In this area, increased oxygen supply shifts cell metabolism from anaerobic to aerobic glycolysis. This allows the oxygenation of lactic acid to carbon dioxide and water via the citric acid cycle, and therefore considerably increases the energy yield per molecule of glucose. Thus the energy needs of a cell can be met by the consumption of considerably less glucose (NIINIKOSKI 1977; 1980a).

Increasing the wound oxygen tension therefore promotes healing whereas hypoxia inhibits it (NIINIKOSKI 1977; 1980a;b; POLLACK 1979b). On a microscopic level, the beneficial effect of oxygen results from 1) enhanced accumulation of collagen, 2) slightly augmented collagen cross-linking, and 3) increased differentiation of wound cells (HUNT & ZEDERFELDT 1969; NIINIKOSKI 1980b). The availability of molecular oxygen is also important to epithelialization and to the generation of free radicals by leucocytes during intracellular microbiocidal activity (POLLACK 1979b).

Wound oxygen.

"The discovery that oxygen is a pivotal nutritional ingredient of healing has dramatized the importance of efficient oxygen supply" (NIINIKOSKI 1980b). Supply to incisional, primarily closed wounds is almost exclusively from blood circulation. (Secondarily granulating wounds probably also recieve some diffused oxygen at the wound surface) (POLLACK 1979b).

Because of its rapid consumption, and the fact that the injury which incites repair also damages the local circulation, a gradient of oxygen supply develops across the wound from the vessel to the centre of the wound dead space. (This gradient also applies to other nutrients and to carbon dioxide and wastes in reverse). By measuring the oxygen tension of the wound at various points across this distance, a gradient

profile can be established so providing a measure of the efficiency of the local circulation in supplying the metabolic needs of the wound (HUNT & ZEDERFELDT 1969). A typical oxygen gradient is illustrated in FIGURE 6.1.

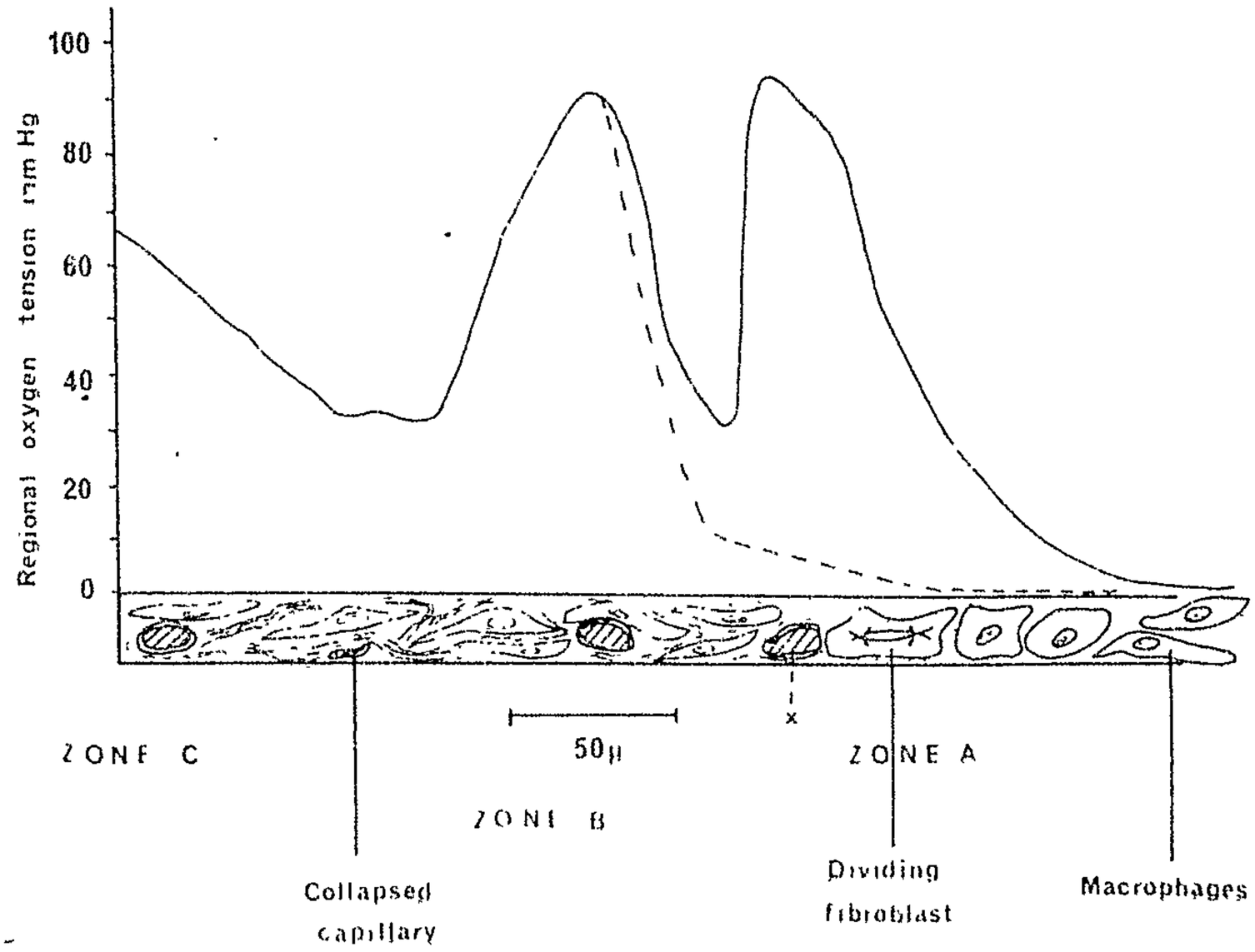

FIGURE 6.1 Diagrammatic section through new tissue growing in an ear chamber, with oxygen tension profile superimposed. Mitotic activity is almost confined to the leading capillary zone. Collagen cross-linking is occuring in the zone of shallow oxygen gradients. Zone A is the growth zone. Zone B is the synthetic zone. Zone C is the established zone. In shock or hypovolemia, if capillary "X" is underperfused, the oxygen profile changes to that shown by dashed line (from SILVER 1980, p20).

This gradient illustrates that wound oxygen tensions are much lower than the mean capillary partial oxygen pressure of approximately 50 mmHg (HUNT 1976a). This relative hypoxia is exaggerated by the increased oxygen requirements of repair tissue (NIINIKOSKI 1980a). Thus the oxygen tension of the wound dead space may be quite low - in the 5 to 20 mmHg range. As the functioning of cells such as fibroblasts in these tissues is highly dependent upon the oxygen concentration, these levels may be insufficient for normal proliferation and synthesis. In these situations the term "critical oxygen tension" is applied; below this level (approximately 20 mmHg, NIINIKOSKI 1977; 1980a;b) cellular oxygen consumption is dependent upon the oxygen tension (HUNT 1976a).

While the wound oxygen tension of primarily closed incisions normally exceeds the critical level, dramatic alterations may occur if blood flow is impaired (see below). Under these conditions, the oxygen level rapidly falls and the concentration of metabolic waste products progressively increases as cell metabolism turns more and more to anaerobic pathways.

Such reductions in blood flow can occur in inflammation as a result of intravascular thrombus formation, suturing (6.3.7), haematoma and oedema formation, and venous stasis (COHEN et al 1975; HYMAN et al 1975). Thus, where injury (and therefore inflammation) is most severe, the oxygen tension is often lowest and the carbon dioxide tension and pH are high (HUNT 1980). Reparative cell functioning (including collagen synthesis) is impeded by such ischaemic conditions (NIINIKOSKI 1977; 1980a).

Any factors which further increase the distance which oxygen and other nutrients must diffuse may therefore tip the tenuous balance by which tissues maintain vitality. The resulting necrosis further increases and prolongs the inflammatory response and may cause massive wound breakdown. A large wound dead space is particularly important here, as is oedema formation (see Chapter 9) since oxygen appears to readily diffuse only to a distance of approximately 120 microns from a capillary (CARPENTER et al 1977; GOODSON et al 1979; DIMITRIEVICH et al 1981; SCHUMANN 1982).

Oxygen availability to the tissues is also determined by its arterial partial pressure, by its dissociation curve from haemoglobin (see ARTIGUE et al 1977; KLITZMAN 1983; SHIGA 1983), and by any local vascular pathology which may be present such as arteriosclerosis, diabetic angiopathy - see Chapter 5. Normal physiological functioning

is generally considered optimal.

In addition to dominating the function of reparative cells, the oxygen concentration gradient across the wound is also highly significant in these cells' spatial arrangement. Thus, inflammatory cells such as polymorphs and macrophages (being able to tolerate hypoxia) are situated closest to the wound edge. These are followed by proliferating fibroblasts and endothelium which are closely dependent upon each other, the former for oxygen supply and the latter for fibrous support.

While it appears that macrophages are particularly significant in guiding the direction of fibroblast and endothelial proliferation, some suggest that the hypoxic tissue gradient is also mandatory for wound healing angiogenesis (HUNT et al 1978; KNIGHTON et al 1981; CHVAPIL & KOOPMANN 1982). This concept comes from observations that oxygen tensions above a certain level actually inhibit neovascularisation. Similarly, fibroblast proliferation is inhibited by oxygen tensions above or below 30 to 40 mmHg (HUNT 1980; KNIGHTON et al 1981). The function of these cells is obviously critically dependent upon tenuously balanced environmental conditions in which the oxygen tension is pivotal.

Summary.

Since injury essentially devascularises the wound edges (HUNT et al 1969), the wound is inherently hypoxic. Its oxygen tension is therefore critical to many aspects of repair. If the oxygen level falls below the so-called "critical" level, cell synthesis and proliferation are impaired, possibly even leading to cell necrosis. In such circumstances, the processes of inflammation are markedly prolonged and exacerbated, collagen synthesis is delayed and slowed, and wound

breakdown may follow if ischaemia is sufficiently severe.

Several factors have been identified as causing impairment of oxygen supply. These include wound size, suturing, local intravascular thrombosis and oedema formation. A variety of pathological states (such as diabetes (5.3.1), irradiation (see following), and arteriosclerosis (5.3.3)) have also been implicated.

6.2.2 Irradiation.

As was mentioned above, wound oxygen tensions reflect the oxygen content of blood and its ability to diffuse out of the erythrocytes and vessels and into the tissues. This is also applied to other nutrients. Ionizing radiation is significant because it damages the vasculature in a manner which impairs such nutrient and cell diffusion.

The observed effects of radiation on blood vessels depend on the radiation dose and the time interval since radiation was administered (FROGGE 1982). Progressive and irreversible tissue changes may occur including oedema, endarteritis, hyalinisation of small vessels, narrowing of vessel lumina, and a gradual decrease in tissue perfusion (CARL et al 1973).

Immediately following radiation, changes in vessel permeability and other signs of inflammation occur in a similar manner to inflammation from other injuries, though blood flow is usually decreased for the first few hours (KEYEUX 1977). After this time, ultrastructural changes may be seen in endothelial cells: the endoplasmic reticula cisternae are dilated and lysosome-like bodies appear. Some nuclei display discrete widening of the perinuclear space and segregation of nucleolar components. At this time, the intercellular junctions are generally intact, though endothelial cell

membranes may be altered and disrupted in some areas. In areas where endothelium is destroyed or lost, platelets and fibrin adhere to the BM (MAISIN et al 1977).

A few days after irradiation (early changes), the lesions within the endothelial cell are more striking. Also, endothelial disruption is more apparent, some cells forming loops separated from the BM (MAISIN et al 1977). One to two months after irradiation (intermediate changes), the capillary lesions are still limited to a small number of areas but are more pronounced. Some lumina contain greatly altered platelet aggregates. The lumen of other capillaries may be obstructed by lipid inclusions or by collagen fibres (MAISIN et al 1977).

Within four weeks of radiation, the cytoplasm of many endothelial cells shows gross changes including autophagic vacuoles and an excess of free ribosomes. The basement membrane at this time is thickened or oedematous (Note: animals given high dose whole body radiation may die between two and seven months after radiation) (MAISIN et al 1977).

Animals which do survive this intermediate phase (late changes) show many areas of sclerosis of parenchymal tissues, extreme thickening of the BM, and replacement of the capillary lumen after 8 to 15 months. Sometimes new capillaries are seen growing into the old sclerotic vessels (MAISIN et al 1977; YORDAN & BERNHARD 1982).

Functional effects.

It is difficult to describe the functional effect of these radiation-induced changes since the cardiovascular system tends to compensate for them, at least partially maintaining relatively normal function (KEYEUX 1977).

Generally speaking, there is a significant dose-dependent decrease in microvascular length and area following radiation; less effect is seen on the larger vessels. Also, the capillary density and mean density between capillaries and larger vessels is considerably decreased with increasing doses of radiation. This may produce areas where the intervessel distance exceeds the oxygen diffusion distance (see 6.2.1.4), thus creating areas which are relatively anoxic (DIMITRIEVICH et al 1981). It is thought that the parenchymal hypoplasia which occurs as a result of organ exposure to radiation may be a consequence of this functional limitation (KEYEUX 1977; MAISIN et al 1977). An additional effect is that the regenerative capacity of affected tissues, particularly endothelium, is diminished by approximately 50% after 125 rads (DIMITRIEVICH et al 1981), though this is disputed (REINHOLD 1977).

Radiation and wound healing.

As would be expected, local irradiation of tissue causes markedly delayed healing of the affected tissue (NEWCOMBE 1972; HORN et al 1979; ARIYAN et al 1980). This impaired healing is very significant if wounding follows within three weeks of irradiation or if radiation is given within 48 hours of wounding.

Whole body radiation in doses of over 1,000 rads also delays wound healing (NEWCOMBE 1972). This is due both to the local effect of radiation, and to its suppressive effect on leukopoiesis in the bone marrow (SCHILLING 1976).

In view of these considerations it is generally recommended that any surgery which must be performed in association with radiation should, where possible, be 1-2 weeks before or 4-8 weeks after

radiation, that is, before the development of occlusive changes (NEWCOMBE 1972; ARIYAN et al 1980).

Particularly significant to oral surgical healing is the observation that, although most clean wounds in irradiated tissue heal without any apparent consequences, (though slightly slower than normal), contaminated wounds have a significantly increased incidence of infection (ARIYAN et al 1980).

In summary, tissues which demonstrate late radiation changes also demonstrate suppression and prolongation of all aspects of repair. The poor vascularity of the tissue is however, unlikely to lead to the production of marked oedema. Any oedema which does form, however, may significantly compromise the vitality of tissue which is already hypoxic.

6.2.3 Wound Microbiology.

Whilst it is not the purpose of this thesis to review wound infections occurring following oral surgery, microbial organisms form an inseparable component of the environment in which such surgery is performed. In the general schema of wound classifications (MACLEAN 1975), oral wounds must generally be classified as "contaminated" or, at best, "clean-contaminated". Consideration of oral flora cannot therefore be excluded from this discussion of wound repair in the mouth.

