	**1 ORN** **6 HEALED**

There was 1 (14%) case that had a full dental clearance, together with removal of mandibular tori and perioperative antibiotics. This healed without any complications.

Another case (14%) had removal of an exposed bone plate plus excision of an associated sinus tract, and perioperative antibiotics. This healed successfully.

One case (14%) had extraction of teeth from both arches, removal of mandibular bone plates and perioperative antibiotics. This case healed successfully.

Overall with the control group, 86% (6) of cases healed and 14% (1) developed ORN.

All patients (100%) received perioperative antibiotics based on empirical grounds. The general consensus was that these patients had irradiated tissues that lacked defence capabilities and placing them on perioperative antibiotics prevented the risk of wound infection and subsequent breakdown. There are no studies to support this practice however.

9.2 Osteoradionecrosis Group

Of the 18 patients who had ORN, 15 were included in the study and 3 were excluded. The 3 who were excluded were: one deceased patient for whom there was insufficient information for the study; a second patient who received presurgery HBO, but died at time of cancer recurrence resection in hospital; and a third patient who

received 4 HBO dives and stopped because of claustrophobia. This third patient did not have any further treatment for ORN and moved interstate with an untreated radionecrotic mandible. We had no success locating him and the only available information we could obtain from his interstate hospital notes was that he continued to have unresolved ORN in his mandible. In some ways this third case was the only control case that we had in this group because practically he did not receive any effective HBO therapy. He did not fit the criteria for a control case as he did not have any surgical debridement. However this case illustrates that the ORN process will usually continue unresolved if left untreated.

There was no control group of patients with the ORN group due to ethical reasons and the nature of this condition. The disease is extremely painful and frequently refractory to treatment, so to withhold HBO treatment is unethical. None of the patients, except for the case described in the above paragraph, had any contraindications to HBO therapy. There was no one who could be used as a control. Prior to the availability of HBO in the Royal Adelaide Hospital, many cases of ORN were treated. This was usually a protracted and often unsuccessful endeavour.

Approximately 150 patients per year receive irradiation to their head and neck region for treatment of malignant tumours at the Royal Adelaide Hospital Radiotherapy Department (personal communication). For the period of this study (9 years) the incidence of ORN in this hospital was 1.3%. (Table 9.12)

Table 9.12 Incidence of osteoradionecrosis.

INCIDENCE OF ORN
~ 150 Cases of Head and Neck irradiation per year
over 9 years (1987-1995) = 1350 patients with 18 ORN Cases
Incidence of ORN 1.3%

The age and sex distribution is presented in Table 9.13.

Table 9.13 Age and sex distribution of patients in osteoradionecrosis group.

OSTEORADIONECROSIS GROUP					
Number	**Age Range (yrs)**	**Range (yrs)**	**Mean**	**Std. Dev.**	**Age Profile**
15	45 - 73	28	61.47	8.42	14 patients > 50yrs 1 = 45yrs

Sex distribution	14 Males	1 Female

The age and sex distribution were consistent with that of head and neck cancer epidemiology. with the age ranging from 45 to 73 years. The majority (93%) of patients were 50 years or older. The mean age of the patients with ORN was 61.5 years.

Gender were predominantly males, with a ratio of 14:1.

A summary of patient data regarding tumour characteristics, surgical management and radiotherapy administered is presented in Tables 9.14 to 9.17. Again it is not the purpose of this report to try to identify aspects of tumour characteristics or radiotherapy which increase the risk of ORN. This report attempts to identify a group of patients with proven ORN and then draws conclusions as to the benefit of hyperbaric oxygen.

The tumour type and site is presented in Table 9.14 and 9.15.

Table 9.14 Malignancy type requiring radiotherapy.

OSTEORADIONECROSIS GROUP	
Numbers	**Malignancy Type**
13	Squamous cell carcinoma
1	Pleomorphic adenoma
1	Hodgkin's lymphoma
15	

The pathological diagnosis in most cases [87%] was squamous cell carcinoma. The remaining cases were pleomorphic adenoma and Hodgkin's lymphoma.

Table 9.15 Site of primary tumour.

Numbers (n)	Site of Primary Tumour
7	Tongue-Floor of mouth
2	Anterior fauces / Tonsillar region
2	Lower lip
1	Nasopharynx
1	Larynx
1	Palate
1	Parotid
15	

The sites of primary tumour occurrence varied; however, they mainly involved the oral and pharyngeal regions. The majority (47%) were located in the floor of mouth/tongue. Other sites included anterior fauces/tonsillar region, lower lip, nasopharynx, larynx, palate and parotid.

The Head and Neck surgical treatment type is presented in Table 9.16.

Table 9.16 Surgical management of primary malignancy.

Numbers (n)	Malignancy Treatment
7	Radical neck surgery
7	Conservative surgery
1	No surgery (Radiotherapy only)
15	

Almost half the patients (47%) had local excision of primary tumour only, followed by radiotherapy. An equal number (47%) had resection of primary tumour together with a radical neck dissection followed by radiotherapy. There was one case that received irradiation only and no surgery.

The irradiation dose is presented in Table 9.17.

Table 9.17 Irradiation dose administered.

Numbers (n)	Radiotherapy Dose
1	27 Gy
7	54 - 60 Gy Average 57 Gy
7	Not known
15	

All patients had irradiation of the primary tumour. Radiotherapy dosages for 7 cases were not known. The known radiation dosages received by patients varied from 27 to 60 Gy. The majority of patients received dosage schedules in the range of 54 to 60 Gy. The patient who received 27 Gy was the only case that received less than 54 Gy and unexpectedly developed radionecrosis involving the maxillary tuberosity. All patients received external beam irradiation with single daily dose fractionation.

In examining the radiation dosage administered, it is seen that ORN can occur despite fairly low-dose radiation, as occurred with the one case that received 27 Gy to the maxilla.

The site of ORN is presented in Table 9.18.

Table 9.18 Site of osteoradionecrosis.

Numbers (n)	SITE OF ORN
11	Mandible
3	Temporal bone
1	Maxillary tuberosity
15	

The mandible was the most common (73%) site of ORN involving the facial bones. Other sites include three involving the temporal bone and one unexpected case involving the maxillary tuberosity.

The predisposing factors involved in the initiation of ORN are presented in Table 9.19.

Table 9.19 Causes of ORN observed in study.

Numbers (n)	CAUSES OF ORN (Excluding Radiation)
9	Tooth extraction
1	Denture irritation
1	Osteotomy site for mandibular split (pre-radiotherapy)
4	Spontaneous (Idiopathic)
15	

Possible factors relating to the development of ORN following irradiation were analysed. The majority (60%) of cases were triggered by tooth extraction. They included 1 patient who had a dental clearance immediately before radiotherapy, at the time of surgical clearance of the tumour. This patient is now deceased and developed ORN 3 months after radiotherapy. It is unclear whether the extraction sockets had healed prior to commencement of radiotherapy. The other 8 cases developed ORN as result of dental extractions at some stage after irradiation. (Table 9.19)

There were 4 cases of spontaneous radionecrosis and 3 of these involved the temporal bone. The fourth spontaneous case involved the mandible.

The only case of maxillary ORN involved the tuberosity and was secondary to denture irritation.

There was also 1 case where ORN developed 8 months following irradiation at the osteotomy site (which had been fixated with plates) for the mandibulotomy for tumour access.

The time duration from radiotherapy to the onset of ORN in both the mandible and temporal bone is presented in Table 9.20.

Table 9.20 Duration from radiotherapy to onset of osteoradionecrosis.

Numbers (n)	Time duration from radiotherapy to onset of ORN (Mandible + Temporal bone)
3	3 - 6 months
2	6 - 12 months
6	2 - 3.5 years
2	5 - 6 years
2	30 - 36 years
15	

The range of time for the development of ORN was 3 months to 36 years from the time of primary radiation. Interestingly, 3 cases developed within 6 months following irradiation and a further 2 cases developed within 6 to 12 months. The majority (40%) of cases developed between 2 and 3.5 years following irradiation. There were 2 cases that developed between 5 and 6 years. No ORN cases developed between 6 and 30 years.

The longest time duration from radiotherapy to development of ORN involved 2 cases of spontaneous radionecrosis. Both were in the temporal bone, presenting 30 and 36 years later respectively.

The stages of ORN is presented in Table 9.21.

Table 9.21 Stages of osteoradionecrosis.

Numbers (n)	Stages of ORN
6	Stage I
8	Stage II
1	Stage III
15	

All patients had some visible exposed bone. The majority of patients were classified as either a Stage I (40%) or Stage II (53%) ORN. There was one Stage III case in the series. It is obvious from this study that these cases were diagnosed fairly early in the necrosis process, except for the one Stage III case which had developed a pathologic fracture.

The Hyperbaric Oxygen (HBO) management is presented in Table 9.22.

Table 9.22 Hyperbaric oxygen management.

Numbers (n)	Stage of ORN	HBO Treatment (dives)
6	Stage I	22-37 (Av. 32)
8	Stage II	37-94 (Av. 51)
1	Stage III	80
15		

All 15 patients with a diagnosis of ORN were treated with HBO therapy following the current unit protocol. The number of hyperbaric treatments increased with the severity of the disease process. We also noted that the total dive cycles of the Unit protocol were exceeded because clinical improvement appeared still to be occurring.

Treatment options used in addition to HBO and oral hygiene regimens included antibiotics and surgery. All 15 patients received a dental evaluation, regular follow-up, and regular oral hygiene care.

The surgical management of the ORN and outcome is presented in Table 9.23.

Table 9.23 Surgical management of osteoradionecrosis.

Stage of ORN	Numbers (n)	Surgical Treatment	Perioperative Antibiotics
Stage I	6	No surgery (Conservative Tx)	1 (Inpatient care)
Stage II	8	Local debridement	5 Intraop + postop
Stage III	1	Segmental resection + reconstruction	1 Intraop + postop
	15		7

The outcome of our combined HBO-Surgical approach is presented in Table 9.24. Surgery was required in 60% of the cases, but all cases in the study healed with mucosal coverage of the exposed bony sites. Antibiotics and oral rinses were used in most cases.

Table 9.24 Outcome of ORN management.

Stage of ORN	Numbers (n)	Outcome (12 mth follow-up)
Stage I	6	All healed completely
Stage II	8	All healed completely
Stage III	1	Healed completely
	15	All healed completely

The criteria for success according to Marx (1983) in this treatment are presented in Table 9.25. These criteria were met in all cases.

Table 9.25 Marx's criteria for resolution of osteoradionecrosis.

FOUR CRITERIA OF RESOLUTION
1. Freedom from pain.
2. Retention or reconstruction of mandibular continuity.
3. Restoration of mandibular function and wearing of prosthodontic appliances, if needed.
4. Maintenance of intact mucosa over all bone for the length of follow-up (minimum acceptable time is preferably 12 mths).

Conservative management of ORN included irrigation and gentle debridement of the sites with removal of loose bony spicules as indicated. All six Stage I cases showed complete resolution of ORN with HBO alone and one of these received antibiotics. The case that had antibiotics received this as a prophylactic cover against potential secondary infection of the wound. The same principle applies to the rest of the cases that received perioperative antibiotics. Only 1 case received less than 30 HBO dives due to hyperbaric complications in the form of a left ear barotrauma,

which required myringotomy and pressure equalisation tubes. At twelve months review all Stage I cases satisfied the criteria of resolution.

Surgery was used in conjunction with HBO in Stages II and III cases. HBO cannot revitalise necrotic bone and hence surgery is required in a high percentage of cases. Surgery was performed to remove sequestra and to obtain soft tissue closure to aid healing. With these cases, surgery was preceded by preoperative HBO. The surgical procedures varied from local debridement of bone, to wide mandibular resections requiring reconstruction.

With all the Stage II cases surgical sequestrectomy was carried out and none required mandibular resection for the management of ORN. The Stage II patients had a marked variation in the number of hyperbaric dives, which reflects on the unpredictability of this disease and the unpredictability of HBO. Normally patients in Stage II receive 30 HBO treatments first, followed by surgical debridement of necrotic bone, then a further 10 post-operative hyperbaric oxygen dives. In all cases, nonviable bone was debrided to a base of bleeding bone and primary wound closure was attained for each case.

Four Stage II patients received a total of 37 to 39 hyperbaric dives which was consistent with our HBO treatment protocol. However 3 patients received 49 to 60 dives and 1, 90 dives. These latter 3 cases followed the Unit protocol but developed wound dehiscence at the operative site two to three weeks post-operatively. Following consultation with the Hyperbaric consultants it was felt

on empiric grounds that these patients should have a further 10 dives before a second surgical debridement, followed by another 10 post-operative hyperbaric dives. The amount of bone exposure was minimal and did not fit the criteria of Stage III. These four problematic cases clearly demonstrate how ORN is frequently refractory to treatment.

One Stage II ORN case received a total of 90 HBO dives. This particular case was the first ORN of the mandible to be treated in early 1987, when we were in the early days of developing and refining our treatment protocol. It was a problematic case which required two surgical debridements under general anaesthesia, and three months of postsequestrectomy HBO treatment. The patient kept producing small sequestra which were removed on three successive occasions in Outpatients over a four-month period. The healing process was slow, and it was felt that HBO should be continued until the wounds healed completely, hence the long postoperative HBO course. In many ways it reinforces the difficulty and variability in managing this disease process. It also illustrates how each case is different, although they may be staged the same.

There was only 1 case of Stage III ORN which was treated successfully using the protocol. This case was treated with 30 preoperative HBO dives, followed by a transoral sequestrectomy to bleeding bone, and primary closure of soft tissues. A further 10 HBO dives was given postoperatively, and a 10 week period was allowed for good soft tissue healing before the patient was advanced to Stage III R (reconstruction). In this final stage the

mandible was reconstructed via a transcutaneous approach to minimise the risk of infection. Corticocancellous bone was harvested from the anterior iliac crest, compressed and packed into a dacron (alloplastic) mesh tray, which was used to reconstruct the discontinuity defect in the mandible. The wound was closed primarily. A further 10 HBO dives was given postoperatively. Regular follow up review was maintained. Three years postoperatively the patient maintained a good functional mandible with good continuity and no further evidence of ORN. This case satisfied Marx and Ames (1982) criteria for successful reconstruction.

The majority of patients with Stage II (and Stage III) ORN received various combinations of treatment including HBO, perioperative antibiotics and surgery. The antibiotic used was either intravenous penicillin 1.2g or Amoxycillin 1g or cephalothin 1g intraoperatively, followed by a short 5 day oral course postoperatively. Metronidazole was used in combination with penicillin in one instance. No patient was on antibiotics for more than a week.

The Hyperbaric Oxygen therapy experience of patients who received treatment for ORN was reviewed. Only 7 patients in the ORN treatment group participated in the HBO experience questionnaires. This was due to 6 deceased patients and 3 who failed to return their forms. Table 9.26 is a summary of their subjective experience.

Table 9.26 Hyperbaric oxygen therapy experience of patients treated for osteoradionecrosis.

OSTEORADIONECROSIS HBO TREATMENT GROUP			
HYPERBARIC OXYGEN EXPERIENCE: HOW THEY FELT AFTER COMPLETING HBO TREATMENT			
	SAME	**BETTER**	**WORSE**
GENERALLY	57%	43%	
EATING ABILITY	71%		29%
TALKING	71%	14%	14%
JAW OPENING	100%		
MOUTH DRYNESS	71%	14%	14%
PAIN	71%	14%	14%
CHAMBER EXPERIENCE	86% BEARABLE	14% PLEASURABLE	
HAVE SAME TREATMENT AGAIN?	86% YES	14% NO	
RECOMMEND HBO Tx TO SOMEONE ELSE	86% YES	14% NO	

Of the patients who participated in the questionnaire, 43% felt generally better and 57% felt that HBO therapy made no difference to their general state. In assessing patients masticatory ability, 71% felt HBO made no difference and 2 (29%) patients claimed

their eating ability was worse. However, this disability was due to difficulty wearing dentures and was not directly related to HBO therapy.

Jaw opening was the same after HBO therapy in all (100%) patients. Reviewing xerostomia, 71% of patients felt HBO made no difference, 14% felt better and 14% felt their mouth dryness was worse.

With pain levels in these patients, 71% felt HBO therapy made no difference to their facial pain. One patient felt his pain had resolved, and another stated his pain was worse. With the case that felt better, the pain ceased following resolution of his ORN from a combined HBO and surgical approach.

Although 86% of patients described being in the hyperbaric chamber as bearable, these same patients would also have the same hyperbaric treatment again, and would recommend the same treatment to others with a similar problem. One patient (14%) described the chamber experience as pleasurable while another (14%) was disappointed. This latter patient would not have the same treatment again nor would he recommend it to anyone else. He was the same patient who stated his pain was worse.

Similarly, the Hyperbaric Oxygen therapy experience of patients who received prophylactic HBO treatment for prevention of ORN was evaluated. A total of 19 patients responded to the HBO experience questionnaire. Their subjective experience is presented in Table 9.27.