Oral flora.

Analysis has shown that the concentrations of bacteria in the mouth are enormous, and that there is a vast array of bacterial types (as many as 64 species have been identified on a single tooth, BARTLETT & GORBACH 1976). These include both gram positive and negative bacilli

and yeast organisms in addition to staphylococci and streptococci (BAQAI & HAFIZ 1979a; SEFER & BOANCHIS 1979). Anaerobes generally predominate (BARTLETT & GORBACH 1976; BAQAI & HAFIZ 1979b; BYSTEDT et al 1981).

An important observation regarding these organisms is that bacterial populations of the mouth and upper airways form distinctive ecosystems (or "ecological niches") at various anatomical sites. Thus the flora of the nose, pharynx, tongue, buccal mucosa, tooth surface and gingival crevice are each unique (BARTLETT & GORBACH 1976). (See also RUSSELL & MELVILLE 1978). Strep. salivarius, for example, preferentially colonizes the tongue and buccal mucosa, whereas the dominant streptococci on the tooth surface are S. mutans and S. mitis. S. pyogenes adheres well to oral epithelial cells and is thus common on mucosal surfaces. Fusobacteria, Bacteriodes melaninogenicus and anaerobic spirochaetes tend to aggregate in the gingival crevice (BARTLETT & GORBACH 1976).

The selection of these sites appears to be governed by factors including the selective affinity of certain bacteria for specific cell types, and local environmental conditions such as oxygen tension and pH, and upon bacterial antagonism (BARTLETT & GORBACH 1976).

Another major influence on the oral flora is the saliva (see later). In addition to its various antibacterial and buffering components, salivary flow will tend to wash non-adherent micro-organisms off the tissue surface (RUSSELL & MELVILLE 1978). However, whilst it is generally believed that the microbial count is highest in the fasting saliva, BAQAI et al (1979) were not able to demonstrate any significant difference in microbial count from fasting and non-fasting salivary samples.

Microorganisms and inflammation.

Normally, the oral flora have limited invasive properties unless their ingress to deeper structures is permitted by trauma or disease states (BARTLETT & GORBACH 1976). Surgery therefore significantly reduces the local defence mechanisms by breeching the mucous membrane and placing an inoculum of bacteria in open tissue (LINDHE & SOCRANSKY 1979).

It might be expected that the size of this inoculum would have important consequences on the length and severity of the subsequent inflammatory response since many of the oral microbes contain components which are chemotactic for PMNs, or which mediate increased vascular leakage (LINDHE & SOCRANSKY 1979). Further, PMNs are required to inactivate and phagocytose contaminating microbes. This correlation between numbers of contaminating organisms and numbers of PMNs is supported by LANGE and FOLKE (1975), CARPENTER et al (1977) and G.RYAN (1983) who report increased PMN infiltration and prolongation of the inflammatory response with increased microbial contamination, especially if combined with large amounts of necrotic tissue/haematoma. However, FAHMY et al (1976) found no correlation between the severity of clinical signs of inflammation and the type and number of conjunctival bacteria. The reasons for this unexpected finding are unclear.

Some advocate the use of intraoperative wound culture to aid in the selection of appropriate antibiotic therapy for the prevention of sepsis and in the assessment of contaminating organisms (MACLEAN 1975). However, HOWE (1964) demonstrated that approximately half of the observed wound infections were caused by organisms other than those cultured from the wound immediately prior to closure. It was suggested

that the causal organisms could possibly survive host defences in numbers too small to be cultured if they were particularly virulent, or if they were contained within a section of necrotic tissue and therefore protected. Bacteria adhering to the wound surface are also reported to be significant in prolonging inflammation (LANGEBAEK & BAY 1976). Oral wound biology is further reviewed by MACGREGOR and HART (1969) and BROWN et al (1970).

Factors relating to bacteria are apparently not necessarily the most important in the development of wound sepsis (HOWE 1964). While infection obviously cannot occur in the absence of bacteria, several authors state that local enhancing factors, and the presence of devitalized tissue and/or foreign substances appear to be the most important components in up to 50% of cases (SCHILLING 1976; HARRIS 1979b; FORRESTER 1980b).

What effect do bacteria have on wound repair?

The most severe alteration produced by inoculation of the hamster cheek pouch preparation with oral flora was the presence of frank haemorrhage and oedema after 48 hours (LANGE & FOLKE 1975). In this same preparation stasis and haemorrhage were the most significant microvascular changes reported. Reduced and/or intermittent flow was consistently present, particularly in the venules, as was marked vasodilatation and tortuosity. In these studies, the degree of the response was clearly dependent upon the severity of the trauma and the size of the inoculum (LANGE & FOLKE 1975).

Thus, the organisms' virulence, the size of the microbial inoculum and the amount of necrotic tissue/foreign material present, along with the adequacy of host defences must be considered as the most significant factors in determining the outcome of a contaminated wound

(LANGE & FOLKE 1975; BARTLETT & GORBACH 1976; SIMPSON 1977). The presence of tissue hypoxia is also important in allowing the establishment of organisms within the tissues (SIMPSON 1977), especially as oral organisms are predominantly anaerobic.

The opinion of most surgeons concerning maxillo-facial wounds which communicate with intra-oral tissues commonly assumes that such wounds are grossly contaminated. Surprisingly, this is not supported by experimental results (PATERSON et al 1970). Thorough wound debridement immediately prior to closure may account for this. It is nonetheless important to minimize aspects of the wound which may facilitate bacterial growth and to maximise the ability of the injured tissue to resist infection by striving to maximize nutrient supply to the wound.

In summary, the presence of microorganisms within tissue contributes to the degree of resulting inflammation, both from the effect of the organisms or their products, and from the consequent PMN infiltration. It would appear however, that where wound dead space is small and debridement is thorough, the effect of the bacterial inoculum on inflammatory oedema and wound repair may generally be considered small, even in intraoral wounds.

6.2.4 Saliva.

In several aspects, the physiology of oral mucosa is inherently different from that of other integumental structures such as skin. Foremost of these (and perhaps the major governing factor) is the moist environment provided by the continuous secretions of the oral salivary glands. Saliva is important, not only for its hydration and lubrication of the oral mucosa, but also because of its interactions (physical and biochemical) with the microorganisms and cells which are present.

The effect of hydration on mucosa is as yet poorly defined. Its importance is clearly evident in the severe mucosal effects which follow impaired salivary flow (MAYHALL 1975; GERMAINE 1980; GERMAINE & TELLEFSON 1981). However, the structural and functional features which permit mucosal epithelium to "tolerate" continuous moisture are unknown.

With reference to wound healing, saliva is significant in three areas. Firstly, saliva and its components interact with the oral microflora, both promoting and limiting their growth, and thereby maintaining microbial homeostasis (GERMAINE 1980). Secondly, salivary components may interact with the coagulation and fibrinolytic systems. Thirdly, salivary components, particularly from the submandibular glands, appear to stimulate healing. These areas are considered separately.

6.2.4.1 Saliva and oral microorganisms.

Physicochemical effects.

The interaction between saliva and oral microorganisms is multifactorial. There is firstly a physical "flushing" or "rinsing" action which prevents their overgrowth (MAYHALL 1975; GERMAINE 1980). Also, the viscous nature of saliva (attributed to salivary glycoproteins - "mucoids", ADAMS 1975; MAYHALL 1975; GERMAINE 1980) may contribute to salivary bacterial agglutinating activity, thus allowing their removal from the mouth. On the other hand, these glycoproteins probably also assist bacterial adherence to mucosal surfaces (MAYHALL 1975; GERMAINE 1980).

Salivary buffering capacity enables maintenance of a relatively steady state in the oral fluids (though this capacity may be altered by

various physiological effects) (MAYHALL 1975). This, plus the salivary pH, is important in determining the physicochemical environment of the various ecological niches, thereby favouring some microorganisms over others.

Anti-microbial effects.

Several substances having potential antimicrobial activity have been identified as normal constituents of saliva. These may act independently, or in synergism. Some appear to act against specific oral microorganisms (DOWLA 1982). Most however exert non-specific antimicrobial effects. The major effects are outlined below. Research of this area has been confused by observations of differing antimicrobial effectiveness in the same individual at different times (MAYHALL 1975).

Salivary lactoperoxidase is an enzyme which oxidises surface components of bacterial cells. This reaction also requires the presence of hydrogen peroxide (perhaps from anaerobic bacteria) and thiocyanate ion (another salivary constituent) (BOWEN 1974; GERMAINE 1980; THOMAS et al 1981) - the "lactoperoxidase system" (GERMAINE & TELLEFSON 1981). It is not thought that these components are normally present at high enough concentrations to be microbiocidal (THOMAS et al 1981). Rather, they may impair bacterial metabolism thus reducing the "localised bioimpact of the organism" (GERMAINE 1980). This system appears to have significant activity against lactobaccilli (BOWEN 1974).

Lactoferrin is an iron-binding protein which sequesters the iron needed for the growth of facultative or aerobic bacteria, thereby depleting the local environment of this mineral. Lactoferrin is thus bacteriostatic in action (BOWEN 1974; GERMAINE 1980).

FLEMING (1922, cited by MAYHALL 1975) discovered an agent in saliva and other body fluids which was able to lyse certain microorganisms. Termed "lysozyme", this agent has been found to be a normal constituent of saliva. Along with other similar cationic proteins, lysozyme is bacteriocidal through its disruption of cell membranes (BOWEN 1974; MAYHALL 1975; GERMAINE 1980). Although a large variety of microorganisms have cellular structures which are susceptible to its effects, bacteria normally in the mouth are apparently somewhat resistant to its effects (BOWEN 1974), perhaps through the inhibitory effects of salivary mucoids (MAYHALL 1975).

Also important in limiting the growth of oral microorganisms is the presence of significant concentrations of secretory immunoglobulins in saliva (principally immunoglobulin A, IgA) (BOWEN 1974). Salivary IgA, like the mucoids, is important in physical agglutination of bacterial cells, allowing their clearance from the mouth. Specific salivary IgA antibodies have also been demonstrated and these may selectively control microfloral growth (ERICSON et al 1975; MAYHALL 1975; REED 1976; GERMAINE 1980). Salivary IgA may also form complexes with peroxides and lysozyme (GERMAINE & TELLEFSON 1981).

Two other properties have also been attributed to saliva, which may also be related to its antibacterial activity. These properties relate to as yet undefined salivary constituents; they cause increased microvascular permeability and also leucocyte chemotaxis. The effect of these properties is unknown (MAYHALL 1975). It is noted that oral flora may reproduce both these effects (LINDHE & SOCRANSKY 1979).

Importantly, the normal oral microflora occupies all available ecological niches and utilises available nutrients, thereby restricting the establishment of transient microorganisms. Should the normal flora

be depressed, for example, by antibiotic therapy, other organisms may develop dominance (REED 1976; GERMAINE 1980).

Since the oral environment contains numerous biological niches with markedly differing conditions, it must be assumed that the impact of the above anti-bacterial factors shows significant variation. It is likely that their greatest impact is seen in those areas which are continuously bathed by renewed salivary secretion (GERMAINE & TELLEFSON 1981).

The occurrence of various leucocytes in saliva is also noted, sometimes in high concentrations. Individual differences are reported and there appears to be some correlation (inverse) between leucocyte numbers and activity and the caries rate (BOWEN 1974). These cells are thus likely to contribute towards controlling the number of organisms which are present.

In summary, saliva and some of its constituents may inhibit or enhance bacterial growth, promote bacterial cell lysis and inhibit or enhance the adherence of microorganisms to oral tissues. These effects enable the growth of bacteria adapted to this environment, but at the same time tend to limit overgrowth (along with bacterial competition for sites and nutrients).

The formation of a wound in the oral tissues however, disturbs this balance by breeching the mucosal barrier. Nevertheless, the incidence of sepsis is such wounds is low (see 6.2.3), suggesting that the body's antibacterial agents are generally effective. The presence of saliva in these wounds would be assumed to contribute to this, in addition to its effect on the wound surface, where adherent bacteria would otherwise cause additional local inflammation of the wound edges (6.2.3).

6.2.4.2 Saliva and the coagulation/fibrinolytic systems.

Saliva has been reported by some to contain substances which promote blood coagulation, an effect which is suggested to occur if blood and saliva mix before coagulation (VON SCHULTE 1974). (See also MAYHALL 1975). More commonly, authors refer to the promotion of fibrinolysis by salivary factors (VON SCHULTE 1974; RAMSTROM 1975; GERSEL-PEDERSEN 1979; MOODY 1982a).

Fibrinolysis occurs through the activation of the inactive plasminogen, which is included in all clots because of the high affinity between plasminogen and fibrinogen. The addition of a small amount of plasminogen activator may therefore suffice to release plasmin. Such activator activity has been identified in saliva. It was suggested to arise both from salivary secretion and from proteolytic enzymes produced by crevicular bacteria (RAMSTROM 1975). MOODY (1982a) however, found such activity only in association with epithelial cells or cell fragments within the saliva. He suggested that this was the true source of the plasminogen activator activity of saliva.

These effects are normally believed to be prevented by plasma inhibitors of plasminogen activator in the plasma. This protective effect may be absent in some individuals, variously leading to post-surgical haemorrhage and localised alveolar osteitis ("dry socket") (GERSEL-PEDERSEN 1979; MOODY 1982b).

Thus, in the normal individual, there would appear to be little breakdown of the clot by salivary factors. These factors would therefore not be significant to the progress of healing. However, in some individuals, either salivary fibrinolytic activity is abnormally high, or the presence of plasma inhibitors of plasminogen activators in

the clot is reduced. In such a situation, significant plasmin is generated early, thereby leading to increased kinin production, activation of complement, and the release of vasoactive FDP's (see 3.3.1.2). Inflammation in such circumstances is thereby increased, and haemorrhage may persist or recurr, disrupting repair.

6.2.4.3 Saliva and healing.

It has long been observed that animals innately lick their wounds, and that this action seems to aid or promote healing. This observation has promoted intense research into the effect of saliva on repair processes. Several factors are suggested to be involved. Firstly, there is the obvious physical cleansing of the wound which licking achieves. However, studies in which licking has been prevented have shown that licking is important in enhancing wound contraction (LI & KOROLY 1981).

Whilst the action of lysozyme and other antibacterial substances found in saliva may contribute to this enhanced healing by the suppression of microbial growth (HUTSON et al 1979; NIALL et al 1982), recent studies have discovered that saliva contains a group of growth-promoting molecules. These include nerve growth factor (NGF) and epidermal growth factor (EGF), and both are reported to be more effective via topical application than when blood-borne (LI & KOROLY 1981; NIALL et al 1982). Though their site of action is quite different (EGF on epithelium and NGF on neural tissue), these macromolecules produce very similar effects, chiefly, markedly enhanced wound contraction (LI & KOROLY 1981).