Table 9.27 Hyperbaric oxygen experience of patients treated prophylactically.

PROPHYLACTIC HBO PATIENTS			
HYPERBARIC OXYGEN EXPERIENCE: HOW THEY FELT AFTER COMPLETING HBO TREATMENT.			
	SAME	**BETTER**	**WORSE**
GENERALLY	37%	58%	5%
EATING ABILITY	74%	11%	5%
TALKING	84%	11%	5%
JAW OPENING	74%	21%	5%
MOUTH DRYNESS	53%	32%	16%
PAIN	58%	37%	5%
CHAMBER EXPERIENCE	26% PLEASURABLE	68% BEARABLE	5% UNBEARABLE (pulmonary oxygen toxicity)
HAVE SAME TREATMENT AGAIN?	95% YES		5% NO
RECOMMEND HBO Tx TO SOMEONE ELSE	100% YES		

Generally, 63% of patients felt better and 37% felt the same as prior to HBO treatment. With masticatory function, 74% felt HBO

made no difference to their eating ability, 21% felt it was better, and 1 patient (5%) felt it was worse. It was uncertain why this last patient's eating ability got worse. It was probably related to ear barotrauma and some difficulties he had with swallowing.

With speech, 84% felt there was no change, 11% felt it was better, and 1 patient (5%) felt it was worse. This last case was experiencing mouth swelling in the morning which improved later in the day, for the last 6 months before HBO treatment. The swelling was due to lymphoedema secondary to irradiation. The difficulty with talking was not due to HBO.

In relation to jaw opening, 74% felt it was the same, 21% felt it was better, and 1 patient (5%) thought it was worse; however he failed to elaborate further.

Reviewing mouth dryness, 53% said HBO had no effect, 32% experienced improvement and 16% felt it was worse. This deteriorating xerostomia was most certainly due to the continuing effects of irradiation on salivary gland tissue.

Pain levels were the same in 58% of patients, better in 37% and worse in 1 patient (5%). The worsening pain in the last case was a cumulative effect of increasing dryness of the mouth, burning mouth sensation and difficulty wearing dentures. This same patient also complained that his speech and mouth dryness were worse.

Chamber experience was pleasurable to 26% of patients, bearable to 68% and unbearable to 1 (5%) patient, as a result of pulmonary oxygen toxicity. This last case was a different individual who terminated HBO therapy after 9 dives following complications. Apart from improvement in mouth dryness, this patient felt HBO had no other beneficial effects. Understandably, this patient refused to have the same treatment again. However, 95% of patients said they would have the same treatment again if it was necessary and all (100%) patients would recommend treatment to others with the same problem.

Statistical Analysis

Patients attitudinal responses to HBO therapy were further assessed statistically. (Tables 9.28 + 9.29) The responses to the HBO experience questionnaire were divided into two groups:

Group 1: Patients in whom HBO made no difference or worse.
Group 2: Patients in whom HBO had positive attributes.

The null hypothesis (H_0) is that HBO therapy makes no difference to patients general well being and oral function. The alternate hypothesis (H_1) is that HBO makes a difference.

For the ORN treatment group, the critical t-value at 0.0001 level for 16 degrees of freedom, is well below that of our calculated t value. H_0 is therefore rejected in favour of H_1. That is, HBO therapy does make a difference to the patient's general state of mind. (Table 9.28)

Table 9.28 Statistical analysis of ORN treatment group HBO experience.

OSTEORADIONECROSIS TREATMENT GROUP: HBO EXPERIENCE				
Unpaired t_1-test X: Column 1			Y: Column 2	
Degree of freedom	Unpaired t-Value		Prob. (2-tail)	
6	12.265		0.0001	
GROUP	COUNT	MEAN	Std. Dev.	Std. Error
GROUP 1	9	85.889	12.414	4.138
GROUP 2	9	14.111	12.414	4.138

Table 9.29 Statistical analysis of prophylactic HBO group HBO experience.

PROPHYLACTIC HBO GROUP : HBO EXPERIENCE				
Unpaired t-test X: Column 1			Y: Column 2	
Degrees of freedom	Unpaired t value		Prob. (2-tail)	
16	4.007		0.001	
Group	Count	Mean	Std. Dev.	Std. Error
Group 1	9	71.889	23. 176	7.725
Group 2	9	28.111	23.176	7.725

The result of the prophylactic HBO analysis, where there are 16 degrees of freedom, gives an unpaired t value of 4.007 and with a probability of 0.001, the calculated t value is less than the critical value (4.015). Therefore we retain the null hypothesis. That is, in the HBO prophylactic group, HBO therapy makes no difference to patients.

The HBO complications encountered by patients in both the ORN treatment and prophylactic HBO groups during the course of treatment are presented in Table 9.30.

Table 9.30 HBO complications for both ORN and prophylactic HBO groups.

Numbers (n)	Percentage(%)	Complications
26	59%	No complications
15	34%	Barotrauma of the ear
1	2%	Tinnitus
1	2%	Pulmonary Toxicity
1	2%	Dizziness
44	100 %	

Overall, the majority (59%) of patients suffered no complication of HBO. The commonest side-effect was ear barotrauma, affecting 34% of patients. Other side-effects of HBO encountered include tinnitus associated with one ear, eustachian tube blockage, pulmonary toxicity and dizziness.

Aural barotrauma is ear pressure trauma. Patients usually complain of ear pain and ringing in the ears. In this study, most of those affected (9 cases) experienced mild and unilateral barotrauma. However 4 patients suffered Grade II bilateral barotrauma. Treatment usually involves placement of grommets, or pressure equalisation tubes, into the tympanic membrane, which are left in-situ for the duration of HBO treatment.

Cost Evaluation

The total cost parameters to treat patients with a protocol of HBO versus non-HBO were analysed. These were calculated from a review of the patients' averages in the study. All costs were based on prevailing cost and Medicare Fee Schedule, in Australian dollars as of July 1st, 1996. The HBO fee was $500 per dive, which covered everything including consultation, investigations, nursing and medical treatment (Pirone, C. personal communication). This figure was calculated from the total cost of running the Hyperbaric Unit for the July 1, 1995 to June 30, 1996 financial year, divided by the total number of patients treated during this period. Since the Unit treated fewer patients during this time, consequently the fee was higher as compared to previous years, when the fee ranged from $380 to $450. Other costs incorporated in the calculations include inpatient fees, surgical treatment and outpatient fees over a year.

The non-HBO costs were determined from the average cost of managing Stage II - III size ORN lesions without HBO over a year, plus ongoing surgical retreatment costs over a five year period. In

our experience, these lesions may require annual surgery for up to five years and usually only 50% resolve. For non-HBO cases, Marx et al in 1985 reported a resolution rate of 8%.

Not apparent on the above non-HBO calculations are the hidden costs. These include patients attending other institutions for continuing treatment and unseen social costs of pain and job absenteeism (Marx et al 1985).

The HBO treatment costs is presented in Table 9.31.

The analysis reveals that the average 1-year cost of ORN management using HBO ranged from $24,000 for Stage I treatment to $33,000 for severe cases. These costs parallel the findings of Marx et al (1985). Treating ORN without HBO is more expensive because of the need to continuously treat an unresolving disease. The prevention of this condition was almost $8,000 dollars cheaper per patient than managing the disease. A 96% prevention rate with prophylactic HBO is certainly cost effective.

Table 9.31 Cost evaluation of HBO protocols versus non-HBO.

COST ANALYSIS	
PROPHYLACTIC HBO vs ORN	
Average 1 year cost	**RESOLUTION RATE**
ORN Stage I (Av. 32 Tx) $24,000	100%
Stage II (Av. 51 Tx) $28,000	100%
Stage III (50 Tx) $33,000	100%
PROPHYLACTIC HBO (30 Tx) $15,000	96% PREVENTION RATE
NON-HBO ORN TREATMENT Surgical Cost + Inpatient Cost + Outpatient Cost $14,000 per year Ongoing Surgical cost over 5 yrs $42,000	**8%** RESOLUTION RATE (Marx) **< 50% RESOLUTION**

CHAPTER 10

ANIMAL STUDY RESULTS

Rat no. VIII died from pentobarbitone (Nembutal) overdose following the first irradiation treatment. This rat was excluded from the study. For this reason there was only one rat in Group 2.

The animals tolerated the experimental conditions well initially. However, at week 2, the first signs of the clinical side effects of irradiation started to appear. Half the animals had lost body weight and the other half had no or minimal weight gain. This weight loss was observed at the time acute dryness of the mouth was first noticed. Presumably the acute xerostomia created some difficulty with mastication and swallowing, particularly with the dry solid laboratory pellets. However this was corrected by moistening the laboratory pellets prior to placement in the cages. This resulted in a swift significant weight gain. Rats IX and X were the most significantly affected with dry mouth in the study.

Weekly review of the wounded mandible over a 6 month period showed mucosal closure over the area of the bony injury in all the rats. This was evident from the second week following the injury.

Despite the surgical incision site having an erythematous mucosa, the soft tissues had healed with no evidence of tissue necrosis. Clinically, slower wound healing was observed with increasing radiotherapy, but all surgical wounds healed. (Figure 10.1 & 10.2) At the end of the 6 months period, none of the animals developed ORN.

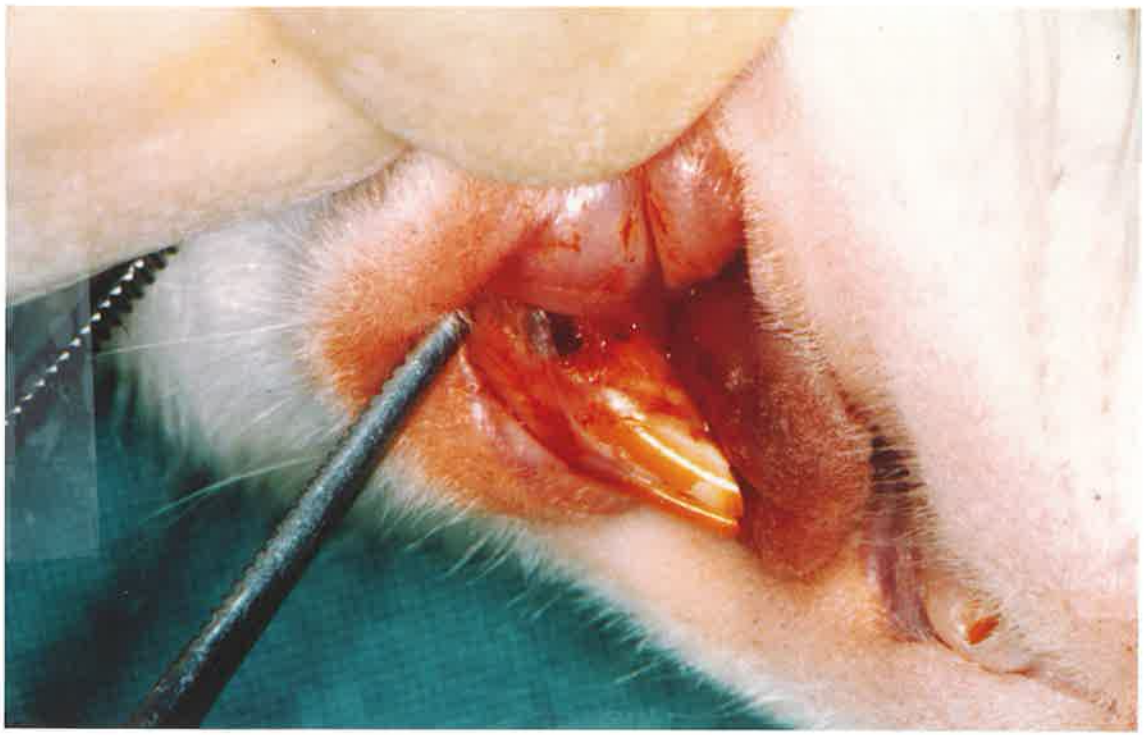


Figure 10.1 Clinical photo of surgically induced traumatic wound in anterior mandible of rat X.

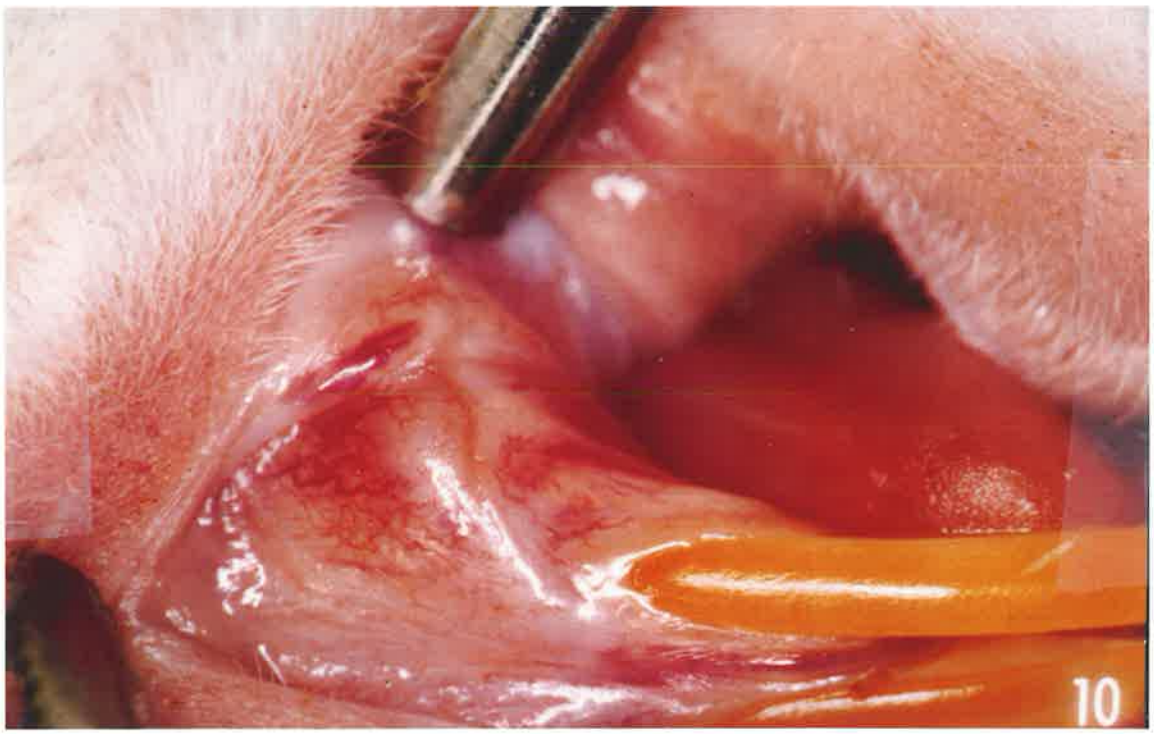


Figure 10.2 Wound at six months healed but with persistent erythema at wound site(rat X).

The histological evaluation of the irradiated mandible is presented in Tables 10.1 and 10.2. They illustrate the osseous tissue cell numbers observed in sections taken from the anterior and posterior mandible respectively.

Table 10.1 Anterior irradiated mandible histological assessment.

RAT No:	BONE CELLULAR DENSITY ANTERIOR MANDIBLE			BONE THICKNESS (microns)
	Lacunae with cells	Empty lacunae	TOTAL CELLS	periosteum to peripheral resting line
CONTROL	22	3	25	15
I	20	3	23	15
II	19	4	23	10
III	22	2	24	15
IV	16	2	18	20
V	18	1	19	20
VI	24	2	26	15
VII	27	2	29	10
IX	30	3	33	10
X	33	4	37	15

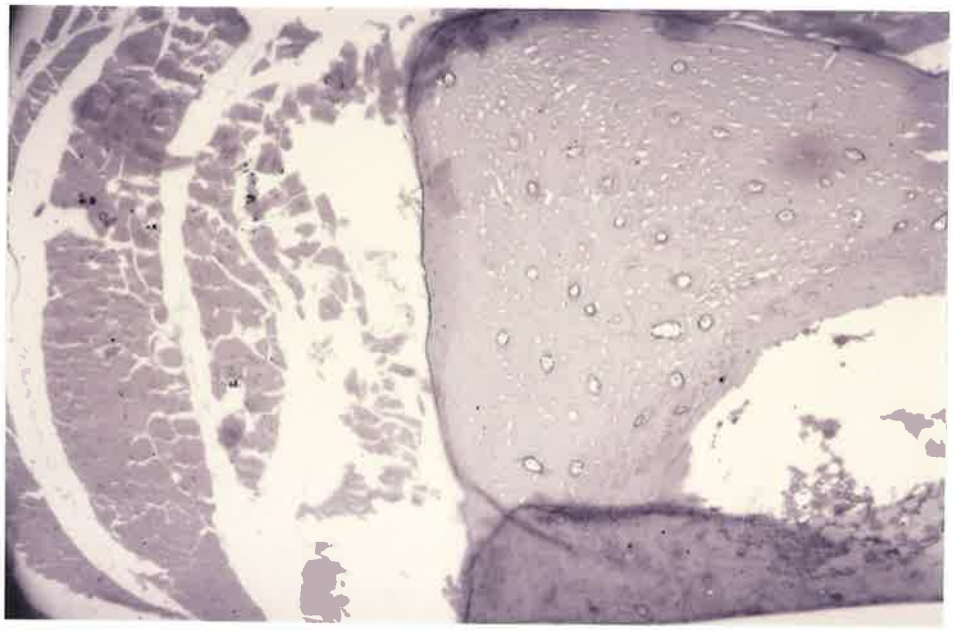
Table 10.2 Posterior irradiated mandible histological assessment.

RAT No:	BONE CELLULAR DENSITY POSTERIOR MANDIBLE			BONE THICKNESS (microns)
	Lacunae with cells	Empty lacunae	TOTAL CELLS	periosteum to peripheral resting line
CONTROL	27	2	29	25
I	22	3	25	25
II	24	2	26	50
III	23	3	26	50
IV	23	3	26	50
V	24	3	27	50
VI	35	3	38	50
VIII	37	3	40	50
IX	32	5	37	10
X	35	3	38	50

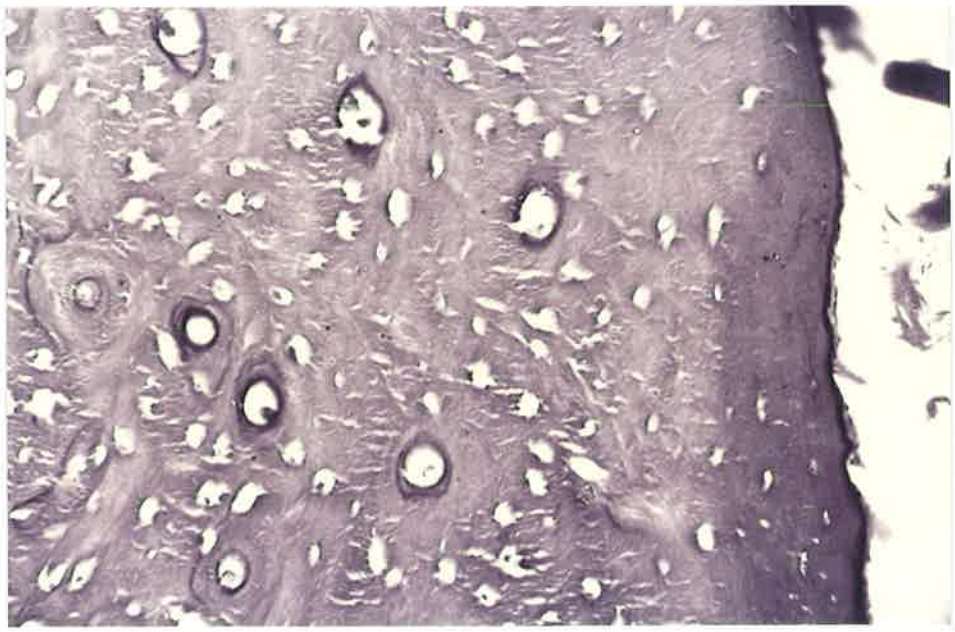
Total cell counts from both anterior and posterior sections of the mandible showed that there were increased cell numbers in rats that received a higher irradiation dosages.

In the cortical bone a few lacunae were empty, indicating osteocytic death. However, the number of empty lacunae were consistently small throughout the tissue sections and no obvious trend was observed.

Figure 10.3 **Photomicrographs of histological section of lower border of posterior mandible from control animal.**

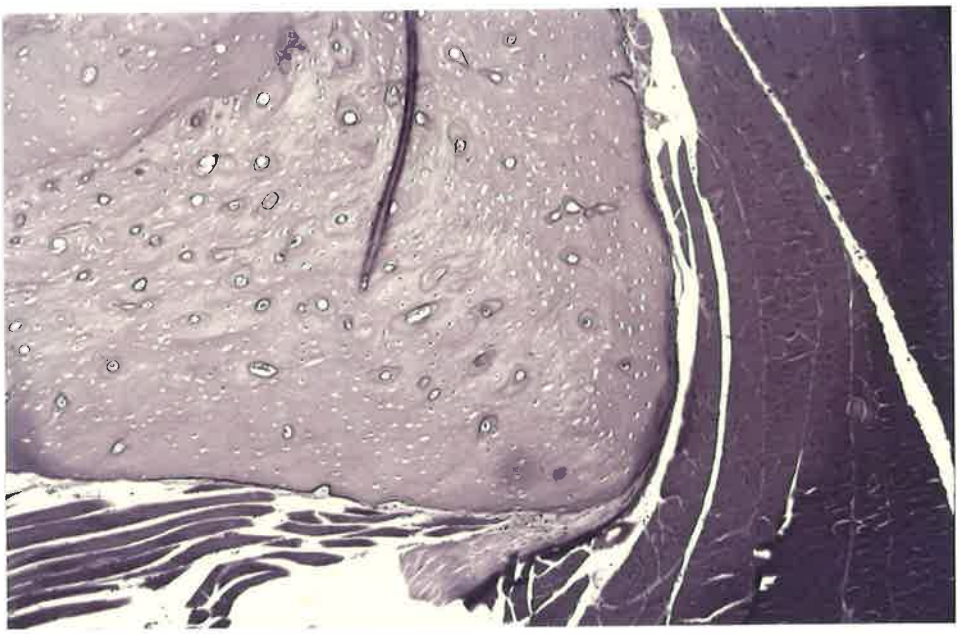


(a) H + E stain (x10 objective)

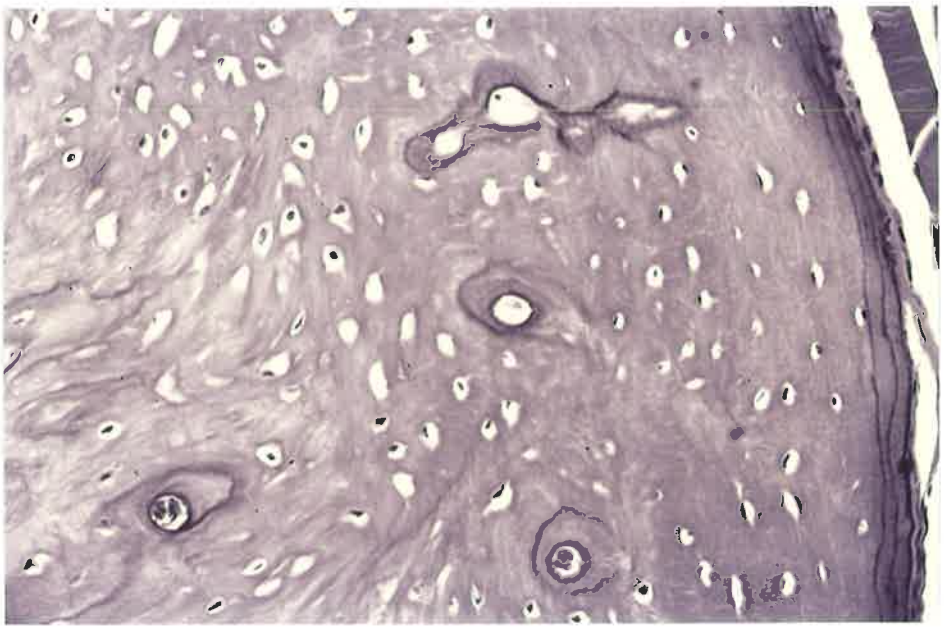


(b) H + E stain (x 40 objective)

Figure 10.4 **Photomicrographs of histological section of lower border of posterior mandible from rat x** (highest irradiation). **Note increased osseous cellularity.**

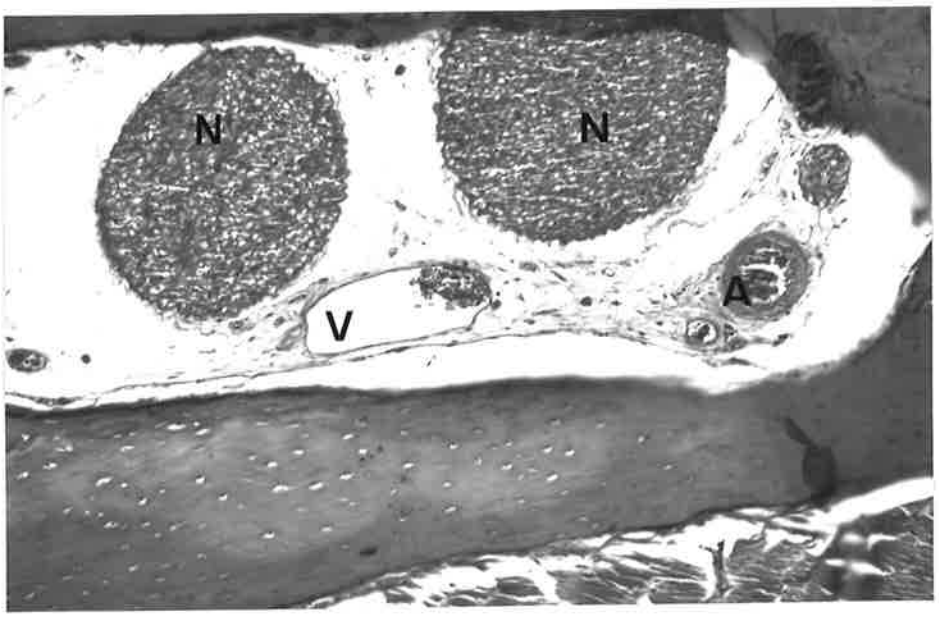


(a) H+E stain (x10 objective)

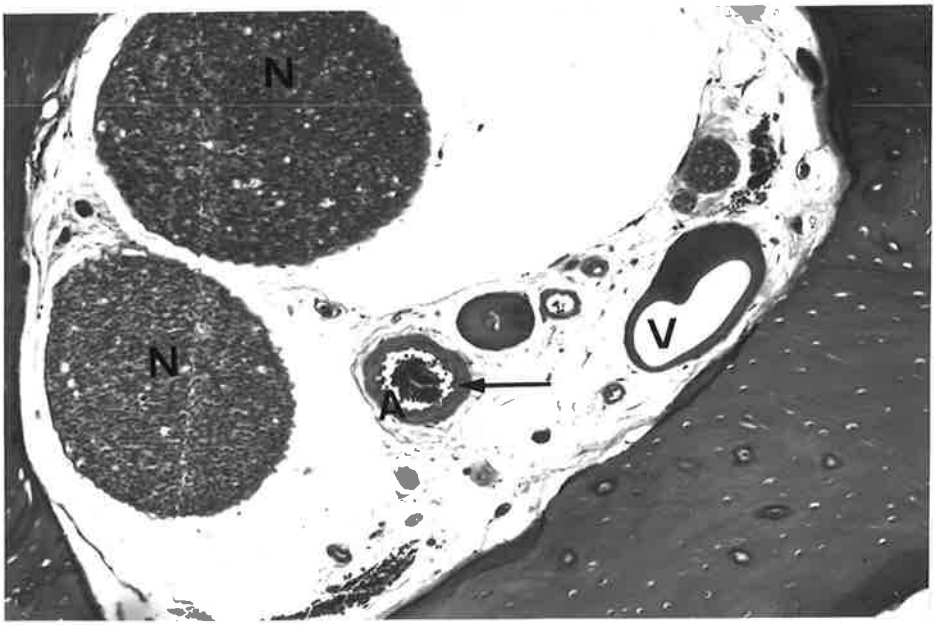


(b) H+E stain (x40 objective)

Figure 10.5 **Photomicrograph of mandibular neuro-vascular bundle of control animal and rat X. Very subtle changes in vessels.** (N= Nerve; A= Artery; V= Vein)



Control animal (H+E stain) X 10 objective



Rat X (H+E stain) X 10 objective

The changes seen in the blood vessels of the mandible following radiotherapy are presented in Table 10.3.

Table 10.3 Changes in the inferior alveolar artery and its branches.

INFERIOR ALVEOLAR ARTERY CHANGES IN MANDIBLE		
RAT No.	**MAIN TRUNK STENOSIS**	**SMALLER BRANCHES STENOSIS**
CONTROL	None	None
I	None	None
II	None	None
III	None	None
IV	None	None
V	None	None
VI	None	None
VII	None	None
IX	Mild	Mild
X	Mild	Mild

Reviewing the status of the inferior alveolar artery in the mandible, only rats IX and X showed very mild stenosis of the main trunks and its smaller branches. These were the rats that received the highest dose of irradiation (48 Gy). There was no evidence of stenosis in the other 7 cases.

An attempt was made to differentiate stenosis of the inferior alveolar artery due to arteriosclerosis from radiation-induced obliterative endarteritis. It proved impossible to differentiate between these changes on the basis of the changes in the vessels seen on light microscopy.

V

DISCUSSION

CHAPTER 11

DISCUSSION OF CLINICAL STUDY RESULTS

The results of this study showed that HBO plays a primary role in the treatment and prevention of ORN. This has been shown by the complete healing of all (100%) cases of ORN and a 97% prevention rate in patients from the prophylactic HBO group undergoing jaw surgery. Furthermore, this study has also confirmed the findings of previously published research by Marx 1983 and Marx et al 1985, illustrating the effectiveness of HBO in the management of ORN.

Fifty five patients were referred to the Royal Adelaide Hospital Hyperbaric Unit for hyperbaric oxygen treatment, either for ORN or for ORN prevention to their facial bones between the year 1987 and February 1996. However four (7%) were excluded from the study, either because of insufficient data or because of failing to continue with hyperbaric oxygen treatment due to complications. Patients were evaluated from 1987, the date the Hyperbaric Unit commenced services. It also explains why there was not a large population sample in the study.

The lack of complete management records illustrates an inherent disadvantage with retrospective studies. Incomplete or missing data is a major problem, particularly when an institutional protocol

for data collection exists. This is compounded by dealing with three different departments in two institutions. Some patients in the retrospective ORN group were deceased at the time of the study. Records were often not recorded or written illegibly, or not requested, insufficient, or the patient was lost to follow up.

This last factor was influenced by socioeconomic factors since some of the patients moved from Adelaide in order to pursue work opportunities, or to retire in the country or interstate. A small number of patients were unable to devote their time to regular reviews.

One must agree from this study that data collection tasks are inconvenient and subject to inconsistencies, particularly where several members of staff are involved in patient management. It was experienced that when record gathering duties were assigned to one person, the continuity of record keeping improved significantly.

In comparing the age and sex distribution of the HBO Prophylactic group to the Control group, there is too much variation in the data to facilitate a 'true' statistical analysis. Given the criteria, the area the sample was drawn from, and the time frame involved, it was relatively difficult to make any statistical inferences due to the sample size being too small. Also the age and sex variation between the two groups was too diverse. Although the two groups were drawn from the same population, they differed in certain characteristics.

The Prophylactic group ranged from 20 to 73 years of age with a mean age of 52.6 years, as compared to the Control, which ranged from 47 to 64 years with a mean of 56.3 years. The female to male ratio in the Prophylactic group was 1:2 as compared to 1:7 in the Control group. From a statistical perspective, it would be rather ambitious for one to make an assumption of any statistical significance due to the features noted earlier. Ideally, the two groups should have comprised the same number of individuals, i.e 20 and 20. Having 7 in one group and 29 in the other represents too much variation.

It is recognised that meaningful statistical comparisons between individuals within a small sample population are not realistic, and that this study is further hampered by the inadequacies inherent in any retrospective study. However we will analyse the age distribution in both groups and relate it to head and neck cancer epidemiology. Having discussed the above, the following discussion will stress the outcome of those patients who received HBO treatment versus those who did not (Control).

A combined retrospective and prospective study reviewing the outcome of patients treated with hyperbaric oxygen in the prevention and management of ORN was presented. The definition of ORN used in this study uses 3 months as the time duration for exposed bone not responding to local conservative wound care. This is contrary to Marx's (1984) definition of 6 months, as we felt that 3 months was an acceptable time period to monitor response to local wound management, given that this is often very painful.

To subject patients to a six month period of observation was probably unethical.

The postirradiation complications noted in this series were typical and comparable with reports from other institutions. It has been noted that ORN is uncommon. Approximately 150 patients per year receive irradiation to their head and neck region for treatment of malignant tumours at the Royal Adelaide Hospital Radiotherapy Department. For the period of this study the incidence of ORN in this hospital was 1.3%, which is a low figure compared to those reported in the literature (Morton, 1986; Berger, 1990; Harris, 1992).

On a worldwide comparison the incidence appears to be on a decline (Epstein et al, 1987; Balough, 1989). It remains, however, a grave sequel to radiotherapy administered for head and neck malignancies. In advanced cases it may lead to pathological fractures of the mandibular bone, impaired function and disturbance of the aesthetic appearance of the face. The incidence, predisposing factors, and clinical course of this phenomenon are subject to considerable variability and are dependent upon many complex interrelating factors.