The mode of action of these substances is unknown, though it may occur via direct stimulation of fibroblasts (which also secrete them)

(LI et al 1980). Interestingly, these substances are chiefly produced in the submandibular salivary glands in sites which are sensitive to testosterone. Thus, EGF and NGF occur in higher concentrations in male animals (HIRATA & ORTH 1979; MURPHY et al 1979). The concentration and action of these substances in human saliva is unknown.

How the healing of primarily closed intraoral wounds is affected by EGF and NGF is also not known. There does not appear to be an association with collagen synthesis (LI & KOROLY 1981), and perhaps their only action is in reducing the size of the wound needing repair. It is also not known if the effectiveness of these substances is influenced by any environmental or pathological conditions.

In summary, saliva contains substances which accelerate wound healing, chiefly by enhancing contraction. In combination, with the antibacterial effects of saliva, this may reduce inflammation and enhance early wound strength. However, not all factors associated with wound healing in the mouth have yet been elucidated.

6.2.5 Other Factors.

6.2.5.1 Temperature.

It is apparent, even under physiological conditions, that tissue volume changes in proportion to the environmental temperature. These changes result from changes in blood flow through the skin in response to superficial temperature changes (LEWIS 1941; FAGRELL & INTAGLIETTA 1977). Environmental temperature might therefore be expected to cause some effect on wound repair. That this is so is supported by studies by BEKEMEIER et al (1982) who report that increasing the temperature of the skin led, after a small delay, to increased inflammatory oedema in rat paws.

On the other hand, hypothermia occurring up to the fifth post-operative day, reduces the tensile strength and rate of healing of wounds. This is again believed to result from altered haemodynamics and decreased flow rate. Cold may also slow healing simply by its reduction of tissue metabolism (SILVER 1982). The involvement of the central nervous system in this response is clearly shown in that such hypothermic depression of healing is abolished if the wound area is denervated (POLLACK 1979b). Deep wounds are generally not affected unless the whole body becomes hypothermic (POLLACK 1979b); similarly with intraoral wounds.

The therapeutic use of thermal changes is discussed in Chapter 8.

6.2.5.2 Tobacco smoking.

Cigarette smoke contains 2-3mg of nicotine per cigarette (depending on the brand); most of this is absorbed during inhalation. Nicotine exerts a significant action on the cardiovascular system by increasing heart rate, cardiac output, blood pressure and coronary blood flow. It also causes marked cutaneous vasoconstriction (MOSLEY & FINSETH 1977) acting both locally and systemically, since non-inhaled smoke causes oral mucosal vasoconstriction in the absence of any systemic effects (SHULER 1968).

Also significant is the presence of 20-30cc per cigarette of carbon monoxide (as quoted, MOSLEY & FINSETH 1977). This is rapidly absorbed by the haemoglobin molecule in preference to oxygen, forming carboxyhaemoglobin (MOSLEY & FINSETH 1977; SCHUMANN 1979; SWEET & BUTLER 1979). Nitrous oxides and hydrogen cyanide are also present (MOSLEY & FINSETH 1977).

It is also reported (SWEET & BUTLER 1979) that smokers have a decreased ability to utilise vitamin C. Hence they have an increased requirement for this vitamin.

Thus tobacco smoking may potentially cause significant healing problems both from the nicotine-induced vasoconstriction, and from impaired wound oxygenation due to even moderate levels of carbon monoxide and other components (MOSLEY & FINSETH 1977). Post-operative smoking (at least 24 hours post-operative) is a particular problem (SWEET & BUTLER 1979).

Although such vasoconstrictive effects might tend to suppress oedema formation, there are no reports attributing such a reduction to tobacco usage. It may be that the impaired healing which tobacco smoking is thought to cause arises more from the hypoxic effects of both vasoconstriction and decreased oxygen release than from vasoconstriction per sé.

6.2.5.3 Wound orientation/Langer's lines.

"The concept of skin tension and lines of election (for surgical incision) has its origin in the classic works of DUPUYTREN in 1834 and LANGER in 1861" (FLINT 1976). While there was some confusion about the significance of these lines, FLINT (1976) thoroughly re-examined them and found that the connective tissue fibre arrangement was generally along the lines as outlined by Langer.

Cleavage lines are similarly described in oral mucosa (See FIGURE 6.2). Significant scarring is evident when the incision traverses such lines, whereas scars are almost invisible (even without suturing) when the incisions were placed along them (MOTEGI et al 1975).

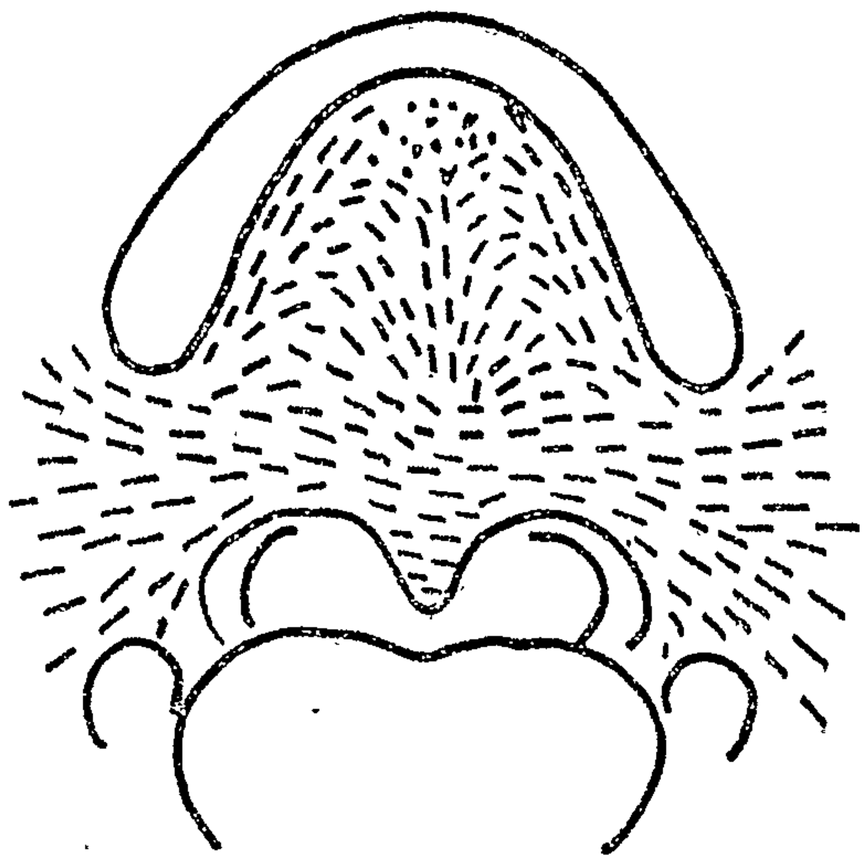

FIGURE 6.2 Mucosal clearage lines in the palate and surrounding areas (from MOTEGI et al 1975, p158).

The connective tissue fibre arrangement described by these lines is such that tension is greatest lengthways and least crossways along them. Thus, an incision placed along Langer's lines tends to naturally appose whereas one placed across them tends to gape.

Tension at the wound edge is important since it compromises wound strength, decreases contraction (and thus increases the width of the final scar) and restricts the flow of blood to and from the wound, possibly devitalising tissue (HARRIS 1979b). Therefore, tension, plus the asymmetric blood supply of mucosa adjacent to teeth, may produce flap necrosis and hence, very prolonged healing. Alignment of the incision so as to minimise this tension is therefore essential.

Suturing to achieve closure under circumstances where wound alignment is poor may further contribute to tissue ischaemia, promoting further inflammation and local oedema. It is significant that the normal tissue response to ischaemia (namely intense vasodilatation) may, under these circumstances, significantly increase oedema and thus

ultimately further impair oxygen supply to the wound (6.2.1.4).

Another significant feature in planning the direction of oral wounds is the orientation of gingival vessels (2.7). Based on the vertical alignment of gingival vessels, and the increased collateral supply in papillary regions, vertical incisions in this region suffer the least ischaemia (MORMANN et al 1979). Horizontal incisions demonstrated the greatest ischaemia (of the attached gingiva) although collateral supply from periodontal ligament vessels is often sufficient to prevent complete devitalisation (MORMANN et al 1979).

Wound alignment is thus critical to ensure minimal wound tension and maximal blood supply. Tissue ischaemia/necrosis is discussed further in 6.3.

6.2.5.3 Local anaesthetic/vasoconstrictor.

Both the local anaesthetic and vasoconstrictor agents are variously described to affect early wound healing.

Of the various local anaesthetic (LA) agents, both lignocaine and procaine have been reported to significantly depress early wound strength. This effect is dose-dependent and appears to relate to depressed proteoglycan and collagen synthesis (MORRIS & TRACEY 1977; MORRIS & APPLEBY 1980). It has been suggested that these agents also inhibit collagen secretion by fibroblasts, possibly by interference with the microtubular system (CHVAPIL et al 1979; MORRIS & APPLEBY 1980). CHVAPIL et al (1979) demonstrated that bupivacaine produced similar dose-dependent suppression of connective tissue synthesis. It is noted that this local anaesthetic-induced suppression is mostly corrected after seven days (MORRIS & APPLEBY 1980).

An obvious effect of any vasoconstrictor such as adrenaline is that it reduces wound blood flow if injected locally. The vasoconstrictor is probably also significant because it prolongs the exposure of the tissues to the local anaesthetic thus potentiating the LA-induced depression of healing (MORRIS & APPLEBY 1980).

An interesting clinical effect of the use of vasoconstrictors in local anaesthetic surgery was forthcoming from the work of SVEEN (1979). As would be expected, this author observed significantly decreased blood loss at surgery if a vasoconstrictor was used (compared with wounds in which local anaesthetic was used alone). However, the group of patients in which the vasoconstrictor was used demonstrated a significant increase in post-operative haemorrhage. Of these, 83% showed healing by secondary intention.

These results suggest that there may be some basis to the clinical observation that wounds made under general anaesthetic heal faster than similar wounds made under local anaesthetic (MORRIS & APPLEBY 1980). It is obvious however that the use of local anaesthetic remains the technique of choice in many cases. It is thus essential to avoid excessive use of these agents, particularly where they are used in combination with vasoconstrictors.

6.2.5.5 Exercise/mobility.

As mentioned above, movement across the early wound can shear new capillaries and collagen bridges within the granulation tissue, and thus lead to persistance of transudation and oedema formation. (ANDERSON 1962; SCHILLING 1976; SILVER 1982). A major difficulty with oral surgery in this regard is that facial soft tissue structures cannot be immobilized. In fact, for the patient to obtain the adequate

food intake necessary to meet wound nutritional requirements, movement is unavoidable. Social functions, such as talking, are also important for a person's sense of well-being. Nonetheless, some limitation of movement is advisable in the first few days following surgery until collagen deposition has stabilised the wound.

In addition to the mechanical disruption of the wound, SILVER (1982) suggests that hard exercise and other stresses reduce the rate of healing by increasing the levels of circulating glucocorticoids and by mechanical breakdown of newly formed collagen.

On the other hand, movement is important in assisting the lymphatic clearance of oedema fluid from tissues. Also, mild tension and slight movement in a wound is beneficial in orienting the deposition of newly formed collagen across the wound (and possibly in stimulating synthesis and reorganisation, CHVAPIL & KOOPMANN 1982) (SCHILLING 1976; SILVER 1982). Inactivity is described as leading to decreased wound strength, perhaps as a result of tipping the balance of collagen synthesis/degradation towards degradation (VAILAS et al 1981).

Thus, a balance must be sought so that the positive influences of movement are emphasised and those which are negative are minimised. Once wound strength has begun to rise, active movement should be encouraged so as to disperse the accumulated fluid and fibrin adhesions which accompanied it.

Because of these factors, conditions which impair or delay the development of early wound strength (outlined above) become increasingly significant in the oral surgical wound since any such delay in repair potentially allows movement and shearing forces to persist across the wound edge. The maintenance of this low-grade trauma

in association with poorly supported new vessels may promote continued inflammation and potentiate the continued formation of oedema.

6.3 INTRA-OPERATIVE FACTORS.

A wide variety of intraoperative factors has been implicated in the development of post-surgical oedema. These range from the instruments used (for example, chisel vs bur) to flap design and the method of closure. All of these items must be regarded as central causative factors since they constitute the direct tissue injury. For this reason, Halstead's principles of surgical technique are reiterated in 6.3.6.

In view of their complexity and variety, each of the major intraoperative factors is discussed separately. Interactions between them are mentioned where appropriate. Discussion roughly follows the average operative sequence, considering the surgical removal of the third molar tooth for illustrative purposes. Such a procedure is described as involving the surgical manipulation of soft and hard tissue with the exposure of susceptible tissues to a septic environment (CACI & GLUCK 1976).

6.3.1 The Incision.

Two basic incisions are described in the literature: horizontal ("envelope") and vertical ("L-shaped"). These are illustrated in FIGURE 6.3. As can be seen, some adaptation of these may be obtained by minor variations should additional access be required.