Many factors play a role in ORN (Beumer et al, 1984; Epstein et al, 1987; Kluth et al, 1988). Epidemiological evaluation of these patients showed that they were in their mid 50s, which typically reflects the age of patients treated for head and neck cancer, and has some relation to atherosclerotic disease. The age of patients treated by irradiation for head and neck cancer who develop ORN

is similar to the age for those who do not. Although there does not appear to be any predisposition based on sex, the patients in this study were predominantly males, which again is reflective of head and neck cancer epidemiology (Bonett et al 1992).

Overall, general medical health is frequently compromised when there is a history of tobacco and ethanol abuse. It was observed that there was a high rate of smoking and alcohol usage in these patients. However, these factors alone do not account for the changes associated with ORN, nor do they predict who will develop the problem. Kluth et al (1988) reported the persistent smoking and drinking habits of those patients who develop the complication. This makes treatment difficult, because many of the patients who develop these cancers have poor compliance and long-standing abuse practices.

As expected, the malignancy that required radiotherapy was predominantly squamous cell carcinoma (87%), although there was a case each of salivary gland tumour and Hodgkin's lymphoma. The sites of these tumours varied; however they were predominantly in the oral and pharyngeal regions. Thus the mandible, including the inferior dental artery and the major salivary glands, were in the primary beam of radiotherapy. This is a significant factor in anyone who has received irradiation or is being worked up for radiotherapy to the head and neck region.

One of the critical factors in determining whether a patient is at risk of ORN is to know the proposed irradiation port or the irradiated field. Having the mandible, or maxilla or any other

facial bone, in the irradiation field predisposes such tissues to ORN. Irradiation not only has a direct effect on the destruction of osteoblasts, osteocytes and epithelial stem cells, but it also damages the endothelial cells of blood vessels, with the resultant secondary effects of progressive obliterative endarteritis. So in assessing whether a patient is at risk of ORN, besides the radiotherapy dosage, it is critical to know whether the mandible, the maxilla, the inferior dental artery and the facial artery were in the irradiation field.

With increasing age, and particularly with this population sample, there is a progressive change in the blood supply to the mandible, from a centrifugal (central artery) source to a centripetal (periosteal) blood supply (Bradley 1972). Bradley demonstrated an apparent decreasing capacity of the inferior alveolar vessels that occurs with aging, which is particularly prominent in edentulous mandibles and in older individuals. This ultimately results in the mandible being in an 'endartery' situation. So the periosteum and soft tissue envelope around a skeletal structure becomes the main source of nutrient supply to the bone.

Understanding this endartery situation has surgical clinical implications when dealing with irradiated tissues. Although in general good wide surgical access is better, with irradiated tissues you want minimal access and minimal stripping of periosteum when debriding necrotic bone. The aim is to preserve as much periosteum as possible attached to bone, so preoperative surgical planning is crucial. Depending on the individual case, it may mean leaving the medial (lingual) periosteum intact and minimal

reflection of lateral (buccal) periosteum only during debridement. This is to avoid cutting off the blood supply and devitalising bone, which could result in more radionecrotic tissue. Hence in the surgical management of patients with ORN and, in general, any irradiated tissue, the surgeon has to bear these factors in mind.

The type of ionizing radiation employed, as well as the manner in which it is delivered, has some effect on the incidence and severity of ORN. The idea of a direct relationship between the dose of radiation delivered to the jaws and the incidence of ORN appears to be popular. In some series, the onset of ORN correlates with total dose, (Epstein et al, 1987; Marciani & Ownby, 1986; Morrish et al, 1981; Rankow et al, 1971; Schweiger, 1987), although this is disputed by others (Bedwinek et al, 1976; Kluth et al 1988).

A dose of 60 to 70 Gy has been implicated as a critical point because regimens requiring higher doses are said to sharply increase the risk and severity of ORN (Bedwinek et al, 1976; Morrish et al, 1981; Beumer et al, 1984). In some but not all series, greater than 65 Gy carries an increased risk of radiation necrosis. Greater than 70 to 75 Gy is associated with a higher incidence of ORN.

The majority of patients in this study received dosage schedules in the range of 54 to 60 Gy. All patients received external beam irradiation with single daily dose fractionation. In examining the radiation dosage administered, it is seen that ORN can occur despite fairly low-dose radiation, as seen with the one case that received 27 Gy to the maxilla.

This was a 70 year old debilitated man who had had four recurrences of Hodgkin's lymphoma over a span of 7 years. It was first diagnosed in his right axillary region. One of the recurrences involved his palate for which he received irradiation to his maxilla and mandibular alveolus and ramus. He also had 2 courses of chemotherapy, 12 months apart, and suffering significant side effects each time which required hospitalisation. During this period he was plagued with cardio-pulmonary problems and generally being unwell. He was also on lengthy intermittent courses of dexamethasone, either alone or in combination, with chemotherapy, to control his recurrences.

In retrospect, his age, his debilitated medically compromised state and the suppressant drugs he was on probably made a significant contribution to this rare occurrence of ORN in the maxilla. Although this case is unusual, it does emphasise the need for precautionary measures when dealing with irradiated tissues no matter what the dose.

The onset of facial ORN in this study ranged from 3 months to 36 years post-irradiation. MacComb (1962) stated that the development of ORN may occur at any time, from a few weeks following completion of therapy to the end of the patient's natural life.

The mandible was the most common (73%) site of ORN involving the facial bones. It is apparent from this data, and has been suggested by Myer, that the mandible is more frequently affected

because it is more often in the field of radiation and also receives a higher dose of radiation. Others (Engelmeier et al, 1983; Galler et al, 1992) have suggested that the mandible possesses a reduced blood supply as compared to other skeletal bones, which predisposes its bone and adjacent soft tissues to the destructive effects of this necrotic process.

Experimentally, Gowgiel (1960) showed that when a whole skull was irradiated, the mandible was still more frequently affected by ORN. Gowgiel felt that the more dense compact configuration of the mandibular bone led to greater scattering of radiation, with consequently increased radiation to mandibular osteocytes. It has also been suggested that the better blood supply to the maxilla protects it from ORN (Rubin & Doku , 1976).

The age-related vascular changes in the inferior dental artery (Bradley,1972) have already been discussed. They could also play an important role which could well be one of the main anatomical reasons why the mandible is more susceptible than the maxilla. It is probable that a combination of the above factors is responsible for the noted prevalence of ORN in the mandible.

There appears to be a relationship between dental extraction and ORN (Coffin, 1983; Epstein et al, 1987; Marciani & Owenby, 1986; Morrish et al, 1981; Schweiger, 1987). It seems apparent from this study and the reports of others (Murray et al, 1980a & 1980b) that the extraction of diseased teeth within the radiation treatment volume is the major predisposing factor in the aetiology of ORN. There is no doubt tooth extraction is an aetiological factor; however

there is still uncertainty as to the optimum timing of the extractions (Daley et al 1972). Daly et al (1972) proposed that postradiation extraction may decrease the risk of ORN. However this is not currently accepted (Morrish et al, 1981; Widmark et al, 1989). Our data, and that of Murray et al (1980a & 1980b), make it apparent that the conservative policy of extraction of teeth proposed by Daly et al appears not to be justified. The suggestion by some authors (Francisco, 1966; Meyer, 1970) that extraction of teeth prior to irradiation decreases the incidence of radionecrosis seems more appropriate. However, pretreatment extraction of nonsalvageable teeth is not a guarantee that ORN will not occur.

Data from this study and others (Murray et al, 1980; Beumer et al, 1984) show that extraction of diseased teeth within the irradiated field seems inappropriate. It is well accepted in the literature that the rate of necrosis following postradiation extraction is unacceptably high (Murray et al, 1980; Beumer et al, 1983). Clearly, the patient's dental status prior to radiotherapy treatment has an effect on the incidence of ORN. The incidence is higher in dentulous patients than edentulous patients. This is associated primarily with postirradiation extractions. Patients without extractions, or who undergo extraction before irradiation have the same risk of ORN as do edentulous patients (Haber-Cohen & Debuski, 1990; Morrish et al, 1981).

The only practical means of avoiding this consequence is dental extractions at least three weeks prior to irradiation to allow for good soft tissue healing (Marx et al 1985). The alternative is prophylactic HBO therapy in irradiated patients prior to any tooth

extraction or surgical procedure. The irradiated tissues are incapable of normal homeostasis. Interestingly, the incidence of ORN following dental extraction is not always proportional to the total dose of radiation (Sanger et al 1993).

Thus, we continue to believe that an aggressive policy of removal of diseased teeth within the radiation treatment field, particularly in the mandible, will minimise the incidence of necrosis. All teeth with questionable prognosis should be removed. Generally teeth with advanced caries involving the dental pulp and/or evidence of periapical infection, and teeth with significant periodontal disease, should be considered for removal.

The periodontal status of the individual is very important. Dentitions with significant periodontal disease are difficult to maintain, and are very susceptible to caries as well as periodontal infections after radiation therapy. Also, involvement of the furcation area of the mandibular molar teeth within the radiation treatment port, whether or not in association with pockets, is grounds for extraction. This can be confirmed using a periodontal probe in conjunction with appropriate x-rays. There is no indication for extraction of sound teeth within the proposed irradiation field, and it probably increases the risk of bone necrosis (Beumer et al 1984), particularly in those patients with a healthy dentition and a history of good dental compliance.

The risk factors for ORN are presented in Table 11.1.

Table 11.1 Risk factors for osteoradionecrosis.

RISK FACTORS FOR ORN
Age
Smoking and alcohol abuse
Radiation exposure
Medical debility
Irradiation dose
Radiation implants
Preirradiation extraction without alveoloplasty and without primary closure
Postirradiation extraction without prophylactic HBO
Mandibular extractions/surgery
Poor patient oral care
Sharp bony spicules

Any decision concerning pre- and post-radiation extraction or oral surgical procedure should be made with these factors in mind. With irradiated patients, emphasis should be placed on atraumatic extractions and osseous surgery. Sharp spicules of bone should be removed and primary wound closure should be the objective. Great care is required to avoid unnecessary trauma to the soft tissues during procedures. The benefits of maintaining functional dentition, and thereby precluding the placement of prosthodontic

appliances over severely compromised, dry, thin mucosa, are apparent.

The time interval between the completion of radiotherapy and the development of ORN in this study varied from 3 months in the dental surgical extraction cases to more than 30 years in the spontaneous group involving the temporal bone. In 5 cases (33%) of the dental surgical group it developed in less than 12 months following irradiation. In the other 10 cases (67%) it occurred more than one year later.

Drake and Oishi (1995) state that radiation therapy given 1 week after wounding has no detectable clinical effects on wound healing or tensile strength. It has been categorically stated that it takes 6 months for irradiated tissues to develop a hypovascular-hypocellular-hypoxic state, and that surgical treatment, such as dental extractions, could still be carried out without any potential danger during this period (Marx, personal communication, ANZAOMS meeting 1995). This study showed 3 cases that developed ORN within 3 to 6 months following radiotherapy, with the earliest at 3 months post-irradiation. It is clear from this study that there are early cellular or tissue changes occurring immediately following irradiation. This explains the 3 cases of ORN developing within 3 to 6 months following irradiation. The majority of cases (6) developed ORN between 12 and 24 months following irradiation.

The 15 patients with facial bone ORN included 3 (20%) cases involving the temporal bones, 1 (7%) involving the maxilla and 11 (73%) involving the mandible.

The 3 cases of temporal bone ORN all appeared to be of spontaneous origin. Earlier work by Daly and Drane (1972), and later Marx & Johnson (1987), showed that about 40% of ORN occur in a spontaneous fashion. It has been claimed by some (Daly & Drane, 1972; Marx, 1983) that this type of ORN is in general more severe and requires more aggressive treatment.

In a large series, Marx and Johnson (1987) found that approximately 39% of ORN of the mandible was spontaneous in onset. The spontaneous cases appeared between 6 and 24 months after irradiation and fell dramatically after 2.5 years. Marx and Johnson felt that spontaneous ORN represented a greater outright cellular kill of normal tissue elements. Furthermore they suggested that in this type of ORN, the radiobiologic tissue damage causes necrosis to develop directly.

This is in contrast to initial tissue recovery to a less than normal homeostatic level that becomes necrotic only when a secondary wounding, such as tooth removal, occurs. However, this theory fails to explain the long latency periods noted in the spontaneous cases of temporal bone ORN. We believe the long latency period observed in our cases was the result of the progressive ischaemia and the altered homeostasis in the irradiated tissues. The tissues cannot sustain the aging process because they are incapable of renewal. Two of the 3 temporal spontaneous radionecrosis cases in

this study developed 30 years after irradiation. Delayed onset is a feature of ORN in the temporal bone and is well documented in the literature.

In the series presented by Ramsden et al (1975), the latency period extended up to 23 years, with an average interval until presentation of 7.5 years following radiation. Other series have suggested latency periods as long as 35 years, with mean time to presentation as long as 20 years (O'Neill et al, 1979; Thornley et al, 1979; Wurster et al, 1982).

The duration of the latent period depends on total radiation dose absorbed by the tissue and the degree of vasculitis. Delayed osteitis after moderate radiation doses may not become clinically apparent for decades. Ewing (1926) attributed the long latent period to low metabolic rate and slow turnover of bone as compared to other tissues. We believe it is most certainly related to the progressive obliterative effect of endarteritis obliterans on tissues which gets worse with time, and the consequential inability of irradiated hypocellular tissue to sustain and replace normal cellular loss.

The clinical results show that HBO is not only curative, but like surgery, is a primary treatment modality in the management of advanced disease. This is proven by the fact that the use of HBO therapy alone resulted in clinical improvement and complete resolution of ORN in all (100%) of the Stage I cases treated. The irreversible effect of radiation on bone and soft tissues has been well documented (Murray et al, 1980; Marx, 1984). Subsequently

microangiopathy develops which results in a shallow oxygen gradient in irradiated tissue. This compromised tissue is incapable of sustaining the normal collagen and cellular loss and is the major cause of persistent ORN (Marx 1983). Considering this pathophysiology, it is not surprising that HBO therapy, which increases blood to tissue oxygen tension, promotes resolution of ORN.

Only 40% of our patients with ORN responded in Stage I and this illustrates that, depending on the amount of necrotic bone present, HBO alone cannot usually heal radionecrotic wounds. Also it shows that the amount of tissue damage following radiation treatment is very variable, even following identical doses and fractionations. For this reason it is impossible to predict which patients will require surgery. The extent of hypocellularity and hypoxia differs and is impossible to predict clinically. Marx (1983) describes this variation as due to some patients having a greater residual and peripheral cellular pool that can respond to HBO.

Surgery was required in the other 60% of our patients with ORN. This was due to the fact that HBO cannot revitalise dead bone. Depending on the degree of radionecrosis, in moderate to severe cases, a certain amount of necrotic bone remains unresorbed due to the poor vascularity. The problem with not using HBO is that the wound healing processes will not take place without improvement in tissue oxygenation. This applies particularly when tissue oxygen demand is increased by surgical wounding or continuous long term exposure of bone. To date, HBO is the only treatment modality that

can correct this and thus should be a primary aspect of all therapy for ORN (Marx, 1983).

One of the difficulties with nonsurgical approaches, even when HBO is used, is that significant amounts of necrotic bone prevent wound healing. With moderate to severe ORN cases, despite HBO induced angiogenesis and cellular proliferation, most contain too great a quantity of necrotic bone for resorption and complete healing to occur. This necrotic bone needs to be surgically removed before healing can take place.

As highlighted by Marx (1983), the merits of this protocol rest with the interrelationship of hyperbaric oxygen and surgery in a progressive sequence. Both are used for diagnostic and prognostic modalities, as well as for treatment modalities. For example, when Stage I ORN responds to HBO, it gives a diagnostic impression of the person's actual local radiation injury. Furthermore, it provides a relatively reliable impression of the person's prognosis as to whether the lesion will heal with hyperbaric oxygen alone or whether surgery is indicated. Similarly, a person's response to combined Stage II treatment gives us both diagnostic and prognostic impressions, as well as definitive indication for resection (Marx, 1983).

Local wound care and maintenance of good oral hygiene play a major role in the management of ORN. They promote healing and may prevent bacterial superinfection. Other adjunctive conservative measures used in the management of ORN include irrigation, oral rinses, antibiotics, gentle removal of loose bony

spicules as indicated and nutritional support. These are all important components of total patient care, which in the past were the mainstay of treatment for ORN, with hyperbaric oxygen and surgery being adjunctive measures. However, our data further support Marx's (1983) findings, strongly advocating that hyperbaric oxygen and surgery should be the primary treatment modalities for ORN and that all others are adjunctive to those two.

There were four Stage II ORN cases that were difficult to treat and required a modified treatment approach different from the usual protocol. Initially these patients were managed according to the standard unit protocol, but developed further wound breakdown and exposed necrotic bone. The amount of bone exposure was minimal and did not fit the criteria of Stage III. These four problematic cases clearly demonstrate how ORN is frequently refractory to treatment.