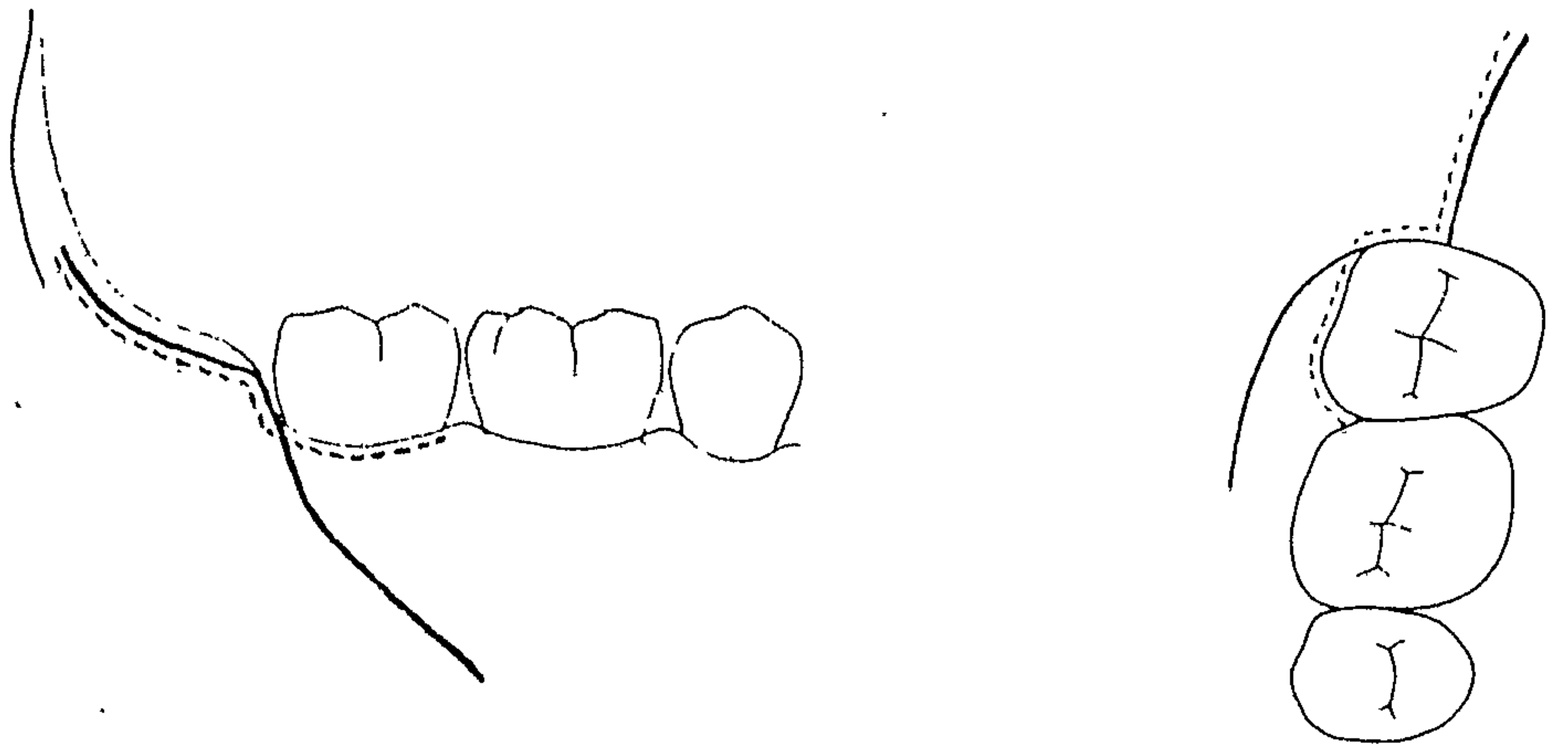

FIGURE 6.3 Horizontal (---) and vertical (——) incisions for the removal of mandibular third molars (from TEN BOSCH & VAN GOOL 1977, p23).

Both incisions are supported by groups of authors. For example, RUD et al (1963) and RUD (1970) recommend the horizontal incision. Others, including HUTCHINSON et al (1978) and CAMERON (1980), favour the basic vertical or "L-shaped incision or a modification of it. In both cases, a full thickness, mucoperiosteal flap is raised following incision.

Few authors have compared the effects of these differing flap designs. MACGREGOR and HUTCHINSON (1975) observed that the use of the horizontal design appeared to reduce post-operative swelling, pain and trismus. They qualified this with the comment that when pain did occur with such an incision, it was generally more severe and of longer duration. They therefore recommended further investigation.

In a large series, TEN BOSCH and VAN GOOL (1977) and VAN GOOL et al (1977) carefully examined these flap designs and their post-operative sequelae. These authors found that the type of incision was of no importance, though the vertical "relaxing" incision is said to make flap elevation easier and to allow better visualisation and access. They concluded that the primary surgical insult which promoted oedema formation related more to the reflection of the mucoperiosteum

than to the presence or absence of the buccal relieving incision. This observation was based on comparison of these results with the effect of forceps extraction or elevation of third molars on oedema. As is the experience of this author, VAN GOOL et al (1977) found that incisions with minimal flap elevation caused little pain, trismus or oedema.

Interestingly, VAN DER ZWAN et al (1982) quote these authors as recommending the use of vertical relieving incisions to relieve oedema. This recommendation is not explained but some believe that leaving this aspect of the wound unsutured allows fluid to seep from the wound (see 6.3.7).

Several features of the incision are important. Firstly, and most obviously, it is chiefly the incision which severs the vasculature. This damage is extended when the periosteum is elevated from bone, thus severing the transosseus collateral supply. Thus, the larger the incision, the larger the vascular injury, and the proportionally larger increase in inflammatory cells required for repair. In other words, the larger the wound, the larger the metabolic requirements and the greater the impairment of nutrient supply (GOODSON et al 1979).

This must be balanced by the fact that inadequate exposure produces increased soft tissue tension and trauma, in addition to making the surgical procedure more difficult (SCHILLING 1976; YORDAN & BERNHARD 1982). Thus, wound size should be large enough to allow adequate access to achieve the surgical task with the minimum trauma, but not so large as to dramatically increase wound dead space and thereby mar tissue vitality.

Secondly, incisions should be in harmony with local anatomy. That is, they should be aligned so as to minimize tension in the margins (in harmony with connective tissue cleavage lines - 6.2.4.3) and to minimize the vascular injury. They should also consider vessel orientation (2.7) and position. For example, the alveolar mucosa of the buccal sulcus is highly vascular. Vertical relieving incisions which penetrate deep into this region should be avoided since they are likely to sever numerous vessels. In addition, severing or elevation of the attachment of buccinator to the external oblique ridge is also reported to markedly increase buccal oedema (HUTCHINSON et al 1978).

Thirdly, incisions and tissue elevation should be made cleanly and sharply so as to avoid tissue maceration and dissection of anatomic planes (YORDAN & BERNHARD 1982). These factors may greatly increase the extent of vascular and tissue damage.

6.3.2 Instruments.

It is certainly not the object of this discourse to describe the many alternative instruments which may be used to achieve the removal of third molar teeth. However, discussion of the alternative instruments used in removing bone may be relevant here.

Surgical bur versus chisel.

Few studies have compared the effect of the use of surgical burs or chisels on post-operative sequelae. Both constitute a variable component of the surgical trauma though their biological effects are likely to be quite different.

Chisels may be used to remove large portions of bone fairly quickly. However, their action is less well-controlled than that of burs and the resultant defect may be larger.

Burs however, cause significant frictional heating of the local bone. Even with the maintenance of saline irrigation, the temperature adjacent to powered saws and drills may reach 60 degrees Celsius or above (ERIKSSON et al 1982). It is generally considered that temperatures above this are deleterious to bone tissue, causing denaturation of the hard tissue proteins. "Doughnut" or "ring sequestration" may follow (ANDERSON & FINLAYSON 1943; THOMPSON 1958, both cited by GRIFFIN 1981). The longer the frictional stimulus of bur cutting is applied, the more widespread is the heat effect and the longer the time required for the heat to dissipate (GRIFFIN 1981).

These effects obviously increase the necrosis of wound tissues as well as impairing collateral blood supply within bone. They may also produce delayed healing as a consequence of continued sequestration of devitalised bone. However, if the bur is used with only moderate pressure, for limited periods and with copious irrigation, its use is probably not significant in increasing wound trauma.

The relationship between the bony wound and soft tissue oedema has not been established. It is conceivable however, that the transudate resulting from intrabony inflammation may contribute to general oedema of the overlying tissues. If sequestration occurs, the soft tissue wound certainly exhibits delayed resolution of inflammation and often, wound breakdown.

6.3.3 State of Eruption.

The state of eruption of a third molar may affect the surgery and its consequences in several ways. Firstly, a tooth which is deeply impacted will most likely require more extensive exposure, increased removal of bone and increased time of operation than a tooth which is

relatively superficial, and probably at least partially erupted (see VAN GOOL et al 1977).

Secondly, the exposure of a tooth to the mouth, even only via a periodontal pocket, means that microbial factors are automatically part of the environment. Further, in the case of such a tooth, acute or chronic pericoronitis may be present.

The effect of these factors is disputed. RUD et al (1963) and RUD (1970) report no effect from either the state of eruption or the presence of acute infection. However, MACGREGOR and HART (1969), and HELLEM and NORDENRAM (1973) both reported significantly worsened post-operative sequelae if the tooth removed was unerupted, because of increased surgical difficulty. This would suggest that surgical factors are normally of more importance than microbial (see 6.2.3).

6.3.4 Length of Surgery.

Several factors may increase the length of time required to remove an impacted third molar tooth. Obviously the level of experience and expertise of the surgeon is significant, with less experienced operators requiring longer to achieve the same result. In addition, the type and depth of impaction are important, as is the root configuration, the need for tooth sectioning and the access to the surgical site. The latter, in the author's experience, appears to be highly significant to the degree of post-operative oedema, as evidenced by the degree of oedema which follows the removal of maxillary third molars where access is severely limited. Difficulty in obtaining haemostasis may also prolong the surgical procedure.

The literature describes contradictory effects of increased surgical time. Some authors (MACGREGOR & HART 1969; BYSTEDT 1976;

LEVIN & GROWER 1977; CAMERON 1980) found that the length of the surgical procedure was not significant. Similarly, HARVO-NOPONEN and SEPPALA (1968) found that the length of "surgical trauma" was not significant in the degree of oedema which developed following labour, childbirth and episiotomy.

However, the widely held clinical view is that the length of surgical trauma considerably influences the degree of post-operative swelling (HELLEM & NORDENRAM 1973; CACI & GLUCK 1976; WARD 1976; VAN GOOL et al 1977; VAN DER ZWAN et al 1982), and it is difficult to resolve these conflicting opinions. The clinically expected effect is that increasing the time during which the tissues are traumatised would increase the inflammatory response. Increased bacterial contamination is also reported to occur in these circumstances (NICHOLS 1982). Further controlled studies are required to assess this question.

6.3.5 Haemorrhage.

It is reported that the blood loss incurred during the removal of impacted third molar teeth may be compared to that lost during an uncomplicated appendicectomy (SVEEN 1979). Blood loss would increase if damage were to occur to the rich supraperiosteal and muscle vascular beds (ANDERSON 1962). It may also be increased when surgery is performed in the presence of a low-grade chronic or subsiding infection and possibly just prior to, during and immediately after menstruation (ANDERSON 1962).

Ignoring the systemic effects of haemorrhage, persistent or recurrent haemorrhage occuring after wound closure is highly significant in the region of the local wound.

Firstly, it may open tissue planes, and collect to form a haematoma. Where haemorrhage has been large, such a haematoma may occupy a large volume and thereby possibly compromise the patient's airway (GOLDSTEIN 1981).

Secondly, in addition to continually disrupting repair, a continuous haemorrhagic ooze dramatically increases tissue colloidal pressure until coagulation. The reabsorption of fluid in the venules is therefore decreased.

Thirdly, the persistent vessel leakage allows increased fluid, cells and proteins to enter the tissues. This must also cause the continued activation of plasma mediators.

Fourthly, once clotted, the haematoma is essentially non-vital and is treated as a foreign body. This mass must be lysed and phagocytosed and its presence necessitates a much higher leucocyte infiltration. Further, this clot increases wound dead space, perhaps leading to loss of vitality of tissue as a consequence of inadequate nutrient supply.

Fifthly, this mass, being non-vital and anoxic, while at the same time containing many nutrients, provides an ideal medium for bacterial proliferation.

These factors may potentially combine to produce a situation of massive oedema and delayed healing, and perhaps wound sepsis.

6.3.6 Surgical Trauma.

The literature repeatedly states that minimizing the amount of surgical trauma reduces post-operative oedema (STUCKER 1974; WARD 1976; VAN DER ZWAN et al 1982; YORDAN & BERNHARD 1982). While these comments

are obvious, that they are repeated so frequently suggests that surgeons may need to be reminded that they inflict the major component of surgical trauma and that this trauma may be exacerbated by careless handling of the tissues.

While the normal physiological healing processes cannot be accelerated, "the surgeon, by haemostasis, asepsis, suturing, approximating dead space and debridement reduces the time course of wound healing by reducing the wound quantitatively, though not altering it qualitatively" (SCHILLING 1976). This remark merely re-emphasises Halstead's classical principles of surgical technique, namely "gentleness, haemostasis, adequate blood supply, asepsis, no tension, careful approximation, and obliteration of dead space" (SCHILLING 1976). Schilling claims that approximately half of the post-operative complications within the wound can be directly linked to abuse of Halstead's principles.

Such abuse may increase the direct and indirect tissue injury (see 3.2.1.3), it may restrict vascular supply to the wound or it may increase wound volume. In all cases, the inflammatory reaction must be both increased and prolonged with concomitant exacerbation of post-operative sequelae and possible wound breakdown or infection. Tissue necrosis or devitalisation in the wound may be increased, for example, by rough or prolonged retraction and the excessive use of electrocautery. Tight suturing (see 6.3.7) and excessive force in tooth elevation (VAN DER ZWAN et al 1982) are also significant, as is the size of the extravascular clot (CARPENTER et al 1977).

The presence of such non-vital tissue within the wound places additional load upon wound defences, as well as supporting the growth of bacteria. These effects result from the fact that necrotic tissue:

1) acts as a culture medium, 2) inhibits leucocyte phagocytosis (due to its hypoxia and low pH), and 3) excessively occupies leucocyte functioning. Leucocytes are therefore unable to devote time to bacteriocidal activity (HAURY et al 1980). Such tissue should therefore be excised where possible. If complete excision is not possible due to the presence of specialised structures, thorough irrigation and debridement may suffice (HAURY et al 1980; RILEY 1981).

6.3.7 Sutures.

Connective tissue formation proceeds best in the undisturbed wound. The purpose of sutures is therefore to maintain tissue approximation, providing adequate tensile strength across the incision while collagen is being deposited to secure permanent repair (FORRESTER 1980a; YORDAN & BERNHARD 1982).

The key to successful suturing lies in recognition of the wound as a repair organ (the "wound module" concept - 1.5.1), and in understanding the response which follows injury. It also depends on understanding of the physical characteristics and biological effects of the suture materials (FORRESTER 1980a).

When an incision is closed, marked biochemical changes can be observed in the adjacent normal tissues. As far as sutures are concerned, the most important change is the active collagenolysis which occurs in the first few post-operative days at the wound margin. This lytic process is enhanced if the wound becomes infected. If sutures are to hold securely, they should be placed well back from the wound edge so as to avoid this zone (FORRESTER 1980a).

The oedema which occurs as a consequence of injury must also be kept in mind. Suturing should allow for this increased volume,

otherwise the suture may "strangle" the swollen tissue which it encloses (DUNPHY & JACKSON 1962; YORDAN & BERNHARD 1982).

Also, the insertion of the suture causes partial or complete transection of structures lying in or around the suture needle's path. This "tract" of injury is maintained by the suture until the latter is removed (ORDMAN & GILLMAN 1966b;c). The tract wound is also seen to be associated with epithelial downgrowth, particularly where the suture is retained for some time (BARCLAY 1970). For these reasons, the number of sutures used should be the minimal number required to appose the wound edges (DUNPHY & JACKSON 1962) and they should be retained only as long as necessary, that is until significant collagen deposition has begun (about four to five days, SIMPSON 1977).