Based on these four moderate refractory cases, we have developed a new protocol for so-called Stage II nonresponders or Intermediate Stage II-III, where the amount of exposed bone is minimal and restricted to the operative site and is not severe enough to be classified as a Stage III ORN. The new protocol is a modification of the current stage II protocol as follows: 30 pre-surgery HBO dives followed by surgical debridement of necrotic tissue to bleeding bone, 10 post-operative HBO dives, and review of the operative site weekly for six to eight weeks; if the wound breaks down during this period and fails to heal with conservative measures such as removal of small sequestrum with toothed forceps, then consideration is given to a further 10 HBO dives

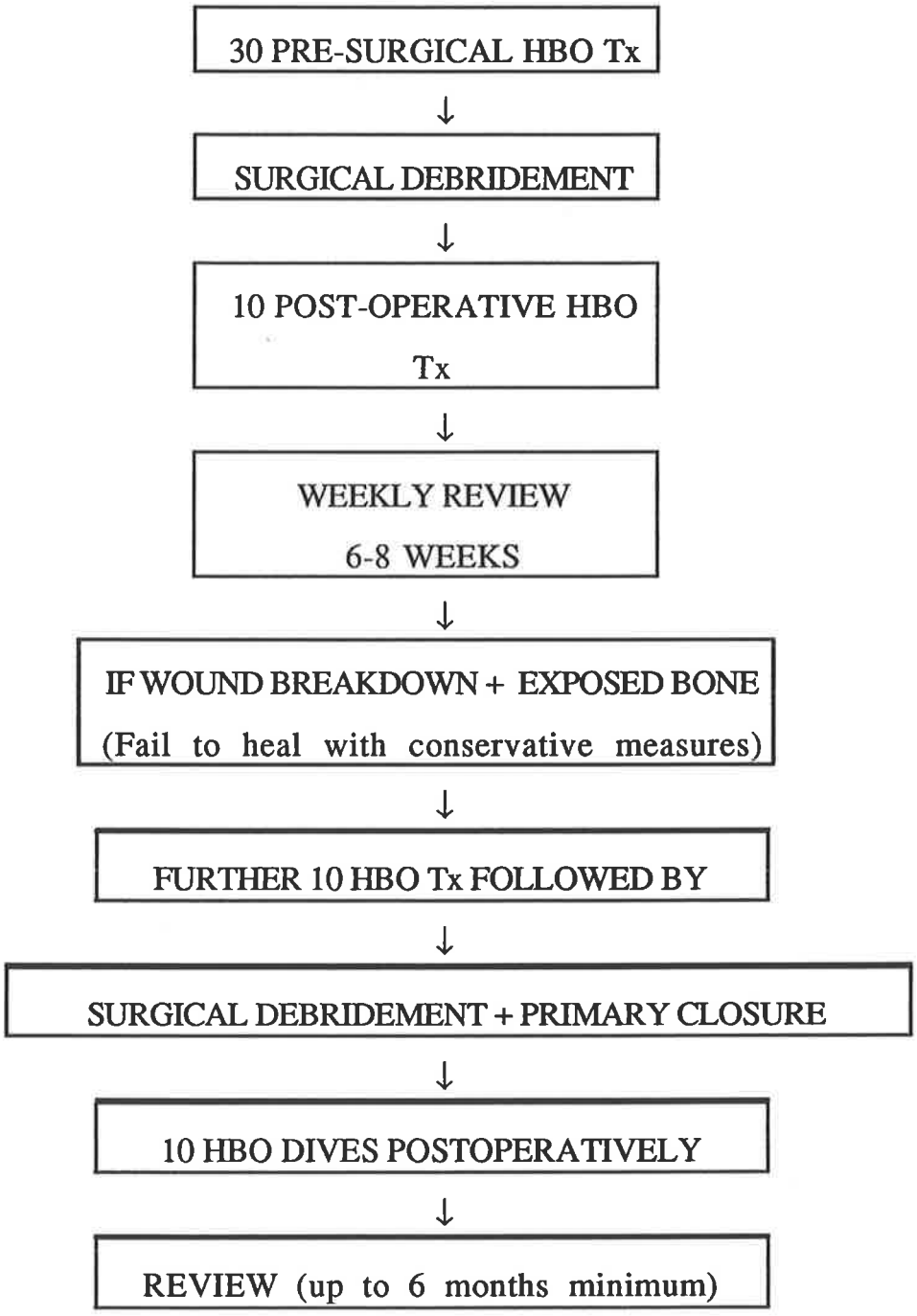
followed by further surgical debridement and another 10 HBO dives postoperatively.

This new treatment protocol is summarised as a flow chart in Figure 11.1.

We have noted how each case can behave differently although they may have had identical irradiation doses and fractionations. Although we can standardise cases into the various stages, they may not all respond to the standard treatment protocol. There is a necessity to assess and treat each case individually, and to closely monitor these cases regularly postoperatively. In fact some cases that show good wound healing initially may later stagnate and fail to heal completely.

Quite often, it is difficult to tell how well tissues will respond to treatment and so regular review for at least 6 months is required. Today, just as it was first stated a decade ago, there is no clinical marker or laboratory test that is available to tell us how irradiated tissues will respond to treatment (Marx 1984). Also there is no effective way of assessing the vascularity and viability of an affected area. Clinically we assess this objectively by debriding necrotic bone to bleeding bone, and this is by far the only effective means of assessing vascularity. The measurement of trans-cutaneous oxygen has been advocated (Marx, 1984). However, this is only relative and applies to soft tissue oxygen tension levels and not bone. When dealing with ORN, we are interested in bone oxygenation levels and vascularity, which transcutaneous

Figure 11.1 Proposed new treatment protocol for Stage II nonresponders / intermediate Stage II-III.



measurements will not tell us. Perhaps further research should be directed towards some way of determining and measuring the extent of the viability of bone in the affected region.

There was no control group to compare with the HBO group in the evaluation of the effects of hyperbaric oxygen on the treatment of ORN because of ethical reasons. The condition is painful, debilitating and frequently refractory to treatment. To refuse to offer patients treatment, and know the high failure rates associated with non-HBO therapy, is unethical and inconsistent with at least a minimal level of care. This was confirmed by the Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide. A request to have a non-HBO Control group was rejected (1993).

A significant feature to be noted in this study is that the majority of patients involved were either Stage I or II and there was only one Stage III case. Six of the Stage II patients were initially classified as Stage I and later categorised as Stage II, after failing to resolve with hyperbaric oxygen treatment alone. These patients had more non-viable bone which required debridement.

An important observation from this study was that the cases were diagnosed fairly early in the disease process, except for the one Stage III case which had developed a pathologic fracture. This reflects the careful monitoring of cases, and the tendency to early presentation by patients in our community. This is a very significant issue because the earlier the diagnosis, the earlier the arrest of the disease process, the less extensive the treatment that is required, the shorter the treatment duration and the better the

prognosis. Also it costs a lot less to treat small lesions (Marx et al 1985). When the sequestrum is small, HBO therapy alone may be all that is required to arrest the disease process. However, once a large sequestrum is present, HBO alone will not reverse the condition. The non-viable bone must be surgically removed.

There is a role for more aggressive follow-up and investigation of patients after radiation treatment in an attempt to detect ORN at a stage where HBO therapy may arrest or reverse the process. This is particularly so in patients who have had dental extractions or any mandibular surgery just before irradiation, when the mandible is in the primary beam.

There are several reasons for the early diagnosis of the disease in this study. One of the main reasons is the high level of coordination and close monitoring of patients by the surgeons, radiotherapists and dentists. With the current establishment at the Adelaide Dental Hospital, there is a dedicated Oral Medicine team that specialises in the management of medically compromised patients, particularly irradiated patients. These patients are screened and monitored meticulously prior to and following irradiation.

This team liaises directly with surgeons and radiotherapists in the planning and management of patients to be irradiated. Furthermore, they monitor and review these patients regularly on a long term basis, so any significant oral changes is diagnosed and managed early. Without doubt a combined team effort involving the various specialists is crucial in the management and prevention

of this disease. Also more dental practitioners are now more aware of the potential problems of irradiation and tooth extraction. Thus any poor or delayed healing noted in these patients is usually referred in swiftly for consultation and management. Furthermore, patients treated over the last five years are being counselled thoroughly on potential effects of irradiation and so are more self conscious of oral symptoms. Hence they present sooner rather than later.

The only Stage III case in the study was a 45 year old male who received irradiation to his mandible following resection of a lower lip squamous cell carcinoma interstate. The total radiotherapy dose is unknown, despite determined efforts at retrieving his records from interstate. He presented with a pathologic fracture of the mandible due to ORN. The necrotic process followed the extraction of mandibular molars 5 years post-irradiation. Radiologically, he had extensive osteolysis of the mandible at the tooth extraction site and in relation to the pathologic fracture. He was diagnosed as a Stage III ORN and accordingly was worked up, following our combined HBO-Surgery treatment protocol. He received 35 HBO treatments initially, followed by extraction of the remaining teeth and a transoral left hemimandibular resection of the necrotic bone from the para-symphysis to the angle. This was followed by a further 12 HBO treatments. The wound was left to heal for 6 weeks before the mandible was reconstructed via an extra-oral approach.

The brief delay after Stage III resection permitted a graft to be placed into a vascular and cellular recipient bed covered with an

intact mucosa. Corticocancellous bone was harvested from the iliac crest and packed into a dacron mesh tray to reconstruct the jaw. This was followed by further HBO treatment. His postoperative recovery was slow, however it healed uneventfully. Clinical and radiological review 12 months postoperatively revealed a good functional mandible. He maintained good mandibular continuity, good bone height and arch form, and good aesthetics.

Although this was the only Stage III case in the study, it does show that the treatment protocol can work. The techniques reported by Marx and Kline (1983) have contributed immeasurably to the improvement of function and aesthetics in patients with advanced ORN of the mandible. Inherent to the success of treatment is HBO therapy. When it is not available, microvascular techniques and myocutaneous flaps appear to be reasonable alternatives.

At least 47% (ORN group) and up to 86% (HBO control group) of patients in the 3 groups reviewed had radical neck surgery, and some had a suprahyoid dissection, as part of the surgical management of the primary malignancy followed by irradiation. Obtaining this history and knowing the type of surgery an irradiated patient has had is essential, particularly in terms of reconstructing an oral defect.

The use of local pedicled flaps is dictated by its blood supply. For example, if a surgeon is anticipating using a nasolabial flap to repair a defect in the oral cavity then he needs to know whether the facial artery on that side of the face is still intact. This is crucial because of the risk of losing the blood supply and vitality of

the flap. Similarly if a vascular bone graft is being planned, then the surgeon would want to know which vessels are available for anastomosis. Certainly an arteriogram will be part of the work up investigations; however the previous surgical history is crucial in planning reconstruction.

In irradiated jaws, or any skeletal tissue for that matter, there will be sections that have been significantly irradiated which have not developed either spontaneous or trauma-induced ORN. These areas should be considered as compromised tissue that exists in homeostasis at a reduced metabolic level (Marx et al 1985). Although the tissues have maintained their structural integrity, it is at a measurably reduced oxygen tension, and they have a reduced cellular and vascular density rendering them very susceptible to wound breakdown. Any wounding event creates a huge demand for metabolically active protein synthesis that requires both the cellular elements capable of protein synthesis (fibroblasts), and the vascular network capable of protein precursor delivery to the wound (a functioning capillary bed) (Marx et al 1985).

Current data from this study on the use of prophylactic HBO showed a very promising and successful outcome, in that 96% of patients treated healed satisfactorily without ORN. The results strongly indicated a role for HBO in the prevention of ORN. The outcome confirmed the role of irradiation damage to the cellular and vascular elements of soft tissue and bone. Also the results indirectly supported and confirmed previous studies (Marx 1983,

1984; Marx et al 1985) implicating the minimal role miro-organisms played in the pathogenic development of ORN.

The mechanism by which HBO lowers the incidence of ORN in irradiated bone is probably similar to that suggested by Marx (1983): that is, a tissue angiogenesis in hypoxic, hypovascular tissue induced by intermittent high oxygen tissue levels.

With the HBO prophylactic group, 1 of 29 patients (3%) developed ORN. The unsuccessful case was a 59 year old male who had a $T_4N_0M_0$ squamous cell carcinoma of the lower lip resected followed by radiotherapy. He received a total of 54 Gy to his mandible and upper neck region. Two and a half years following irradiation treatment he complained of discomfort arising from multiple grossly decayed mandibular teeth, which required a full dental clearance. He was worked up for prophylactic HBO treatment according to the Unit protocol, receiving 23 presurgical HBO dives. This was followed by a full dental clearance including 9 teeth in the mandible and 12 in the maxilla. An alveoloplasty was carried out at the same time in both jaws to allow for primary mucosal closure.

During the perioperative period the patient received a 5 day course of Amoxycillin 500mg TDS and Metronidazole 200mg BD. The surgical procedure was followed by a further 10 HBO dives. Despite this prophylactic measure, the right anterior mandible dehisced into a Stage I osteoradionecrotic wound, which was treated following the ORN treatment protocol.

This failed HBO prophylactic case supports work by Marx (1984) that showed the effects of HBO on irradiated tissue in bringing its vascular density to within only 80% +/- 5% of nonirradiated tissue. That is, although HBO increases the healing capabilities of irradiated tissue, it is still somewhat compromised. On the whole, in most cases HBO can protect against the development of ORN, as seen with the 96% success rate in this study. HBO should be considered a prophylactic measure when post irradiation dental care involving trauma to tissues is necessary.

There was one unsuccessful case in the Control group of 7 patients who did not receive HBO therapy prior to surgical procedures. This failed case was a 47 year old male with a $T_3N_0M_0$ squamous cell carcinoma of the tongue, resected together with a radical neck dissection. This was followed by radiotherapy totalling 60 Gy to the mandible and neck. A year following irradiation, the patient required extraction of 6 teeth from the mandible. These teeth were extracted after having 20 presurgical HBO dives followed by a further 10 postsurgically. The mandibular wounds healed successfully. However 6 months later, this patient required a full dental clearance.

This created a dilemma as to whether further HBO therapy was indicated, since he already received prophylactic HBO therapy 6 months earlier. On consultation with the HBO Unit consultants, it was suggested that no further prophylactic HBO was indicated. This patient then had a full dental clearance, alveoloplasty and primary closure without any further HBO therapy and developed ORN. Although this case had previous exposure to HBO therapy,

there is currently insufficient evidence in the literature on the length of effectiveness of HBO therapy. It is currently not known whether further prophylactic HBO therapy is required in patients who require further surgery to their irradiated tissues (Marx et al 1985).

Given this lack of data, we have included this patient in our control group as we felt on empirical grounds that he required a booster HBO therapy to maximise healing potential. Marx et al (1985) indicated that HBO may improve the tissue vascular density to a certain degree but it is not known whether it could prevent the clinical appearance of ORN at a later time.

Retrospectively, we should have done a full dental clearance in the first instance, rather than doing it 6 months later. Also, having failed to do that, we should have given further HBO therapy prior to the full dental clearance. This issue of whether retreatment with HBO is necessary if further surgery or tooth extractions are required has not been specifically addressed in any study, although Marx (1985) thinks not.

Marx et al (1985) claim that reevaluation of these patients at 1, 2, and 3 years after their HBO therapy showed transcutaneous oxygen levels at or within 90% of their initial recordings just after treatment. They claim that there was no evidence of a regression of the tissue angiogenesis induced by HBO. They extrapolated further to state that enhancement of wound healing and repair response in irradiated tissue can be expected for at least 3 years after an HBO course and possibly longer. We can see from our

unsuccessful case presented above that this is not always true. Certainly further studies need to be done to determine whether retreatment with HBO is necessary if further surgery is required.

From our own experience and review of the literature, ORN involves tremendous cost to the health care system and social costs to the patient and their immediate relatives. The condition certainly justifies the investment of time and expense inherent in preventive techniques including the delivery of HBO (Marx et al 1985). This objective is best achieved by aiming at both preradiotherapy and irradiated patients.

Prevention should begin before any irradiation is administered to the head and neck region. All patients should be made dentally healthy prior to radiotherapy. This involves a thorough oral evaluation including the patient's ability to maintain good oral health post-irradiation. A treatment plan is formulated for each patient directed towards providing a disease free state. It must be remembered that if ORN of the jaws occurs, then it is more painful and debilitating than the original malignancy.

Considerations that should be taken in treatment planning are patient cooperation, existing or potential pathology and establishment of good oral and periodontal health. The South Australian Oral and Maxillofacial Surgery Unit adopts an aggressive attitude towards this assessment because of our experience with these cases. Generally any potential foci of infection and any tooth with a poor prognosis are removed 3 weeks prior to irradiation. Furthermore, any patient who exhibits an inability to maintain

good oral care is strongly advised to have a full dental clearance with primary mucosal closure.