6.3.7.1 Suture material.

Wounds heal in spite of sutures since these must always be considered as foreign bodies and as such may adversely affect healing. However, there is often no alternative to their use. The choice of suture materials therefore has a significant effect on the extent of the inflammatory phase (CARPENTER et al 1977; FORRESTER 1980a).

FORRESTER (1980a) identifies three principle considerations:

i) The amount of suture material implanted should be minimized by using the finest gauge appropriate (see also YORDAN & BERNHARD 1982). Note: the volume of suture material rises with the square of the diameter. Thus increasing the gauge by one size significantly increases the amount of material in the wound, and therefore the subsequent tissue reaction (NEWCOMBE 1972).

ii) Suture tensile strength. Materials have different tendencies to lose their strength due to embedding in the tissues. Absorbable sutures

rapidly lose strength; however, they may persist for some time in the tissues, continuing to be a foreign body, but providing no strength to the wound.

Non-absorbable sutures also lose strength once in the tissues. This is a function of their gauge; for example, fine nylon sutures (such as those found in braided sutures) are chemically less stable, stimulating a brisk tissue reaction and rapidly losing strength (NEWCOMBE 1972).

iii) The extent to which the particular suture irritates the tissues is also important. All sutures elicit some tissue response. In general, the natural materials are the most irritant and synthetic monofilaments, the least.

The tissue responses to the suture depend upon many factors: 1) tissue type, 2) age, 3) sex, 4) immunological status, 5) biohumoral condition of the experimental model, 6) stress, 7) infection, and 8) the extent of the injury in addition to the physical characteristics of the suture material. Of these factors, age and the physical characteristics of the suture are generally the most important in a standard wound under experimental conditions (SANTORO et al 1982). Infection is also highly significant (FORRESTER 1980a; SANTORO et al 1982).

Since all sutures are foreign bodies a certain amount of reaction is inevitable; however, it is rare that a uniform reaction develops along the entire embedded length (POSTLETHWAIT 1969). The histology of the tissue reaction is thoroughly reviewed by ORDMAN & GILLMAN (1966b;c), POSTLETHWAIT (1969) and SANTORO et al (1982).

Thus, sutures produce additional injury by their insertion. This injury is compounded by the irritant nature of the suture material, which promotes further inflammatory exudation. Whether suturing per sé is significant in increasing oedema is disputed. Some authors (VAN GOOL et al 1977) found it had no effect, whereas others (RUD et al 1963) found that suturing increased oedema but that the primary closure so achieved promoted healing (see following section). Suturing to achieve closure is suggested to limit the flow of inflammatory exudate from the wound thus "trapping" it within the tissue.

Perhaps the greatest damaging effect of suturing occurs if sutures are tied too tightly, thus strangling the tissues and potentiating necrosis. This is explained further below.

6.3.7.2 Techniques of suturing.

Little attention has been paid to the effect of different suture techniques on healing and wound tensile strength (NEWCOMBE 1972). However, it is apparent that the major suturing techniques - continuous versus interrupted - have significantly different effects on microvascular kinetics and the healing of an incised wound.

When compared to the wound closed with simple interrupted sutures, the wound closed with a continuous suturing technique shows more extensive and prolonged oedema and induration. More sluggish efferent and afferent microcirculations are also evident (SPEER 1979). After twelve days, the burst strength of such a wound is markedly less than a similar wound closed with simple interrupted sutures. SPEER (1979) attributes these differences to the altered microcirculatory dynamics which prolong the inflammatory process and impair collagen synthesis.

A continuous suture can be conceptualised as a "single-element helical coil fixed at both ends and filled with dermal and epidermal tissue. As the enclosed tissue swells in response to injury, tissue pressure within the spiral increases and stretches the suture" to its limit. Tissue ischaemia ensues, with the tied ends of the suture causing the greatest restriction (SPEER 1979).

In the clinical situation and when care is used, these effects are probably not significant and either technique is satisfactory (NEWCOMBE 1972; SPEER 1979; FORRESTER 1980a). However, where the microcirculation is impaired (as in advanced age, irradiated tissue, and so on) or where early movement is desired (for example, over a joint), the "interrupted technique may offer a greater margin of safety" (SPEER 1979).

6.3.8 Wound Closure.

There are two chief forms of closure - "primary" and "secondary". In primary closure, the wound edges are directly apposed with sutures, leaving only a small wound space. In secondary closure, the wound is left open and the defect is allowed to granulate. On occasions, these techniques may be combined within the one wound (SCHILLING 1976).

As mentioned above (6.3.7.1), primary closure is suggested to lead to increased oedema and pain (DUBOIS et al 1982). Nonetheless, most believe that it allows more rapid healing (COHEN et al 1975; SIMPSON 1977; DUBOIS et al 1982). It is the author's experience, however, that a significant number of primarily closed third molar wounds open either following suture removal or at some later stage. This observation is supported by DUBOIS et al (1982) who found that

approximately 50% of the primarily closed wounds later dehisced!

These authors examined bilateral mandibular third molar wounds which were primarily closed on one side only. The other side was sutured in the portion adjacent to teeth but maintained open distally. No increased incidence of infection was reported. These authors concluded that the secondarily granulating wound enabled easier home cleansing than the gaping primarily closed wound. Thus since so many wounds in fact opened, secondary closure was preferable, particularly since pain and swelling were found to be decreased with this method. Other authors however, did not find that obtaining primary closure by suturing led to increased oedema (VAN GOOL et al 1977). Further examination of these results is definitely indicated. The ultimate status of the periodontium distal to the second molar is another important aspect to this question.

6.4 CONCLUSION.

This chapter has reviewed the numerous environmental and intraoperative factors which have been implicated in the development of the triad of pain, trismus and swelling.

Included has been the gamut of nutritive substances, many of which may contribute to the early repair process. The search for agents which accelerate these processes has not, at this point, been rewarded, and it remains that the "optimal rate of wound healing occurs in nutritionally well-balanced persons and animals" (CHVAPIL 1980). Whilst the role of some of these substances in repair is speculative and probably of minimal clinical significance, factors such as vitamin C and oxygen must be considered pivotal. The oxygen gradient, known to be critical to the spatial arrangement of cells within the wound and to

their function, may also act to stimulate cell proliferation, stopping this activity when normal oxygen tensions are reached.

It has also been shown that the wound environment is detrimentally influenced by irradiation (in a dose-dependent manner) and probably also by tobacco smoking. These agents vitiate microvascular function, thus compromising wound nutrition (particularly the supply of oxygen). Such impairment of microvascular function is likely to cause prolonged inflammation with subsequent delay of collagen deposition. The resolution of oedema is also likely to be delayed.

Delayed healing has also been found in the presence of various local anaesthetic agents (again in a dose-dependent manner). This effect is only evident in the first few days. It may be potentiated by vasoconstrictors acting to prolong exposure of the tissues to the toxic effects of these agents.

Another feature of oral surgical wounds is microbial contamination. This may markedly increase the inflammatory response, both by increasing the quantity of material which must be phagocytosed and by the production of substances which mediate inflammation by the contaminating organisms. Interestingly, this inoculum may not be as large as most clinicians expect. It is certainly the case that most oral wounds heal without developing sepsis, perhaps a partial result of the action of salivary factors. Several factors, including the presence of devitalised tissue and tight suturing, may significantly increase the incidence of sepsis, as does irradiation.

The natural lines of tension within skin and mucosa appear to be highly significant in determining the extent of the ultimate scar and

in the degree of tension in the cut wound edges. The latter appears to constrict vessels, thus restricting flow. Knowing the orientation of these lines and the local blood vessels is thus important in avoiding additional impairment of the blood supply.

In addition, the surgeon must aim to minimize the extent of the surgical injury by applying Halstead's principles where possible. The complexity of this injury may account for the difficulty which has been experienced in clarifying the effect of various components individually. At this time, the raising of the mucoperiosteal flap itself and the state of eruption of the tooth appear to be the most significant. The state of eruption probably relates to the size of the surgical exposure, the amount of bone removed and possibly also to the length of operation, though this is not always seen as significant.

The extent of devitalised tissue/extravascular clot which is present in the wound is also important in determining the inflammatory response. The fibrin and associated plasma proteins are significant initially in altering the colloidal osmotic pressure gradient across the wound, thus drawing water into the tissues. This effect is reduced once the fibrin has polymerised (it then being too large to exert an osmotic effect). However, the vessel disruption which accompanies surgery allows free plasma (and thus plasma protein) ingress into the tissues. Tissue oedema will remain until this excess protein is removed.

It has been shown that sutures - their insertion, their various biochemical properties and the type of technique used - may greatly influence the extent of tissue devitalisation, particularly if tied too tight. It is also possible that achieving primary closure may prevent the loss of oedema fluid from the wound, and thus clinical oedema may

be increased.

It is the assertion of this author (as explained in 6.2.4.5) that any effects which prolong the inflammatory phase and thereby delay connective tissue synthesis (or which delay connective tissue synthesis alone) must increase the potential for oedema to form in the early stages of repair through the persistence of shear forces/movement across the wound. This is especially so with oral wounds in which movement is unavoidable. The effect of various factors on this situation is almost impossible to quantify.

Before discussing the reported methods whereby oedema may be controlled (Chapter 8), Chapter 7 describes a clinical pilot study which examined post-surgical oedema from a morphological standpoint, using ultrasonography as a means of providing insight into the topographical changes which are subsequent to oedema formation. The rationale of and the necessity for oedema control, along with the biological "value" of oedema, are then discussed (Chapter 9).

CHAPTER 7 THE INTERNAL TOPOGRAPHY OF FACIAL POST-SURGICAL OEDEMA: A CLINICAL PILOT STUDY USING ULTRASONOGRAPHY: OUTLINE.

7.1 INTRODUCTION.

While the experimental situation offers the opportunity for direct examination of post-surgical oedema and its effect on tissues (see BERTAMOLI et al 1982), clinicians are largely restricted to techniques of palpation in their examination of such swelling. It is certainly true that experienced clinicians can gain considerable skill in this examination, yet a more detailed understanding and "visualisation" of post-surgical swelling could be considered beneficial. It was therefore decided to employ the techniques of high resolution ultrasonography to examine facial tissues following a typical oral surgical procedure, namely the removal of bilaterally impacted mandibular third molars.

Diagnostic ultrasonography is an accurate and non-invasive procedure which is capable of portraying fine structure in considerable detail. From its inception, the major applications of this technique have been in obstetrics and cardiology (CROCKER & JELLINS 1978). With the development of more sophisticated techniques and instrumentation, new applications for its use as an adjunct to clinical practice continue to be found (BUDDEMEYER 1975). In order to appreciate the operation and limitations of echography and its possible applications to maxillofacial surgery, it is necessary to outline the physical principles which govern the behaviour of acoustic waves.

7.2 THE PHYSICAL BASIS AND TECHNIQUE OF ULTRASOUND.

The phenomenon we perceive as sound is essentially a periodic change in the pressure of air against the eardrum, the periodicity of this change occurring at certain frequencies (normally between 20Hz and 20kHz for the human ear). In order for transmission of the force

necessary to create these cyclic pressure changes, the transport medium (in this case, air) must have some mass. Other like media, such as water, tissue and so on may also transport sound and the sound waves may have frequencies outside the audible range (BUDDEMEYER 1975). Diagnostic ultrasound is distinguished from other mechanical wave forms simply by having a frequency above the audible range (of the order of 1 to 10 mHz) (WELLS 1978; CROCKER 1979; LEOPOLD 1980).

Ultrasonic scanners generate electrical impulses which are converted into high frequency sound waves by a transducer. These sound waves leave the transducer as "acoustic wave packets" and pass into the tissues under examination (BUDDEMEYER 1975) (see FIGURE 7.1). Because of their high frequency, air is an inadequate transport medium and the transducer must therefore be acoustically coupled to the skin using a gel or water bath (CROCKER 1979).

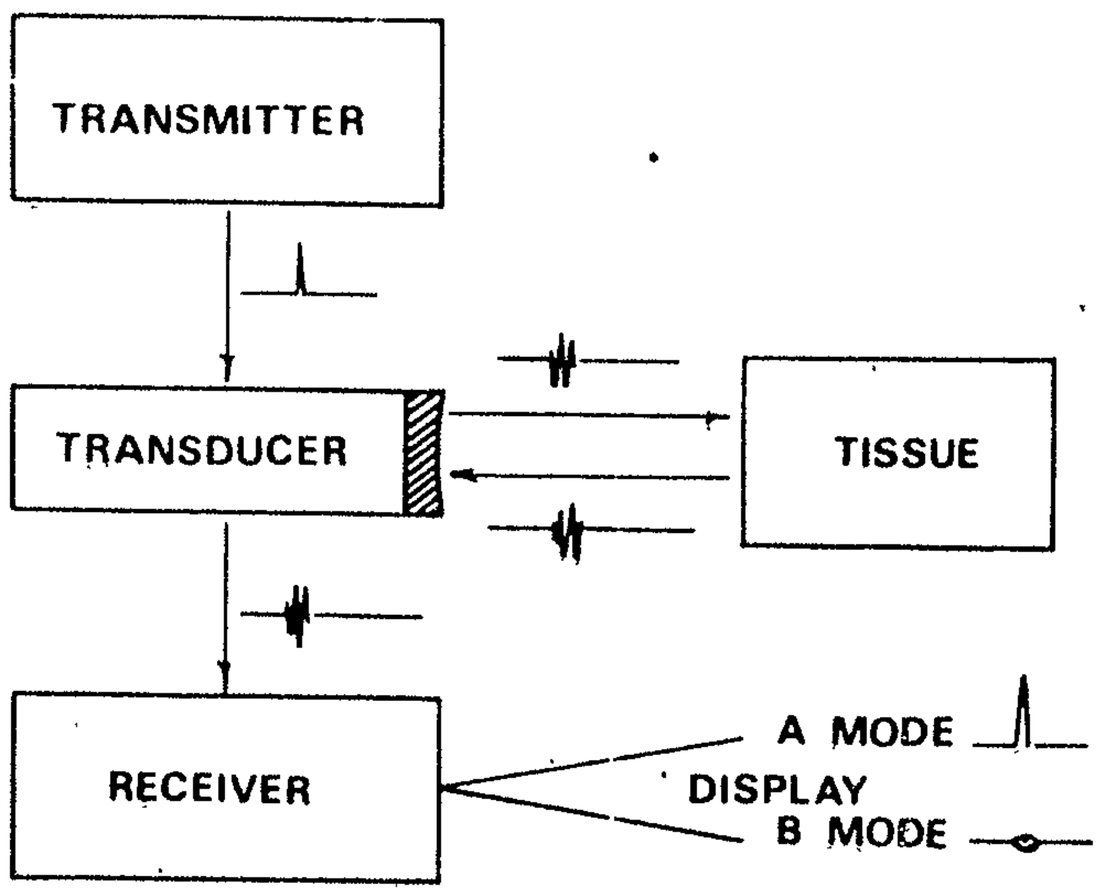

FIGURE 7.1 Schematic representation of ultrasonic echoscope (from CROCKER & JELLINS 1978, p244).

When ultrasonic fields interact with tissue, the characteristics of the field will be affected in a manner which is dependent upon the acoustic properties of the tissue (PRICE et al 1980). Of these, acoustic impedance is perhaps the most important; this is described as the product of the tissue density and the velocity of sound waves in

that tissue (CROCKER 1979). As sound energy passes from a tissue of one acoustic impedance to one of another, some is reflected, some continues to penetrate and some is transferred to particles within the medium in the form of vibrational energy. The echoes reflected back to the transducer are converted back into electrical energy after which they are amplified, processed and finally displayed on a screen (CROCKER & JELLINS 1978; CROCKER 1979; PRICE et al 1980).

Current techniques permit the returning ultrasound information to be updated at a sufficiently rapid frame rate to allow perception of physiologic motion within the field of view (LEOPOLD 1980). This so-called "real-time" imaging is made possible by the interposition of analog or digital computing equipment between transducer and screen. Digital-based real-time instruments provide the widest dynamic echo range, and thus allow the clearest delineation of parenchymal or textural details (JAMES et al 1980).

Whilst the reflected echoes may be displayed in several modes, the most commonly used is B-mode (Brightness mode) scanning (B-scans) (LEO & RAO 1975; CROCKER & JELLINS 1978) (see FIGURE 7.2). In B-mode scanning, the intensity of the reflected echoes are represented as levels of the grey scale. It is the generally accepted theory that the spatial distribution and texture of echoes in such a grey scale image assists in distinguishing between tissue types (PRICE et al 1980).

Current equipment, however, only utilizes a small fraction of information from grey scale imaging since the signal is significantly contracted to allow its display on the screen (ROSENFIELD et al 1980). Nonetheless, experienced clinicians are able to visualise the density and image texture of backscattered echoes from internal tissue structures, and to relate changes in these parameters to tissue

pathology (CROCKER & JELLINS 1978; PRICE et al 1980).

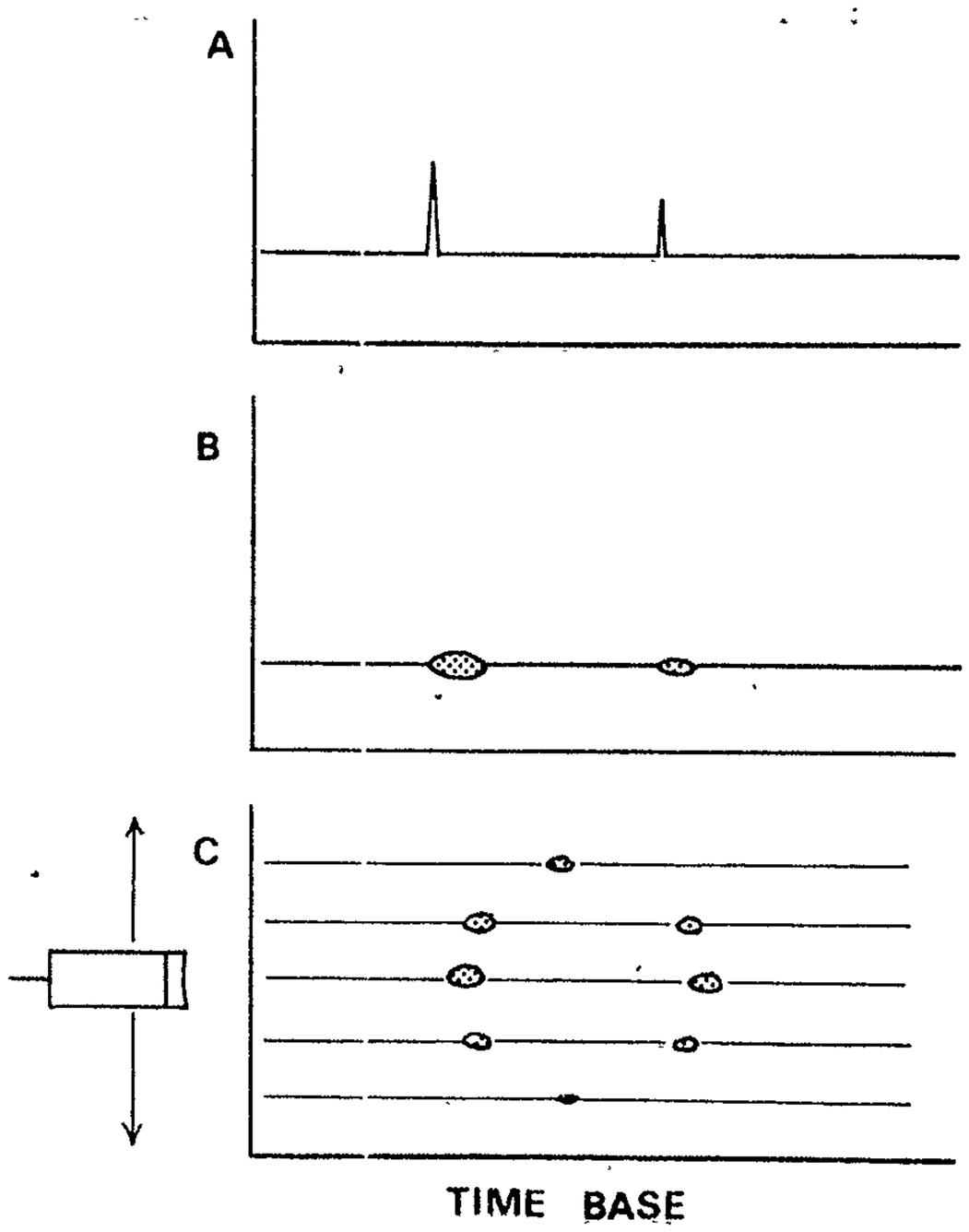

FIGURE 7.2 Diagrammatic representation of A and B mode traces, and of a B mode linear scan through a circular structure (from CROCKER & JELLINS 1978, p244).

As the transducer moves across the tissue being examined, serial B scans are recorded in rapid succession and a two-dimensional echographic section through the tissue is obtained (see FIGURE 7.2c). The various arrangements of the transducer which enable such mechanical motion and the different scanning systems available are discussed by JAMES et al (1980).

Early ultrasonography concentrated on investigating the deep structures of the chest, abdomen and pelvis. More recently, ultrasonic examination has been applied with success to smaller, superficially located organs and structures. Specialised instruments have therefore been developed for this purpose (LEOPOLD 1980).

These more superficial examinations also have theoretical advantages. Conventional ultrasonography generally requires frequencies of between 2 and 5 mHz to obtain adequate penetration. Examination of

superficial structures is possible with higher frequency transducers which have inherently higher resolution (LEOPOLD 1980).

7.3 CLINICAL CONSIDERATIONS OF TISSUE CHARACTERISATION.

The capacity of ultrasound to depict normal structure and to identify tissue pathosis is a result of "visual" tissue characterisation. In the future, it may be possible to describe the unique "signature" appearence of a specific tissue type as a result of research using computerised quantification of echo patterns. Currently however, the basis for interpretation lies in an understanding of the physical principles of ultrasound, combined with a knowledge of anatomy and physiology (PRICE et al 1980).

Tissues absorb, reflect and scatter the sonic waves in a variety of ways. Some, such as the diaphragm, are strong reflectors which behave as mirrors (termed specular reflectors). Sound from specular reflectors returns to the transducer only when the transducer is perpendicular to the reflector (PRICE et al 1980). In the head and neck region, bone is an example of a tissue which tends to produce specular-type reflections.

Most tissues however, scatter the sound in all directions and their image may therefore be perceived by the transducer regardless of its orientation. The visual pattern of relative echo amplitudes returning from scattering-type tissues enables differentiation of normal from pathologic conditions (PRICE et al 1980).

The intensity of the acoustic wave is attenuated by factors such as absorption, reflection and scattering characteristics of the tissues (PRICE et al 1980). Different tissues attenuate the wave in varying, relatively characterisic ways.

In determining the nature of the tissues being examined from the scan, it must be stated that the beam profile produced by the transducer demonstrates variable texture in different areas. This is due to non-linear variations in the lateral resolution of focus. Thus the echo amplitude generated from the parenchyma of an organ is greatest in the focal zone, decreasing in all directions from this zone. The pattern of tissue texture is also altered: in the near field (between the transducer and the focal zone) a fine speckled echo consistency is seen. This gives way to a broader, coarser echo pattern in the far field (distant to the focal zone). Discounting refraction effects, true tissue texture is only accurately delineated in the focal zone (ROSENFIELD et al 1980).

Another major component of the sonographic appearance of tissues is the phenomenon of acoustic shadowing. Acoustic shadowing is produced by the reflection or refraction of the sound beam (ROSENFIELD et al 1980). An example is calcium which produces strong reflected echoes and at the same time markedly attenuates the sound beam. The tissues immediately distal to calcified structures thus demonstrate marked hypoechogenicity, which is termed "acoustic shadowing".

On the other hand, acoustic enhancement occurs distal to fluid-filled structures, the edges of which markedly refract the beam. This feature is a major diagnostic characteristic enabling differentiation between solid and fluid sonolucencies (PRICE et al 1980; ROSENFIELD et al 1980).

The degree to which these effects occur depends upon the relative density of the fluid or calcified structure.

7.4 MATERIALS AND METHODS.

The instrument used in this study was a mechanical sector scanner with an integrated water delay mechanism # (See CROCKER & WALKER 1983). The ultrasonic transducer was a crystalline element mounted in a small, self-contained water bath, the latter being enclosed by a thin but durable membrane mounted at one end of a hand-held probe. The transducer and water bath were small enough to be easily applied to areas of the face and neck, and the scanning probe was attached to an arm which permitted wide flexibility of angulation (see PLATE 7.1).

The transducer provided a 28 degree sector angle and operated at 12 frames per second with a frequency of 8 mHz. It was focussed at 2.5 cms from the face of the water bath, scanning being possible to a depth of 5 cm. At the skin surface, the field of view was 2 cm in length, being 5cm at the depth of the field. Axial resolution was 0.25 cm; lateral resolution varied in relation to proximity to the focal zone. At this zone, lateral resolution was 1mm.

Due to the heavy clinical workload under which the Westmead ultrasound facility operated, sonography was limited to eleven patients. Echograms were taken on these patients immediately before surgery and at the first post-operative review. Some patients were also surveyed one week following surgery (see discussion).

To obtain positioning for each survey, both sides of the face were scanned in the sagittal and transverse planes until the site of maximal dimensional change was under view (see PLATE 7.2). Hard copy records were then obtained of the echogram at these sites.

Smith Kline Instruments 200 Small Parts scanner located in the Department of Nuclear Medicine and Ultrasound, Westmead Hospital, N.S.W.

PLATE 7.1 Instrumentation for facial ultrasonography. The instrument used was a mechanical sector scanner with an integrated water delay mechanism, the crystalling element of the transducer being mounted in a small, self-contained water bath and mounted on the end of a hand-held probe (see 8.3.4). Positioning was assessed on video monitors (right) prior to obtaining photographic plates.

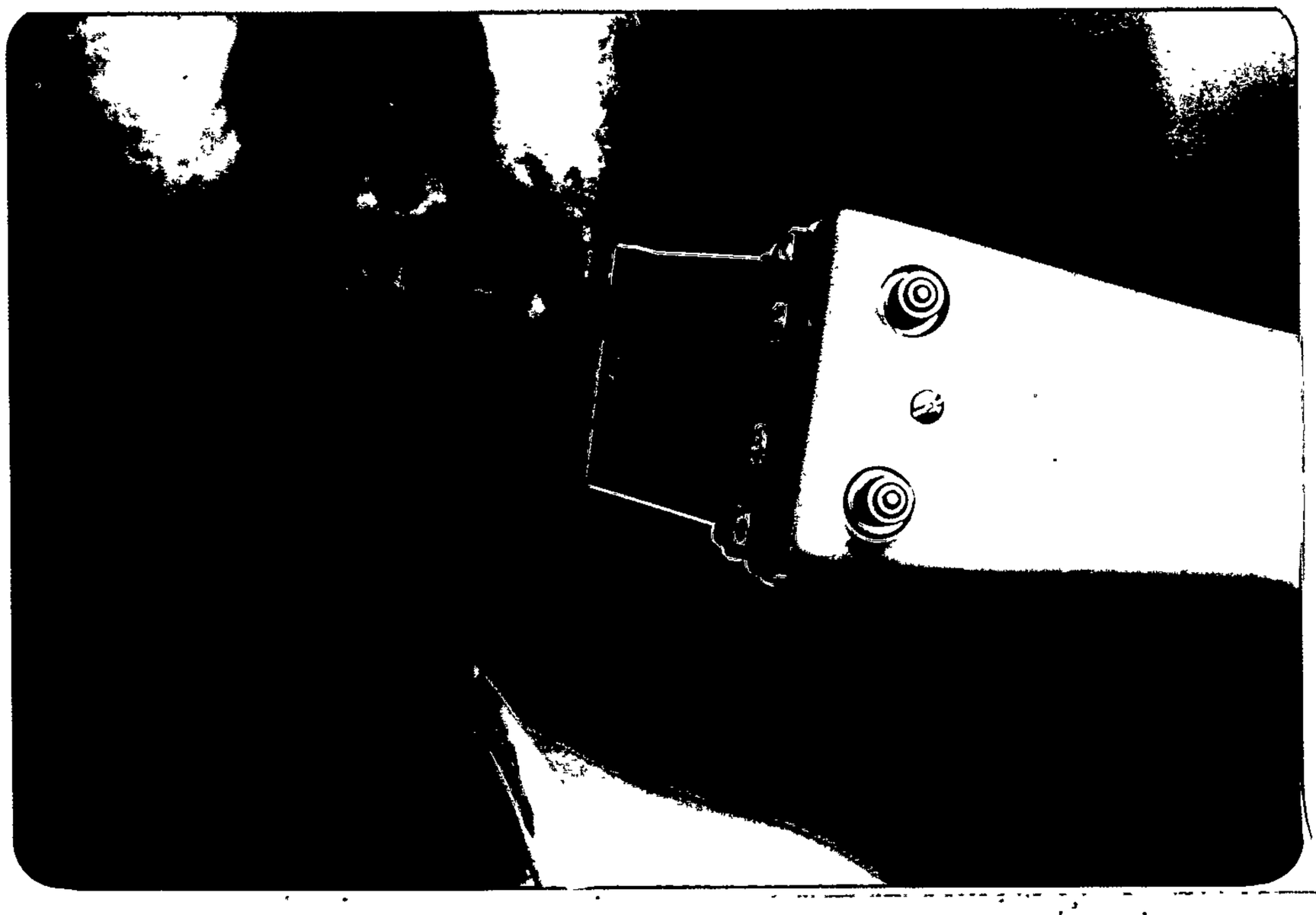

PLATE 7.2 Positioning of the transducer for examination of the facial tissues overlying the mandible.