An integrated and coordinated approach to the dental management of radiotherapy patients is paramount to the success of preventing, reducing or alleviating potential oral sequelae. With our current establishment support, dental services are provided to patients undergoing radiotherapy by specialist clinicians. These include the Restorative Dentistry Unit, the Oral and Maxillofacial Surgery Unit and associated specialties, including Prosthodontics, Periodontics and Preventive Dentistry.

The role of the Oral and Maxillofacial Surgery Unit is to assess the presence of or potential for dental or jaw pathology in radiotherapy patients, eliminate potential sources of infection and manage the more severe oral consequences of radiotherapy. All grossly carious or periodontally involved teeth are removed and primary wound closure is ensured.

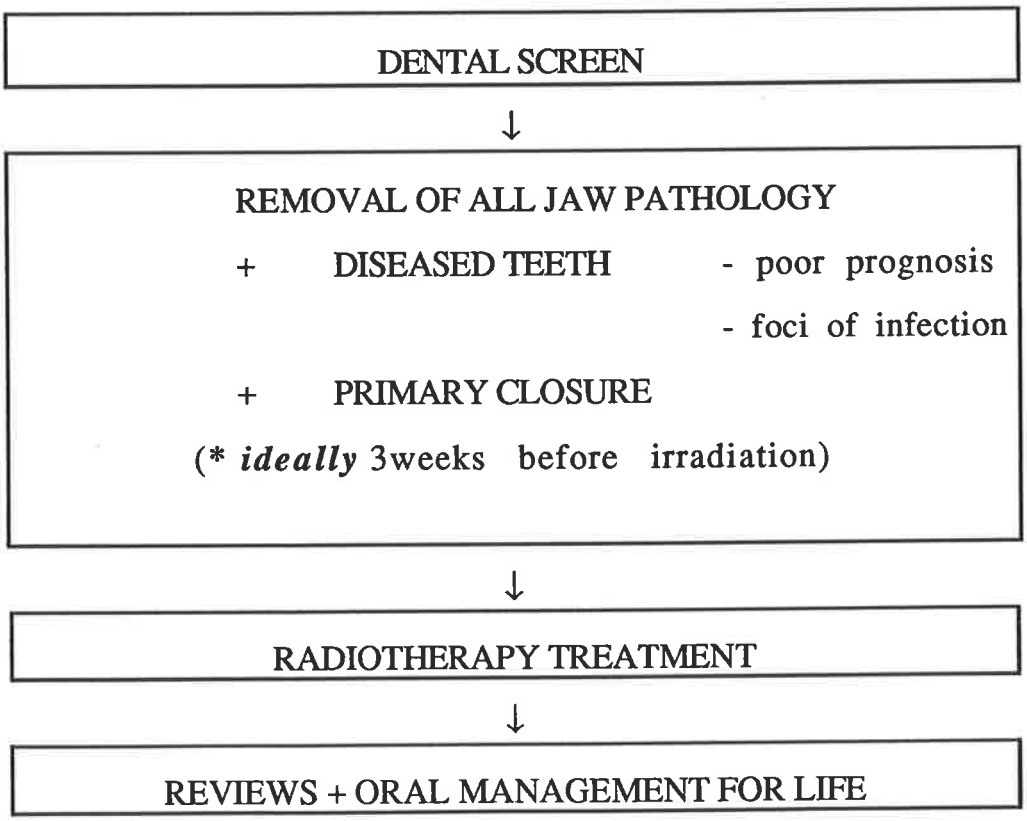
As part of their Admissions protocol physicians of the Radiation Oncology Department of the Royal Adelaide Hospital refer all patients who are to receive head and neck radiotherapy for an oral evaluation by the Dental Coordinator for radiotherapy patients. All such patients are placed on an Oral Health Programme with special emphasis on home care. They receive oral health counselling, personal oral hygiene instruction and establishment of an appropriate self care regime. This continues during radiation treatment to monitor oral health levels, to reinforce preventive

measures and palliatively treat conditions that may arise (mucositis and oral infections).

Upon completion of radiotherapy, definitive treatment of any deferred procedures is carried out and oral health programmes are reinforced. As part of the prevention programme, it is crucial that maintenance of good oral health after radiotherapy in all head and neck patients is upheld. These patients are placed on a six monthly recall for life for continuing dental and oral management.

A summary of pre-radiotherapy management of patients is presented in Figure 11.2.

Figure 11.2 Proposed preradiotherapy protocol.



The potential oral sequelae associated with radiotherapy can be prevented, reduced in severity, or palliatively alleviated when the dental team participates in patient care. Success is based upon early referral of the patient for dental consultation, treatment before initiation of radiotherapy and an effective oral health programme with regular review.

The same preventive measures discussed above can be applied to patients presenting with a history of irradiation to the head and neck region who require oral surgical procedures. With good plaque control, intensive fluoride therapy and regular reviews it is possible for motivated patients to derive years of service from the teeth in the irradiated field.

Likewise these patients are screened by the Oral Medicine Unit Dental Coordinator for radiotherapy patients prior to any oral surgical procedure or tooth removal. The Dental Coordinator liaises with the Radiation Oncology Department of the Royal Adelaide Hospital to confirm the radiation fields and dosages, and to confirm whether the patient is at risk of ORN. A provisional treatment plan is drawn up.

This includes arranging appropriate specialist consultations and the provision of immediate dental treatment to stabilise, control or eliminate oral infections or conditions that may be potential problems. The patient is counselled on the need for hyperbaric therapy as a prophylactic measure and the potential risks of not having HBO. A consultation appointment is arranged with the Hyperbaric Unit for evaluation. The current HBO prophylactic

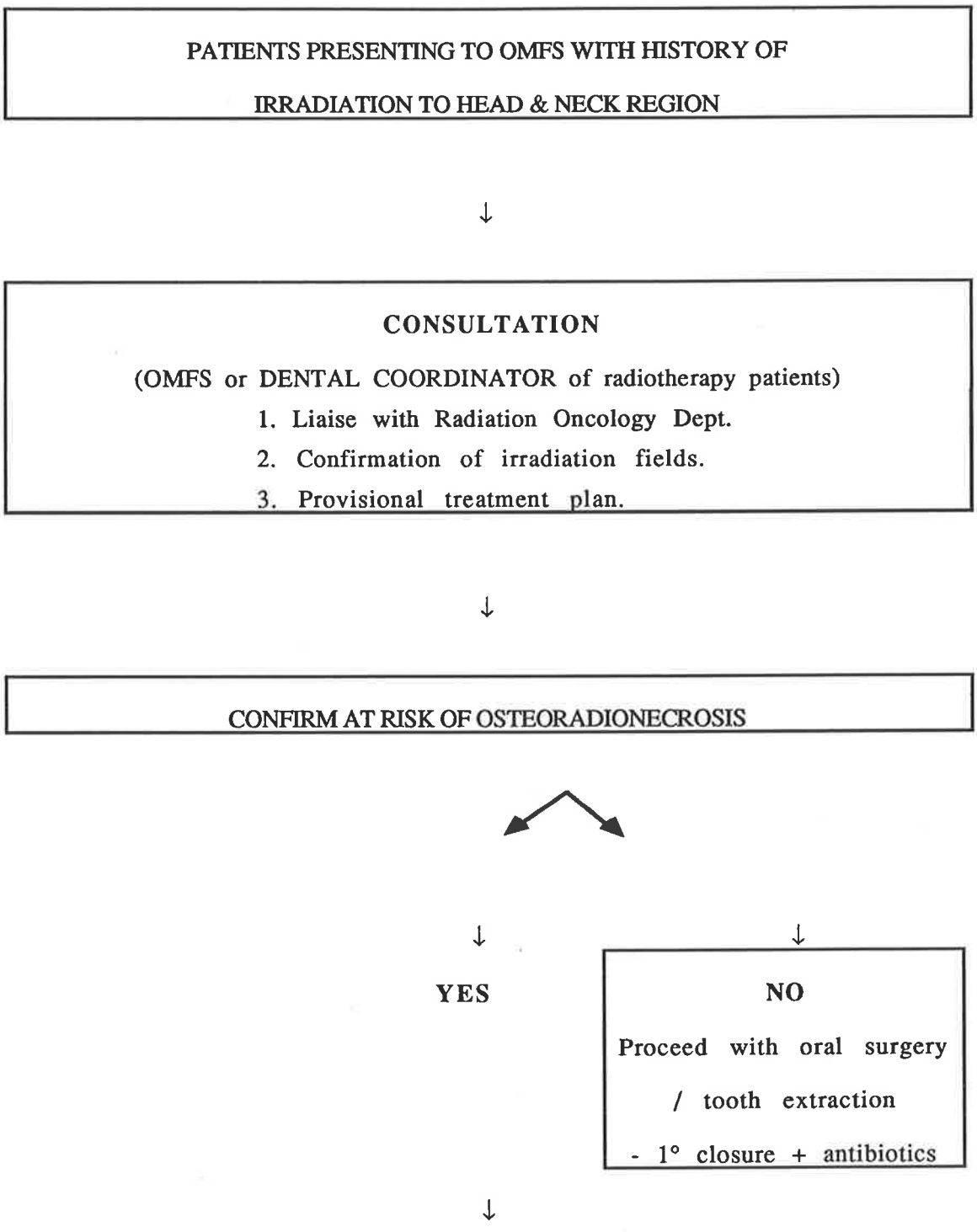
regime is 20 presurgical HBO dives followed by surgery/tooth extraction and primary closure, followed by another 10 HBO dives. Patients are reviewed weekly for the first month, then 3-monthly and then 6-monthly.

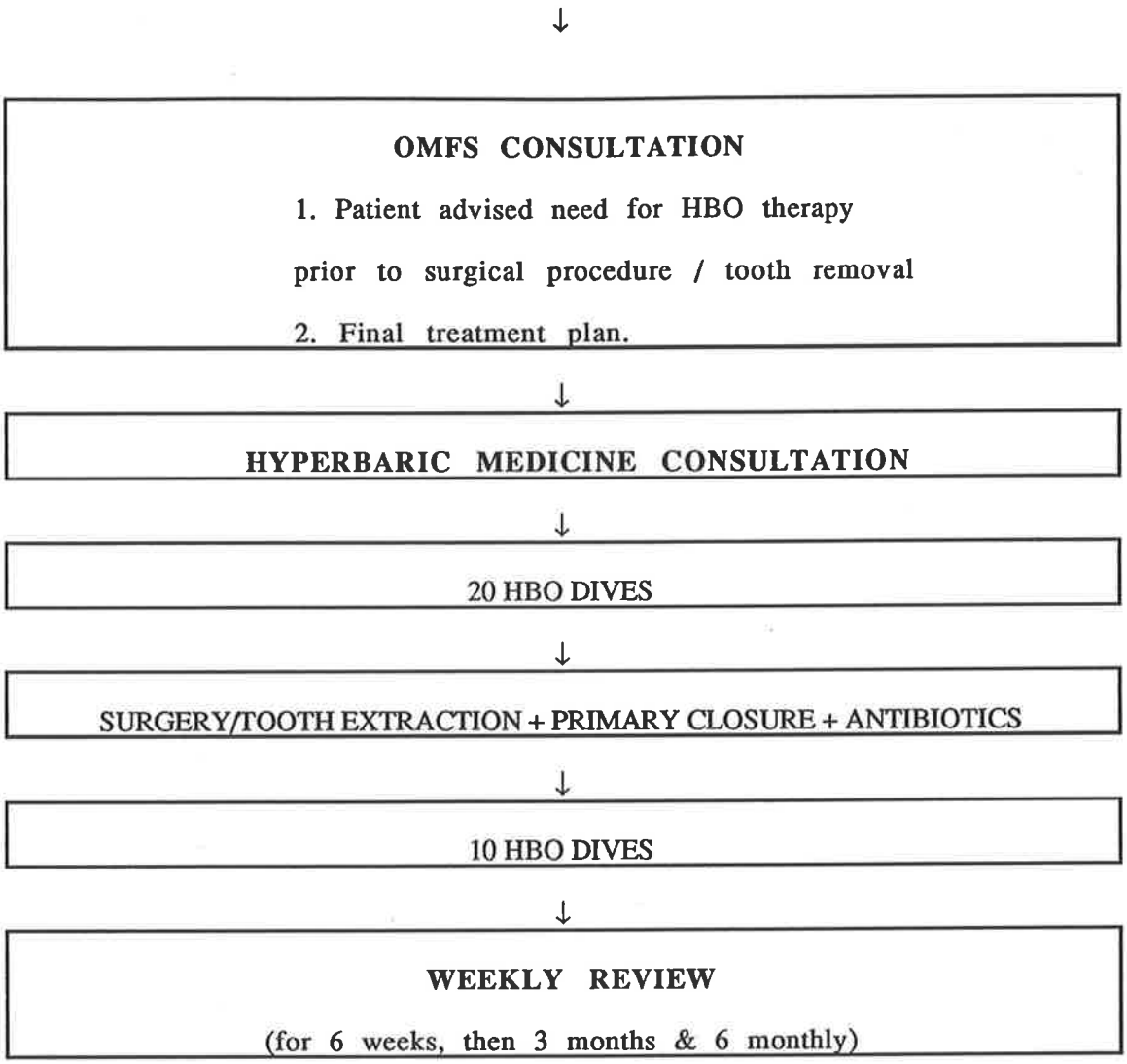
Any chief complaint or oral pathology detected at this reviews is attended to or an appropriate referral for consultation is arranged immediately. Our clinical study shows that this preventive protocol works and it is recommended to everyone. A summary of the proposed Hyperbaric Oxygen Prophylactic protocol for irradiated patients is presented in Figure 11.3.

Noted in the management of these cases is the use of perioperative antibiotics, mainly penicillin or cephalosporins and metronidazole. The use of antibiotics in the management of ORN has not been clearly defined (Marx, Johnson & Kline 1985). A review of the existing literature related to ORN treatment and prevention advocates the use of some antibiotic as an integral part of disease management (Bottomly et al, 1966; Narang & Wells, 1970; Strauss & Spatz, 1972; Marx et al 1985). Penicillin is the most commonly used antibiotic. None of the literature strongly advocates removal of teeth in irradiated bone without the use of some antibiotic. Based on our current understanding of the pathogenesis of ORN, prolonged empiric antibiotic use cannot be justified.

Six (40%) of the 15 patients received perioperative antibiotics. Generally this included 1 to 3 doses of intravenous antibiotics commencing at the time of sequestrectomy, and followed by an oral course for one week postoperatively. Although we believe

Figure 11.3 Hyperbaric oxygen prophylactic treatment protocol.





that ORN is a noninfective process, we are dealing with the oral environment, which contains numerous potential pathogenic micro-organisms. These are capable of infecting these compromised wounds which are incapable of normal defence and repair. Also the preference for antibiotics is dependent on the surgeons involved and what they believe in. Generally most of the operators in the department would prescribe antibiotics for perioperative use only as prophylaxis against contamination for up to one week postoperatively and not on a long term basis.

In reviewing patients' subjective HBO therapy experience, not only was it curative, it was also subjectively beneficial. Around 50% of patients in both the treatment and the prophylactic group felt generally better after HBO therapy. Although in the majority of cases HBO made no difference to oral functions such as talking, jaw opening, mouth dryness and pain, a significant percentage felt better. It is rewarding to know that patients who have suffered severely from the side effects of irradiation can have the added benefit of feeling better generally from HBO therapy.

Only a small minority felt that certain attributes such as eating ability, talking, and mouth dryness got worse. However on close review of their responses, the negative attributes were not due to HBO therapy per se, but secondary to other factors such as difficulty wearing dentures and ongoing post-irradiation effects such as xerostomia.

Reviewing the effect of HBO on pain in the patients, 71% in the ORN treatment group and 58% in the HBO prophylactic group felt it made no difference. One patient from the ORN group claimed his pain was worse after HBO therapy. This patient was receiving HBO therapy for temporal bone ORN. His disappointment stemmed from the development of an ear infection with discharge, which was very painful, immediately after HBO. However, it resolved with antibiotics.

There was only one patient in the treatment group who felt his jaw pain was better after HBO. This was following resolution of his ORN from a combined HBO and surgical approach. Most patients (68-

86%) found the hyperbaric chamber to be bearable and would not only have the same treatment again, but would recommend it to others requiring the same treatment. The majority of these patients would have had their treatment in the old Drager chamber which was very small and claustrophobic (Figure 11.4 & 11.5). The new larger chamber has more space, has 3 very comfortable armed chairs and has eliminated the claustrophobic effect. The newer multiplace chamber (Figure 11.6 & 11.7) has been described by patients as providing a much more pleasurable experience.

In future, institutions planning on installing hyperbaric chambers should aim to have the bigger walk in type rather than the old Drager chamber. However cost will be the ultimate determinant. Thus overall, the HBO experience has positive attributes to patients if anything.