7.5 RESULTS.

7.5.1 Normal Studies.

A representative echogram of a normal, pre-operative facial scan taken at the anterior border of masseter is illustrated in PLATE 7.3.

Normal masseter has a relatively smooth internal texture of moderate echogenicity. Muscle is clearly demarcated from the more superficial tissues and is seen to abut directly against mandibular ramus in the pre-operative scan: the ramus limits the depth of the field. Few other significant landmarks were present in the region examined.

In addition, the axial resolution of the scanner enabled the techniques to provide measurements (to the nearest millimetre) of the depth of soft tissue from skin surface to bone. The dimensions of masseter could also be obtained.

7.5.2 Post-Operative Studies.

The most obvious feature of the 48 hour post-operative studies was the increase in overall dimensional change (see PLATE 7.4). As with the clinical presentation of the facial swelling, the size of this swelling varied between patients and between right and left sides of the same patient.

In reviewing the topographical features of the post-operative scans, several points were evident. Firstly, in all studies, the majority of the volume increase resulting from post-surgical inflammation occurred within the body of masseter. Only mild expansion of the overlying tissues was evident.

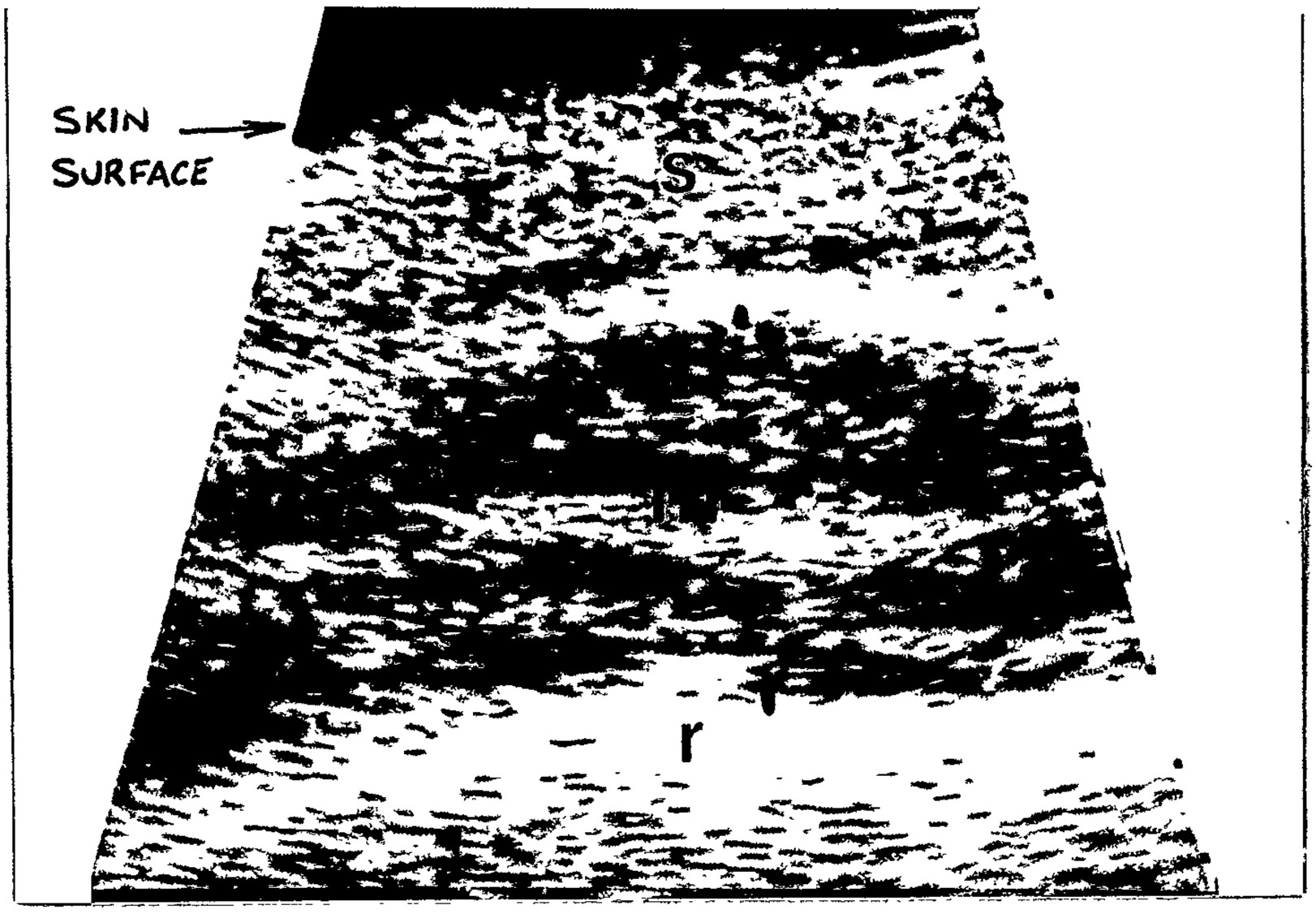

PLATE 7.3 A representative transverse echogram of a normal, pre-operative facial scan taken at the anterior border of masseter showing masseter (m) superficial tissues (s) and ramus (r). The masseter in this case shows some central high echogenicity perhaps associated with tendinous components. The patient in this case had mildly hypertrophic musculature. (SCALE: distance between markings on right = 2.5 millimetres).

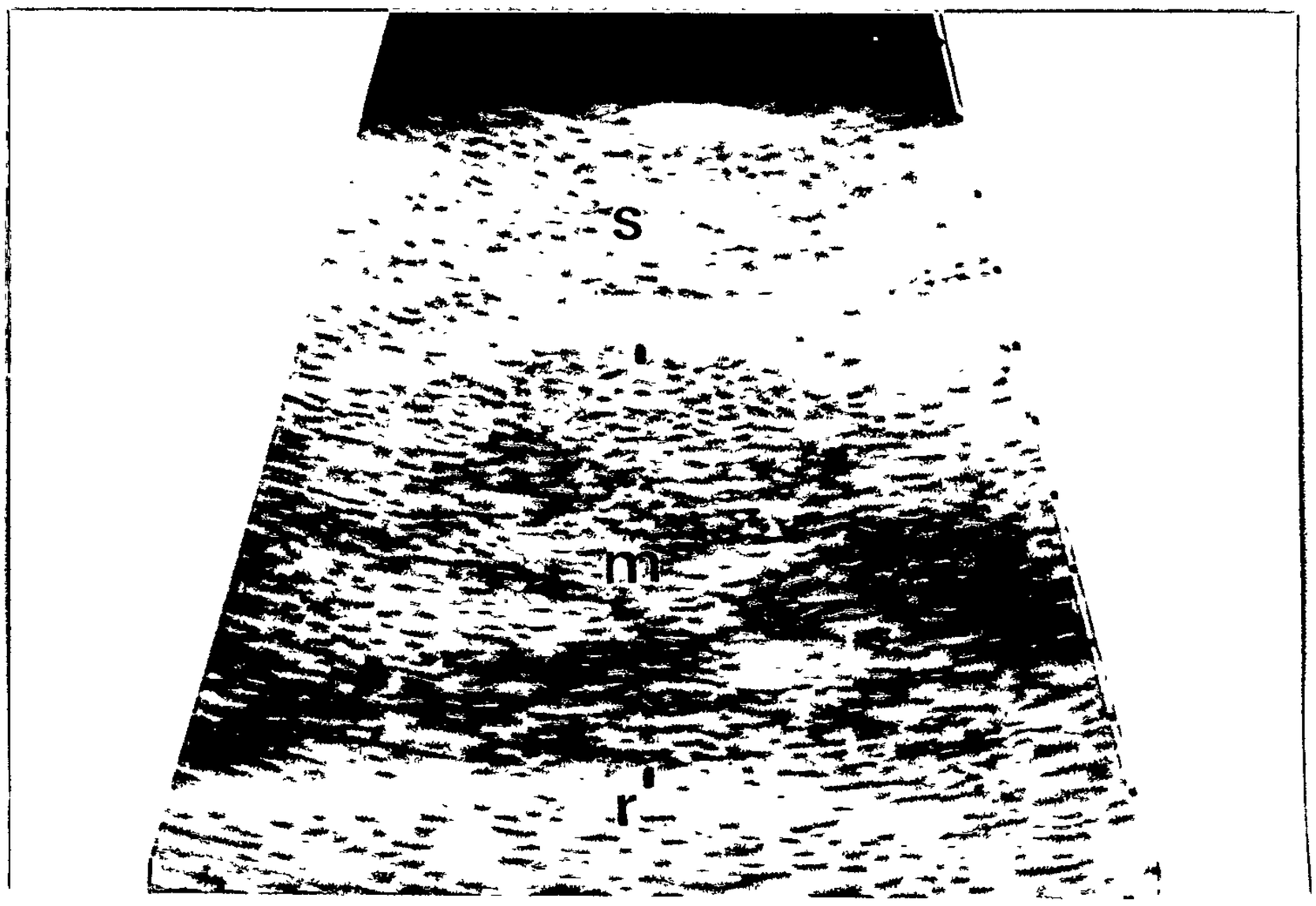

PLATE 7.4 A representative echogram of the facial tissues adjacent to the anterior masseter 48hrs after the removal of mandibular third molars. The most obvious feature is the marked increase in overall dimensions. It should be noted that in this and the other post-operative scans, the gain settings of the ultrasound was varied until scans with the greatest clarity were obtained. With the increased volume of tissue being scanned, this can be illustrated in the lower overall echogenicity of the post-operative scans. (Same patient as in PLATE 7.3). (Symbols and as with PLATE 7.3).

Secondly, most studies demonstrated the masseteric expansion to have uniform echogenicity of only slightly reduced density (allowing for adjustments in gain settings to increase penetration).

In three patients, ultrasonography demonstrated the presence of discrete hypoechogenic areas outside muscle (PLATE 7.5). These had the appearance of haematomata and were of varying size and shape. Located adjacent to bone just anterior to, and slightly beneath masseter, this finding correlated in all cases with the clinical diagnosis.

The haematomata found by this technique were only small in two patients (approximately 5 mm diameter), however, one patient with marked swelling demonstrated a similar low-echo area with dimensions of 5mm (depth) x 23mm (length) x 12mm (height). These dimensions describe a volume of some 7.5cc (see PLATE 7.6).

Those scans taken one week after surgery generally demonstrated complete restoration of normal dimensions and architecture. In the case of those patients where haematomata were noted at the 48 hour review, the review at one week showed partial resolution of these.

7.6 DISCUSSION.

A major factor in the decision to investigate the use of ultrasonography in examining post-surgical oedema was the potential for this technique to demonstrate the internal topography of tissues. The results obtained in this study were initially somewhat surprising, since the majority of the increase in tissue volume occurred within masseter and its fascial sheath.

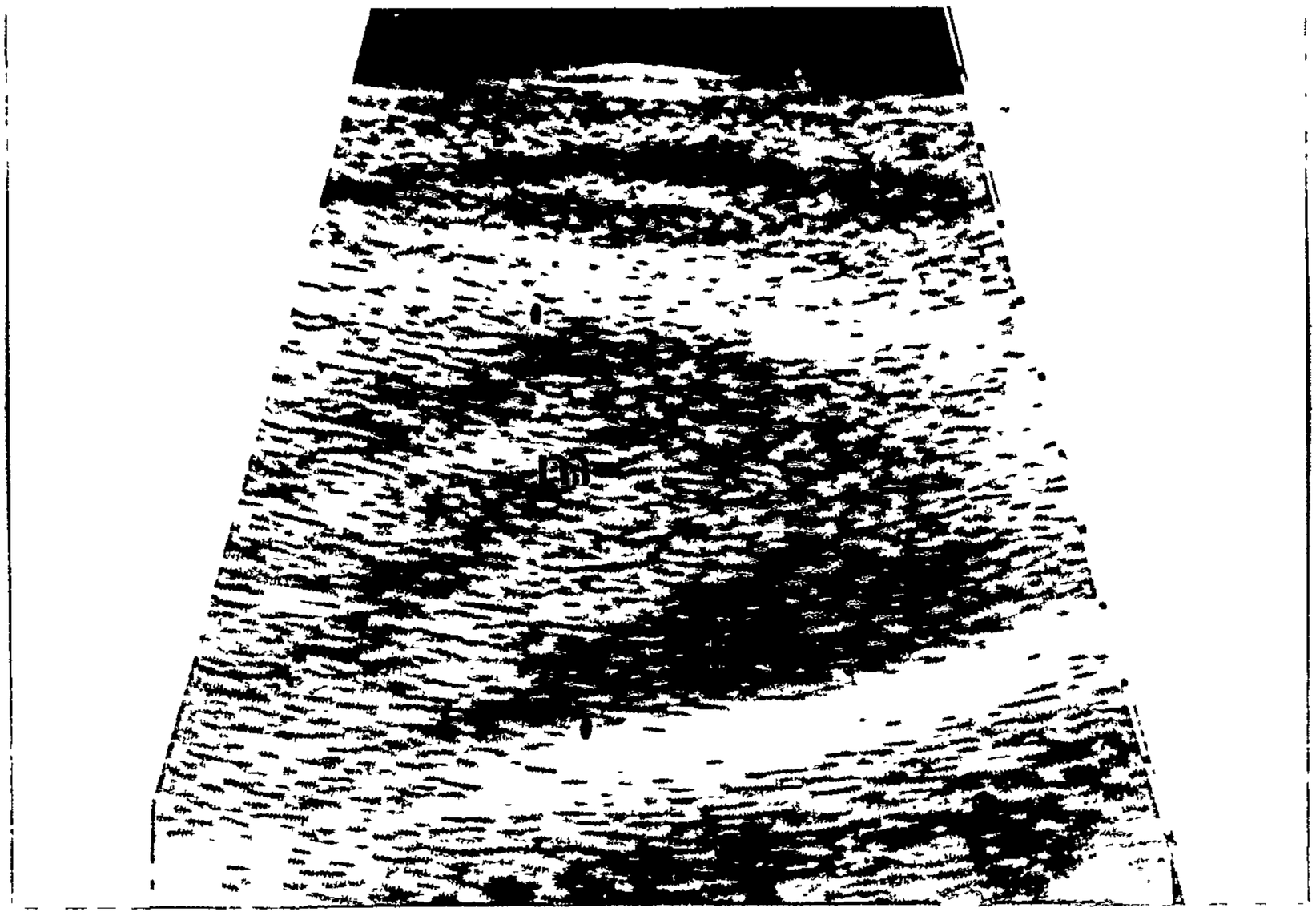

PLATE 7.5 A sagittal echogram of facial tissues 48hrs after removal of third molar teeth showing significant dimensional increase. A discrete hypoechogenic area is also noted outside the muscle sheath. This appearance is consistent with that of a haematoma with a high fluid component. (h) = haematoma (other symbols and scale as per PLATE 7.3).