Barotrauma of the ear or ear squeeze was the most common complication of hyperbaric therapy encountered in this study. Patients complained of pressure and subsequently pain in the ear. The complication is due to difficulties equalising pressure in the middle ear, resulting in blood vessels becoming engorged with fluid and eventually haemorrhaging into the substance of the tympanic membrane itself. In extreme cases haemorrhages lead to blood filling the middle ear and rupture of the ear drum. It is inherently more difficult to inflate the middle ear because the inner ends of the eustachian tubes, located in the fossae of Rosenmueller in the nasopharynx, have slit-like openings. These openings tend to close tighter if they are not opened actively (Davis et al, 1988; Kindwall 1995).

Figure 11.4 Photo of old Drager multiplace chamber at the Royal Adelaide Hospital. Operational November 1986-1994.

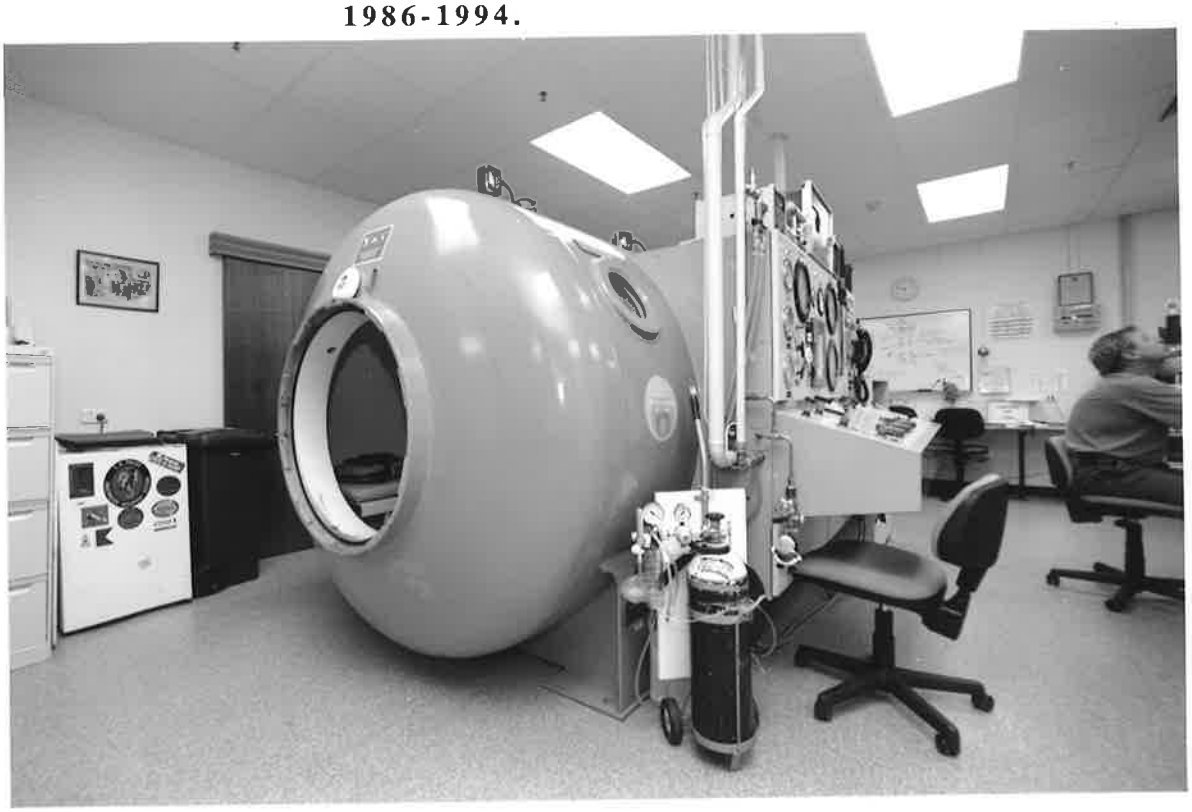


Figure 11.5 Photo of internal compartment of Drager chamber. Note small tight compact nature and lack of space.

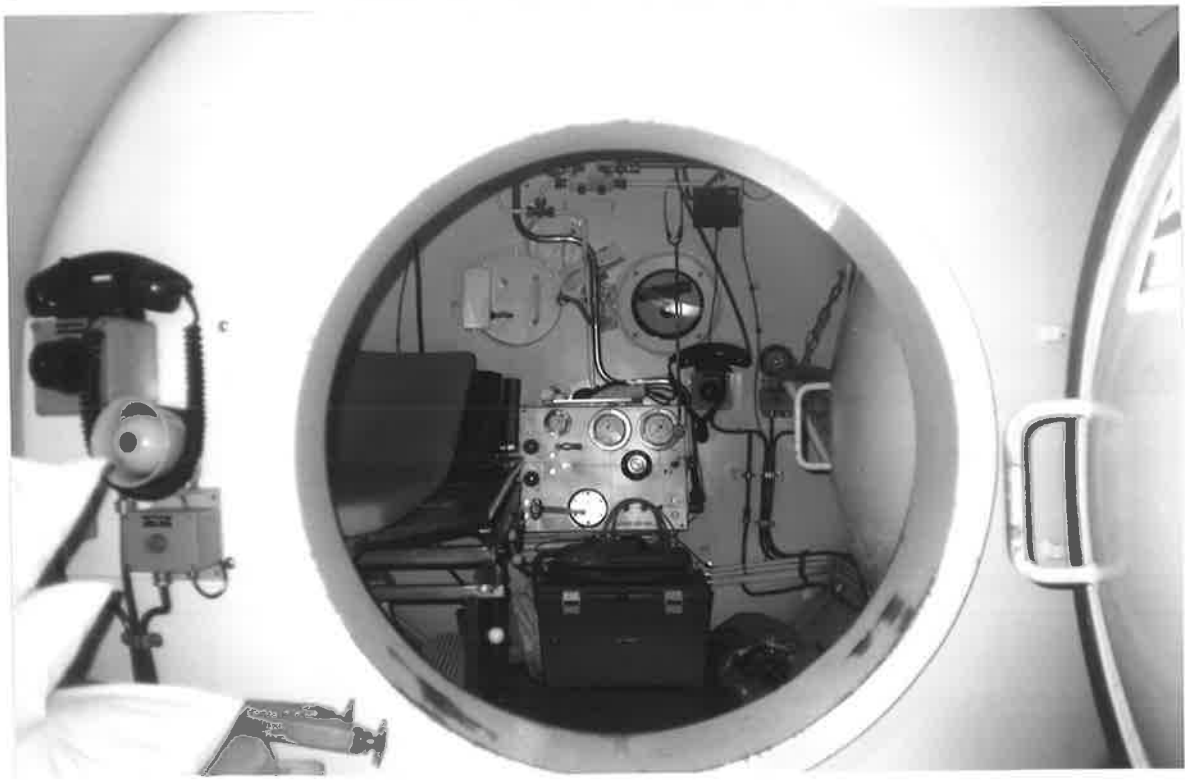


Figure 11.6 Photo of new rectangular multiplace chamber (Cowan Manufacturing Co) with central operating console, at the Royal Adelaide Hospital. Operational since November 1994.

Figure 11.7 Photo of inside of new multiplace walk-in chamber showing patients having HBO therapy and a registered nurse assisting. Note enormous space and comfortable relaxing environment.

Patients are taught ear clearing techniques to voluntarily open the tubes through swallowing, yawning or doing the Valsalva manoeuvre. If a patient has descended more than about one meter without clearing the ears, it will be impossible to voluntarily open the tubes through these techniques, and the chamber will have to be brought up slightly to facilitate ear clearing.

The mild cases of ear barotrauma were treated with either Drixine or Sudafed to help clear their ears. Drixine and Sudafed are topical vasoconstrictors (Drixine contains Oxymetazoline hydrochloride and Sudafed is composed of Pseudoephedrine hydrochloride). They constrict the smaller arterioles of the upper respiratory tract ,especially the nasal mucosa and sinuses, producing a rapid and prolonged decongestant effect which lasts up to 12 hours. By decreasing congestion around the eustachian tube ostia they assist with clearing of the ears. If patients still can not clear their ears then grommets are inserted by ENT surgeons to facilitate equalisation.

Other forms of pressure injury from HBO include sinus and pulmonary barotrauma, however these are uncommon.

Claustrophobia was the commonest HBO contraindication encountered in this study. Davis (1988) reports that approximately 1 out of 50 patients exhibits some degree of confinement anxiety in the multiplace chamber. It is rare, however, that this is severe enough to require sedation. On the other hand, the monoplace chamber can be very anxiety provoking for patients, and approximately 1 patient in 10 will have

claustrophobia severe enough to make treatment difficult or impossible.

In this study there were 4 patients who commenced HBO therapy and had to terminate treatment after 2 to 4 dives as a result of claustrophobia. This was particularly the case with the use of the old conventional Drager multiplace hyperbaric chamber, which can accommodate a maximum of 4 sitting patients or 1 stretcher patient.

This problem has been eliminated since the opening of the new bigger walk-in chamber in 1994. To date we have not had any patient complain of claustrophobia. It is important to reassure the patient of full control at all times and that treatment can be terminated at any time if anxiety arises. If therapy needs to be terminated due to anxiety, treatment may be attempted again with appropriate presedation with one of the benzodiazepines.

It becomes clear from the literature, and is now widely accepted, that most of the current understanding of the pathogenesis, the HBO management and prevention of ORN is biased towards the work of the University of Miami group led by Marx. Further research needs to be carried out to clarify and reproduce this work. To investigate this experimentally, an animal model of ORN needs to be created so that the efficacy of HBO can be properly evaluated at both the tissue and biochemical level. Furthermore, whether HBO therapy could prevent the clinical appearance of ORN at a later time needs to be looked at and an animal model would be ideal for this.

CHAPTER 12

DISCUSSION - ANIMAL STUDY RESULTS

In this study the optimum radiotherapy dose required and time taken to create an ORN in lower vertebrate animals was not achieved. This confirms and supports previous statements by Marx (1995).

Clinical observations paralleled the signs and symptoms noted in human patients receiving radiation therapy to the head and neck. These included dry mouth, inability to eat dry laboratory pellets, and weight loss. All the animals suffered varying degrees of xerostomia with rats IX and X being the worst affected.

A slow healing rate was observed in the traumatic wounds created in the irradiated rats; however, the surgical wounds healed. No subsequent radionecrotic changes developed over the 6 months' observation period. This reflected the high regenerative potential in young growing rats.

The histological evaluation appears to show an increase in osteocyte numbers in rat mandibles that received higher irradiation dosages (42 Gy - 48 Gy). Bone is a highly specialised form of connective tissue and the extent of change resulting from given amounts of therapeutic irradiation is very unpredictable

(Pappas 1969). Bone is characterised by the presence of cells (osteocytes) in cavities (lacunae) with long branching processes located in fine canals (canaliculi). Extrapolating from these histological observations, it appears that the higher irradiation dosages used in this study had a proliferative effect on osseous cells. In an experimental study of dogs, Ng et al, in 1959, concluded that microscopically all mandibles receiving a dose of 3,000 to 8,000 rads showed evidence of actively proliferating osteoid tissue. The effect of irradiation on bone is primarily a lowering of viability, which in some instances progresses to necrosis; however intermediate doses of radiation appear to induce cellular proliferation. This is probably because larger doses of radiation result in cell death, whereas intermediate doses are more likely to result in mutations capable of producing increased numbers of cells (Bernstein 1993). The data from this study mirrored some of Ng et al's (1959) findings. It suggested that the radiotherapy dosages used in their experiment were most probably intermediate, thus stimulating proliferation of cells. It was certainly not high enough to cause cell death and subsequent radionecrosis.

There was little microscopic evidence of obliterative endarteritis. The inferior alveolar artery underwent comparatively little change. Only mild changes were seen in the parent vessel and its small branches in the two mandibles that received the highest irradiation dose (48 Gy). The vessel walls appeared mildly thickened but not to the point of lumen obliteration. This relative lack of vascular lumen change is probably one of the reasons why none of the animals developed ORN. It shows that the irradiation dosages used were most likely too low. However it does imply that, in future, we

should be considering using radiotherapy doses in excess of 48 Gy to have any hope of creating ORN in these animals.

The predominant change observed was the presence of some mild diffuse fibrosis. There is no doubt that some radiation was absorbed by the medullary cavity since the bone marrow tissue was observed to be replaced by fibrous tissue in mandibles that received a higher dose of irradiation.

Although some clinical side effects of irradiation were observed in the animals, none developed ORN. There are probably several reasons for this:

1. It may be that the total cumulative radiotherapy dosage was inadequate. We need to review the dosages used and plan on administering a higher regime based on radiation dose-tissue damage curves.

2. The rats used were probably too young. They were 10 weeks old and at the peak of their growth and regenerative potential. In humans, patients who develop ORN are usually in their mid 50s and this has some relation to atherosclerotic disease, which theoretically is a contributory factor to the disease process. Older individuals do not have the same healing capabilities as the young. To simulate the aging factor in an animal model we need older rats. The young rats probably did not have any vascular disease at that stage. Being young and fit, they had a greater healing

potential, and this is one of the reasons why none developed osteoradionecrosis.

In future we should use an older population of rats. However, it is questionable whether such rats could tolerate the experimental conditions, and there is always the potential for some dying and losing numbers.

The average life expectancy of a laboratory rat is assumed to be about three years, which may be considered as equal to ninety years of human life. Their life spans do vary according to climatic conditions. With favourable conditions, rats have lived over 40 months (Farris & Griffith, 1949). With the above correlation, 1 $^{1}/_{2}$ year-old rats would probably be ideal for a 12 months' experiment.

3. The 2mm to 3mm deep traumatic wound created in the mandible was probably too small. A bigger open wound should be created in the irradiated tissue. To create a typical traumatic wound similar to a human's, a molar tooth should be extracted from the mandible or, alternatively, a larger round bur should be used to drill a cavitating osseous-soft tissue wound the size of a rat molar tooth socket. This latter option is probably a better way of standardising wounds in a group of experimental animals. Extracting a tooth from a rat mandible is not as simple as in humans because of their long slender roots which tend to fracture off.

4. The 6 months' post-irradiation period for the development of the hypocellular-hypovascular tissue was probably insufficient. This time frame was based on time curves from Marx and Johnson (1987). Presumably because the latent period between irradiation and late effects is measured in years, animal models reproducibly demonstrating the effect of late radiation change on wound healing are difficult to develop (Bernstein te al 1993). In future, a longer post-irradiation time period, perhaps 12 months, should be considered.

5. The number of animals used in this study was low as this investigation was intended to be a pilot study with further developments. Increased numbers of animals are necessary to allow for good statistical evaluation and comparison.

6. An alternative is to use a slightly bigger animal which more closely resembles man, particularly in facial and dental anatomy, such as the rhesus monkey. This will allow easier calculations of radiotherapy dosages similar to man. Also it makes possible an experimental comparison with the clinical observations. However, obtaining ethics approval for the use of these animals would be very difficult. Furthermore, they are more expensive, and require far greater resources to use and maintain.

VI

CONCLUSIONS

CHAPTER 13

CONCLUSIONS

The following conclusions and recommendations can be drawn from this study.

1. ORN remains a grave sequel to radiotherapy administered for head and neck malignancies. The results of the study and a review of the literature indicate that, although the incidence of ORN appears to be declining, this disease process still occurs at a frequency of around 1%.

2. The condition is certainly painful, debilitating and deforming. When it does occur it requires extensive management and is often refractory to treatment. It involves substantial treatment expense and social costs, thus prevention is better than cure (Marx et al 1985). Hence, it should be aggressively prevented and treated. Recognition and prevention are the most important considerations in these patients.

3. This study supports outcomes of previous studies (Engelmeier et al ,1983; Robin & Doku, 1976; Galler et al, 1992) showing ORN of the mandible is more common than of the maxilla. In this study 73% (11) were mandibular, 20% (3) temporal and 7% (1) maxillary.

4. The major predisposing factor in the aetiology of ORN in this study was found to be dental extractions carried out postradiation. This is in accordance with the literature (Murray et al, 1980; Beumer et al, 1983), and confirmed by our data that the rate of necrosis following postradiation extraction is unacceptably high. Ideally pre-radiotherapy tooth removal and primary closure of the wounds three weeks prior to irradiation is proposed. The primary objective should be prevention of osteoradionecrosis.

5. Spontaneous ORN does not necessarily occur within two and a half years following irradiation as suggested by Marx and Johnson (1987), nor does it always represent a greater outright cellular kill of normal tissue elements. Although this applies to some mandibular cases, it does not apply to temporal bone ORN. Our data showed that spontaneous ORN in the temporal bone can develop 30 years after irradiation. This is the end result of progressive ischaemia, hypocellularity and altered homeostasis in the irradiated tissues. This finding is supported in the literature (Ramsden et al, 1979; O'Neill et al, 1979; Thornley et al, 1979).

6. There was a 100% cure rate of ORN using HBO therapy in this study, although 60% of cases required surgery and HBO. This was a similar experience to that reported by Marx (1983).

The outcome of this study supports previous findings by Marx (1983) and Hart and Mainous (1976), that HBO and surgery should be considered a primary treatment modality in the management of ORN. All others are adjunctive to these two. The reason that surgery is required in such a high percentage of cases is that HBO cannot revitalise necrotic bone.

7. A great deal of knowledge has been gained regarding the effects of HBO on the healing of radiated wounds. It is possible to standardise hyperbaric oxygen management according to the stage of ORN. It is important, however, that surgeons use this form of treatment properly and time surgical intervention appropriately.

8. The number of ORN cases in South Australia was small. This leads to some difficulty in statistical analysis. However, given the 100% success rate, some meaningful conclusions can be drawn. It is recognised that meaningful statistical comparisons among individuals within a small sample population are not realistic, and that this study is further hampered by the inadequacies inherent in any retrospective study. In future, any further evaluation of HBO effects should be fully prospective.

9. In this study we developed a new protocol for difficult Stage II ORN cases (Stage II Non-responders). This is a modification of the Marx protocol and requires additional HBO dives. It was 100% successful.

10. If ORN occurs, early diagnosis and treatment is essential. This means proper counselling of patients about the long term risks of irradiation, the importance of good oral care and the need for regular follow-up for life. Patients should have greater awareness of their oral health status and any changes should be attended to as soon as possible. It is observed that with Stage I cases, the number of patients requiring concomitant surgery is low. The aim of early diagnosis and treatment is to intervene early in the disease process and thus minimise destruction and surgical management.

11. The results indicated that in irradiated mandibles requiring surgical procedures and tooth extractions, HBO produced one case of ORN (4%), which is excellent. Prophylactic HBO should be considered when surgical procedures including dental extractions are planned in irradiated facial bones.

12. The current team approach adopted by the South Australian Oral and Maxillofacial Unit towards ORN prevention is strongly recommended as shown and supported by the clinical results. Cooperation between the surgeon, the dentist, and the radiation oncologist is essential if the patients are to receive thorough preventive care. The end result should not only be successful treatment of the patient with cancer but also a decrease in the morbidity and discomfort resulting from irradiation.

13. Although HBO may improve tissue vascular density, it is not known whether it could prevent the clinical appearance of ORN at a later time. There is insufficient evidence in the literature on the length of effectiveness of HBO therapy. Further study needs to be carried out to address whether retreatment with HBO is necessary if further surgery or tooth extractions are required. In this study, ORN occurred in a patient who had HBO six months prior to further surgery.

14. HBO is not only curative for ORN, it is also subjectively beneficial to the patient's well being. About half the patients in the study felt generally better after HBO therapy. This added psychological benefit is reassuring, particularly in those patients who have been subjected to prolonged cancer treatments and suffer from continuing effects of irradiation. Overall, HBO has positive attributes to patients.

15. The morbidity associated with HBO in this study was about 40%. The commonest side-effect was ear barotrauma, accounting for 34% of patients. This is a minor side effect. It is critical that all complications are recognised and attended to early as they are usually reversible. On the whole, HBO therapy is very safe under current HBO chamber guidelines and provided patients are thoroughly screened prior to commencing treatment. No patient died or had severely morbid effects.

16. From our experience with the two types of hyperbaric chamber, the larger walk in multiplace chamber is preferred.

The commonest contraindication encountered with HBO therapy in this study was claustrophobia (43%). To date this appears to have been eliminated since the use of the new multiplace chamber. In future, institutions planning to install hyperbaric chambers should aim to have the bigger walk in type rather than the old claustrophobic Drager type. However, cost will be the ultimate determinant. Unfortunately the limited availability of chambers and funding for such treatment remain significant obstacles to the general applications of this modality.

17. It is difficult to create an ORN animal model. Future attempts to create an animal model should consider the following factors:

    (1) Use of a higher radiotherapy dosage. This should be calculated in association with a radiation oncologist.

    (2) Older rats should be used.

    (3) A larger open wound should be created in the irradiated mandible.

    (4) A longer post-irradiation period for the development of hypovascular-hypocellular-hypoxic tissue should be allowed.

(5) Increased numbers of animals are necessary once a successful model has been demonstrated in preliminary trials.

18. This study confirms that HBO is an essential component in the management of ORN. ORN can also be prevented by careful preirradiation management and HBO prior to surgery in previously irradiated jaw bones. The factors involved are presented in detail although limited statistically by the numbers of new ORN cases. Attempts at establishing an animal model were essentially unsuccessful.

VII

APPENDIX

APPENDIX 1

CONSENT FORM, INFORMATION SHEET, AND RECORD SHEETS USED IN STUDY

INFORMATION SHEET

The purpose of this study is to review the outcome of patients that have been treated with hyperbaric oxygen for the side effect of radiation therapy. It will require review of previous medical and dental records which may include those from the Royal Adelaide Hospital/South Australian Dental Services/ and private dental practitioners.

It also will require your attendance for a dental evaluation at the South Australian Dental Service by the Oral and Maxillofacial Surgery Unit.

Your participation in this study may influence future treatment programs for people with this or similar conditions.

Your participation in this study will not alter your current course of medical or dental treatment. However, if any abnormalities are detected on examination you will be offered medical and or dental treatment.

The review of your dental history and further assessment will be carried out by members of the Oral and Maxillofacial Surgery Unit and/or the Royal Adelaide Hospital Hyperbaric Medicine Unit. If publication results from this study, you will not be identified and all personal details of notes will remain confidential. You may withdraw from the review at any stage.

If you have no objection to be included in the study, you will be required to sign the accompanying consent form. Further details may be obtained by phoning:

Alastair Goss 82228225

Roger Capps 822245554

Christy Pirone 822245121

CONSENT FORM

Protocol Name

Hyperbaric oxygen treatment of maxillofacial osteoradionecrosis.

Investigators

1. Royal Adelaide Hospital: Dr. J. Williamson
   Dr. R. Capps
   CNC C. Pirone

2. Oral and Maxillofacial Surgery: Prof. A. Goss
   Dr. R.B. Jones
   Dr. S. Vudiniabola

I have read the information sheet and have had the opportunity to ask questions and discuss this study with the investigators.

1. The nature and purpose of the study is understood by me and I agree to take part.

2. I understand that I may not directly benefit by taking part in this study.

3. I understand that any information gained from the study may be published, I will not be identified and my personal results will remain confidential.

4. I understand that I may withdraw from the study at any stage and that this study will not affect my medical care now or in the future.

5. I have had the opportunity to ask questions about the study and fully understand.

Name: _____

Signature : _____

Date: _____

I certify that explanation has been provided to the patient and consider that he/she understand what is involved.

Signed:_____

Record sheet (a) Study No:

PRESENTATION

PATIENT NAME: SEX

U.R.No: ADH No: D.O.B.

SECTION A. MALIGNANCY

TYPE:

SITE: STAGE:

DATE OF COMMENCEMENT OF TREATMENT OF MALIGNANCY:

SURGERY: Y/N SPECIFY:

RADIOTHERAPY: MANDIBLE IN PRIME BEAM Y/N

1. EFFECTIVE BIOLOGICAL DOSAGE:
2. MAPPING OF RADIOTHERAPY

CHEMOTHERAPY: Y/N SPECIFY:

DENTAL STATE PRIOR TO RADIOTHERAPY:

Edentulous maxilla mandible

Dentate maxilla mandible

Had extractions prior to radiotherapy: Y/N

SPECIFY:

Had dental treatment after radiotherapy:

nil to conserve teeth extractions dentures

SECTION B. OSTEORADIONECROSIS/HBO PROPHYLAXIS: Y/N

IF **YES,** Complete this section, if NO, proceed to **Section C.**

DATE ONSET:

TIME INTERVAL, RADIOTHERAPY TO OSTEORADIONECROSIS:

INITIATING FACTORS FOR OSTEORADIONECROSIS:

none identified trauma tooth extraction other-SPECIFY:

SECTION C EXAMINATION FINDINGS AT TIME OF PRESENTATION FOR HBO

(1) MUCOSAL DEHISCENCE

nil small moderate extensive

DESCRIBE:

(2) SKIN DEHISCENCE

nil small moderate extensive

DESCRIBE:

(3) BONE INFECTION

nil small moderate extensive

DESCRIBE:

(4) PATHOLOGIC FRACTURE YES/NO

DESCRIBE:

(5) RADIOLOGIC IMAGES OBTAINED

(a) OPG	YES	NO	NOT AVAILABLE
(b) TEMPORAL VIEWS	YES	NO	NOT AVAILABLE
(c) MASTOID VIEWS	YES	NO	NOT AVAILABLE
(d) FACIAL VIEWS	YES	NO	NOT AVAILABLE
(e) C.T.	YES	NO	NOT AVAILABLE

(6) IMAGES - AREA OF INVOLVEMENT

(a) RESECTION	YES	NO
(b) BONE GRAFT	YES	NO
(c) EXTRACTION SOCKET VISIBLE	YES	NO

(after 1 year following extraction)

(d) OPACITY YES NO

If YES, localised moderate extensive

(e) RESORPTION YES NO

If YES, localised moderate extensive

(7) STAGE OF ORN (MARX/MIAMI CLASSIFICATION)

NIL STAGE I STAGE II STAGE III

SECTION D. DENTAL STATE

Edentulous maxilla mandible

Dentate maxilla mandible

PROSTHESIS maxilla mandible

TOOTH CHART:

I

SECTION E ORAL FUNCTION

PAIN: absent mild moderate severe

intermittent continuous

ANALGESIC REQUIREMENT DAILY: YES/NO

SPECIFY:

FOOD CHEWING ABILITY:

liquids puree soft chew normal chew not known

MOUTH OPENING

limited moderate normal not known

SALIVA

absent reduced normal not known

Management sheet (b)

MANAGEMENT OF OSTEORADIONECROSIS/PREVENTION

PATIENT NAME: SEX

U.R.No: D.O.B.

SECTION A HYPERBARIC MANAGEMENT

DATE COMMENCED: DATE CEASED:

DURATION: (months)

NUMBER OF TREATMENTS:

DIVE CHARACTERISTICS:

Atmospheres: Duration:

HYPERBARIC COMPLICATIONS: Y/N

Specify:

SECTION B SURGERY (FOR ORN/REQUIRING ORN PREVENTION) Y/N

DATE:

TYPE: local resection segmental resection bone graft

DESCRIBE:

SECTION C. DENTAL TREATMENT: Y/N

DATE:

TYPE: tooth extraction tooth filling

SECTION D. ANTIBIOTICS: Y/N

ANTIBIOTICS WITH SURGERY: Y/N

TYPE ROUTE: ORAL DOSE

DURATION:

ROUTE: I.V. DOSE:

DURATION:

ANTIBIOTICS ALONE:

TYPE: ROUTE: DOSE:

DURATION:

Examination Sheet (c)

EXAMINATION POST-HYPERBARIC

PATIENT NAME: SEX:

U.R. No.: D.O.B.

DATE OF EXAM:

SECTION A MALIGNANCY STATUS

DURATION(FROM FIRST PRESENTATION MALIGNANCY TO EXAM/TIME OF DEATH):

DURATION(FROM HBO TO EXAM/TIME OF DEATH):

CURRENT STATE:

clear local recurrence metastatic neck metastatic distant

CURRENT TREATMENT:

nil further surgery further radiotherapy chemotherapy palliation

IF DECEASED - CAUSE OF DEATH

SECTION B OSTEORADIONECROSIS

DURATION (FIRST HBO TO NOW / TIME OF DEATH)

TREATMENT FINISHED: Y/N

SECTION C EXAMINATION FINDINGS

(1) MUCOSAL DEHISCENCE

nil small moderate extensive

DESCRIBE:

(2) SKIN DEHISCENCE

nil small moderate extensive

DESCRIBE:

(3) BONE INFECTION

nil small moderate extensive

DESCRIBE:

(4) PATHOLOGIC FRACTURE YES/NO

DESCRIBE:

(5) RADIOLOGIC IMAGES OBTAINED AFTER HYPERBARIC COMPLETED

(a) OPG	YES	NO	NOT AVAILABLE
(b) TEMPORAL VIEWS	YES	NO	NOT AVAILABLE
(c) MASTOID VIEWS	YES	NO	NOT AVAILABLE
(d) FACIAL VIEWS	YES	NO	NOT AVAILABLE
(e) C.T.	YES	NO	NOT AVAILABLE

(6) IMAGES - AREA OF INVOLVEMENT

(a) RESECTION	YES	NO
(b) BONE GRAFT	YES	NO
(c) EXTRACTION SOCKET VISIBLE (after 1 year following extraction)	YES	NO
(d) OPACITY	YES	NO

If YES, localised moderate extensive

(e) RESORPTION YES NO

If YES, localised moderate extensive

(7) TIME INTERVAL BETWEEN PREHYPERBARIC X-RAYS & POST EXAMINATION X-RAYS

(1) < - 1 YEAR

(2) 1 - 2 YEARS

(3) 3 - 5 YEARS

(4) > - 5 YEARS

(5) NO POST-OP X-RAYS AVAILABLE

(8) ARE THE PREHYPERBARIC & POST EXAMINATION X-RAYS THE SAME?

YES NO NO POST-OP X-RAYS AVAILABLE

If NO, are the differences due to:

(a) TREATMENT (b) PATHOLOGY

If PATHOLOGICAL, are the differences due to:

(a) INCREASED OPACITY (b) INCREASED RESORPTION

(c) OTHER

(9) STAGE OF OSTEORADIONECROSIS (MARX/MIAMI CLASSIFICATION)

NIL STAGE I STAGE II STAGE III

SECTION D. DENTAL STATE

Edentulous maxilla mandible

Dentate maxilla mandible

PROSTHESIS maxilla mandible

TOOTH CHART:

I

SECTION E ORAL FUNCTION

PAIN: absent mild moderate severe

intermittent continuous

ANALGESIC REQUIREMENT DAILY: YES/NO

SPECIFY:

FOOD CHEWING ABILITY:

liquids puree soft chew normal chew not known

MOUTH OPENING

limited moderate normal not known

SALIVA

absent reduced normal not known

[Patient Questionnaire (d)]

PATIENT QUESTIONNAIRE

1. Compared to when you first needed HBO, do you now feel:

GENERALLY	better	same	worse
EATING ABILITY	better	same	worse
TALKING	better	same	worse
JAW OPENING	better	same	worse
MOUTH DRYNESS	better	same	worse
PAIN	better	same	worse

2. Would you describe being in the Hyperbaric Chamber as:
   pleasurable bearable unbearable

3. Would you have the same hyperbaric treatment again?
   YES/NO

4. Would you recommend the hyperbaric treatment to a patient with the same problem as yourself:
   YES/NO

COMMENTS:

APPENDIX 2

RAT DAILY OBSERVATION and RECORD SHEET

The following is a copy of the daily observation review sheet monitoring each rat's general progress.

POST-OP MONITORING CHART:

DAILY OBSERVATION AND CLINICAL RECORD SHEET

1. DATE:
2. WARMTH:
3. HYGIENE:
4. FLUID INTAKE:
5. FOOD INTAKE:
6. NATURE OF PROCEDURE :
7. DAYS POST-OP:
8. URINATION:
9. DEFECATION:
10. RESPIRATION:
11. SKIN CONDITION/ BURNS:
12. WOUND CONDITION:
13. WEIGHT:

SIGNS OF ACUTE PAIN OR DISTRESS.

ABNORMAL -SLEEPING
" -FEEDING
" -DRINKING
" -SOCIAL BEHAVIOUR
" -STANCE OR MOVEMENT
" -SOUNDS
" -DEFAECATION OR URINATION
ALTERED RESPIRATION
RAPID DECLINE IN BODY WEIGHT
VOMITING

APPENDIX 3

HAEMATOXYLIN and EOSIN STAINING TECHNIQUE USED IN ANIMAL STUDY

The histological sections went through:

DEWAXING AND HYDRATION

(Section brought to water)

1. Xylol 5 minutes
2. Xylol 5 minutes
3. Absolute alcohol 2 minutes
4. Absolute alcohol 2 minutes
5. Rinse in tap water 5 minutes

STAINING

6. Haematoxylin 5 minutes
7. Rinse in running tap water 5 minutes
8. Differentiate in 0.5 to 1.0% hydrochloric acid in 70% alcohol for 30 seconds.
9. Rinse in running tap water for 10 minutes
10. Eosin 45 seconds

DEHYDRATION AND MOUNTING (after staining)

11. Absolute alcohol 1 minute
12. Absolute alcohol 1 minute

13. Absolute alcohol and xylol mix 2 minutes
14. Xylol 2 minutes
15. Xylol 2 minutes
16. Mount in Depex with cover slide.

USE: It is a general purpose stain, staining not only cell nuclei and cytoplasm, but also connective tissue. It distinguishes basophilic materials (blue) from eosinophilic materials (pink).

Results : Nuclei -blue
Cytoplasm - pale pink
Erythrocytes - bright red
Muscle - red
Keratin - red
Collagen - pink
Fibrin - pink

VIII

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