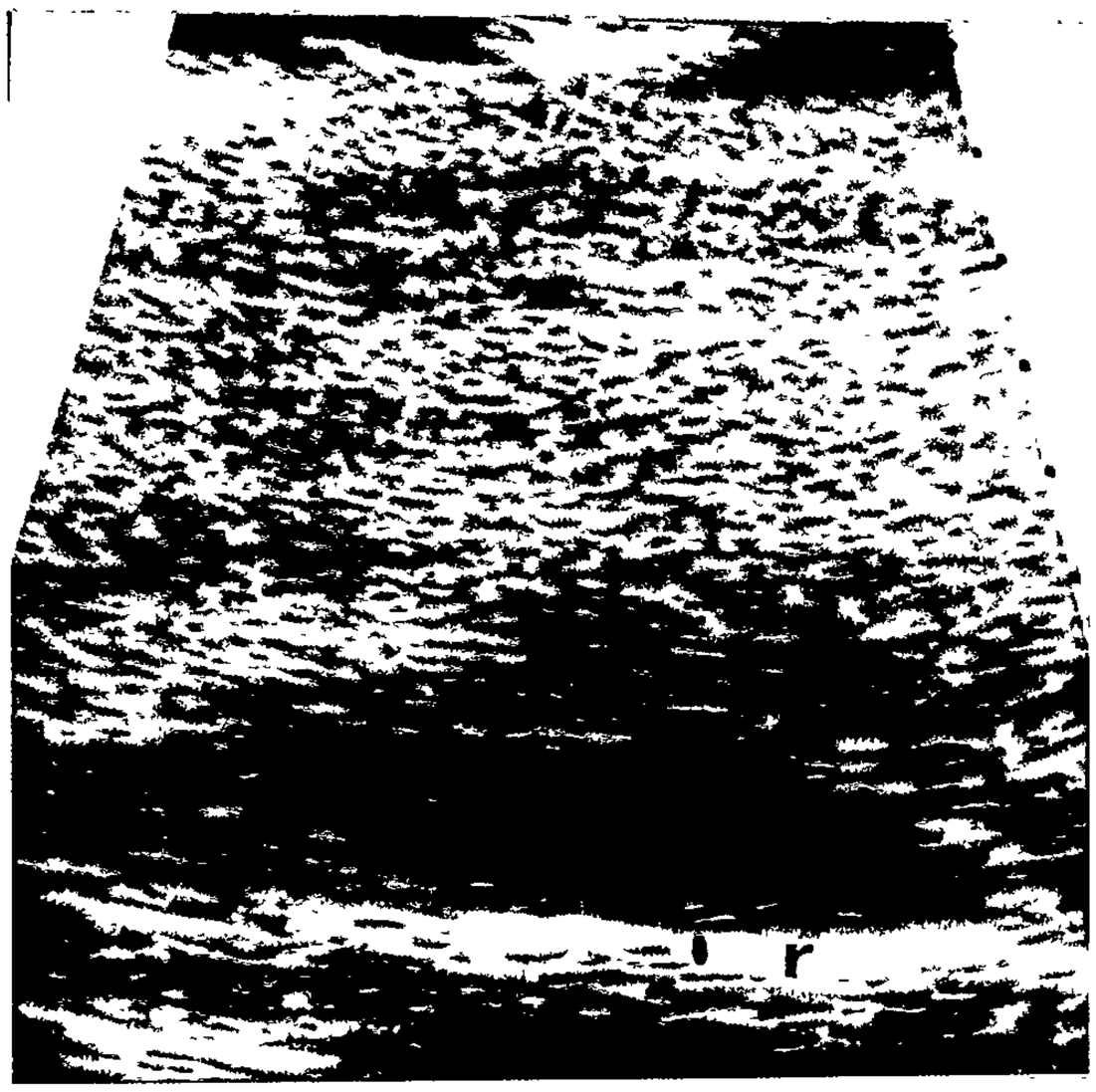

PLATE 7.6 An echogram showing a well defined low-echo area anterior to and partially beneath masseter. This appearance is again consistent with that of a haematoma (symbols as with previous plates). In combination with the other scans in this series, the dimensions of this haematoma describe a volume of some 7.5cc. (Symbols and scale are as per previous plates in this series).

A subsequent examination of textbook regional anatomy, combined with a review of dentate subjects (both clinically and at surgery), may explain this, since anterior masseteric fibres were found to attach up to the external oblique ridge, almost as far forward as the mandibular second molar. Buccinator being relatively thin, the raising and retraction of the conventional L-shaped flap (see 6.3.1), with the periosteal stretching and tearing which this frequently causes, must be assumed to cause its greatest injury to these fibres and the associated blood and lymphatic vessels which are reported to course directly above periosteum (SHAPIRO & RUBEN 1971).

Also noteworthy was the observation that the masseteric expansion was of uniform echogenicity, suggesting that the oedema so developing within masseteric fascia was not localised at the site of injury. Rather, it diffused generally between and around the muscle fibres. This is likely to be a function of the internal fibre/fascia arrangement of masseter rather than a sign of generalised injury.

From a practical viewpoint, the one week survey did not add significantly to that taken after 48 hours in the majority of studies. Therefore, scanning after one week was discontinued unless particular features of the 48 hour scan deserved review.

For the full import of these findings to be gained, further well-documented surveys are necessary. However, this pilot study clearly demonstrated good correlation between clinical and ultrasound findings. Further, the clarity of the internal structure of facial swelling which the echograms provided, particularly in relation to the position and dimensions of any haematomata present, must confirm the need for further assessment of this technique.

For such surveys to provide maximum diagnostic information, the specialists in both oral surgery and ultrasonography must maintain close communication, comparing and correlating the sonographic picture with the known anatomy and physiology of the region. Without this application, it will not be possible to establish what value diagnostic ultrasound has in this previously undescribed area of the body.

7.7 CONCLUSION.

Grey scale ultrasonography has been demonstrated to provide an accurate, non-invasive technique for the assessment of facial swelling. The structural information provided by this technique correlated well with clinical examination and usefully complemented this examination. Of particular interest were the changes (demonstrated sonographically) which occurred in the internal topography of the facial tissues as a result of third molar surgery. The demonstration of the position and size of haematomata present must prove to be of assistance to clinical management of patients with facial swelling. Further well-controlled investigations are necessary to fully outline what role these techniques may play in oral and maxillo-facial surgery generally.

Having considered its aetiology and development in some detail, the question of post-surgical oedema is now addressed from the perspective of its control. What techniques have been suggested to limit its formation and how succesful are they reported to be?

CHAPTER 8 CONTROL OF OEDEMA.

OUTLINE. Page.

8.1 INTRODUCTION.

The patient who has recently undergone surgery for the removal of third molar teeth is readily caricatured in the minds of the public since many are familiar with the more obvious attendant sequelae. Attempts by the profession to ameliorate symptoms have been less than spectacular.

As has been demonstrated, a significant component of the aetiology of post-surgical oedema relates to the surgical insult itself. It is generally accepted that good surgical technique and gentle handling of tissues will minimize post-operative sequelae. (HOOLEY & FRANCIS 1969; CACI & GLUCK 1976). However, some degree of pain, trismus and oedema will still occur despite these intraoperative efforts, and these signs may be both physically and emotionally unpleasant.

It is not surprising therefore that the oral surgeon has continued to investigate a wide variety of measures which may possibly relieve the patient's post-operative symptoms. Measures suggested to be of benefit in reducing oedema include the use of pressure dressings, heat and cold, avoidance of prolonged immobilization, and the administration of an unending variety of pharmaceutical agents including antihistamines, plant and animal enzymes, antibiotics, and nonsteroidal and steroidal anti-inflammatory drugs. (see HOOLEY & FRANCIS 1969; KORBEL 1970).

These measures are based upon the concept that controlling the extent of the inflammatory process which follows surgery will minimize the post-operative oedema (HUFFMAN 1977). Whilst some of these measures may have peculiar application following oral surgery, they almost

universally form part of the surgeon's armamentarium in assisting patient recovery. It is the aim of this chapter to review the many measures which have been suggested to offer control of post-surgical oedema. The rationale for control is more fully discussed in Chapter 9.

8.2 MEASUREMENT OF OEDEMA.

Perhaps the greatest obstacle to appraisal of these measures and their efficacy has been the provision of reproducible and objective means of measuring facial dimensions. Unlike extremities such as the hand, pre- and post-operative tissue volume cannot be measured by simple immersion techniques (see WARD 1976). How then can oro-facial post-operative oedema be reliably evaluated?

Several methods have been proposed. In fact almost each new study presents another alternative method. Most early studies relied upon clinical rating by one or more observers. Thus, oedema was graded as minimum, moderate or extreme, or as 1+, 2+, 3+, 4+ and so on (HOOLEY & FRANCIS 1969). Such observations are simple and, more importantly, an essential component of day-to-day post-operative patient management. However whilst it may be felt that clinical assessment has value in the hands of trained clinicians (MARLETTE & AMEN 1970; McCUE et al 1972; HELLEM & NORDENRAM 1973), it cannot be denied that this technique is highly subjective. LOKKEN et al (1975) found that such clinical assessment is neither accurate nor reliable when compared with more objective techniques.

Part of the problem of clinical assessment of oedema must be that a major component of post-surgical oedema following oral surgery is intraoral (WANG & WAITE 1975). In addition, subjective evaluation of oedema is reported to be unable to readily assess any fluid increase

until it becomes greater than 50% (KORBEL 1970). Hence, investigators have sought more objective measures in an effort to evaluate the efficacy of oedema control.

However, early techniques, whilst being objective proved far from reliable. The biggest problem was that of being able to obtain reproducible points to measure, the skin being relatively mobile over the underlying tissues. Commonly, measurements of facial dimensions were with calipers, total facial width being recorded with a single measurement (SCHNEIDER 1962, cited by CAMERON 1980) or with an eccentric contour tracing device placed from tragus to lip commissure (CRANIN & CRANIN 1964). Interestingly, some thought these measurements to be so inaccurate and non-reducible that clinical evaluation in double-blind circumstances was again adopted (YOUNG 1967).

Various refinements were subsequently introduced in an effort to identify reproducible points for measurement. For example, GALLOWAY et al (1967) measured cheek thickness from the intraoral opening of Stenson's duct to the external cheek surface. Other authors (FLEUCHAUS 1956; SOWRAY 1961) found a fixed intraoral reference point (a suitable lingual embrasure between lower molars) to stabilise the measurement with calipers.

However, some authors still felt that these techniques were too inaccurate, particularly since they only measured oedema in one plane. HOOLEY & FRANCIS (1969) therefore devised a technique using cephalometric photographs which were carefully traced onto graph paper at natural facial size. (This method was also used by GRAFF-RADFORD et al 1979-80). However, the normal cephalostat allows considerable variation of facial posture which may greatly alter apparent dimensions (CAMERON 1980). By means of a bite fork wax record, VAN GOOL (1975,

cited by VAN DER ZWAN et al 1982) removed this variability, providing a technique which has gained some acceptance (VAN DER ZWAN et al 1982).

Other techniques include linear measurement of anatomically determined and marked points on the face (for example, tragus-pogonium and tragus-subnasale) (DIECKMANN 1973; POLLMANN & HILDEBRANDT 1982), contrast radiography (FORMAN 1964), tangential measurements with calipers (CAMERON 1980), and single (PETERSON 1975) or multiple adjustable screw measurements (LOKKEN et al 1975) using individual face bow/bite records. Sophistocated stereophotogrammetric techniques have also been suggested (ERIGUCHI 1976, cited by CAMERON 1980). Some authors (BREYTENBACH 1976) use combinations of the above.

However, these too have problems. For example, the stereophotogrammetric method utilizes very expensive equipment and involves complicated techniques. It is therefore not available for widespread use. Radiographic methods involve additional exposure to ionising radiation, as well as being generally inaccurate. The other techniques mentioned above all have advantages and disadvantages. Some are relatively complicated (for example, the LOKKEN et al and VAN GOOL et al techniques), whereas the simpler methods using calipers demonstrate some variability in the position of the extraoral arm. Linear measurement is also used by other surgical specialties; however, it only represents the dimensions in two planes (McCUE et al 1972).

An important consideration here is the degree of accuracy which is required. This author wonders whether extremely high accuracy is necessary, since the fine differences in effectiveness of oedema therapy demonstrated are of little clinical significance. The important goal is surely the establishment of an objective measure which has reasonable reliability and consistency in the demonstration of

clinically significant reductions in post-operative symptoms.

It is interesting to note that while some authors use specialised techniques such as that of LOKKEN et al (BYSTEDT et al 1980, 1981; BYSTEDT & NORD 1980; LOKKEN & SKEJELBIED 1981), others remain content with merely subjective clinical evaluation (MACGREGOR & HUTCHINSON 1975; BYSTEDT 1976; MACGREGOR & ADDY 1980).

A more recent development to this issue has been the determination of the percentage change in water content of standard tissue cores taken from experimental animals (BERTAMOLI et al 1982). This technique is likely to prove highly significant in experimental situations dealing with facial oedema.

BREYTENBACH (1978) provides a very thorough review of clinical measurement techniques.

8.3 METHODS OF OEDEMA CONTROL.

8.3.1 Physical Methods of Control.

8.3.1.1 Miscellaneous physical therapies.

Before the advent of pharmaceutical means of controlling inflammation, surgeons used various physical methods, often to great advantage. Thus, elevation of the involved part, compression dressings and early immobilization were well accepted principles of surgery (OMER & BROBECK 1971).

Elevation of the hand is reported to decrease local blood volume by 20% and post-operative elevation appears to markedly reduce oedema (OMER & BROBECK 1971; WARD 1976). The effect of the elevation of the head in oral surgery is likely to similarly reduce facial oedema by

assisting gravitational fluid flow however this has not been evaluated. Elevation is best maintained as much as possible for around 48 hours (WARD 1976).

Pressure bandages are thought to discourage oedema and haematoma formation by artifically increasing tissue resistance. Their application was reported to be of benefit following hand surgery (OMER & BROBECK 1971), vasectomy (DE N'YEURT 1972) and oral surgery (sutured intraorally) (HELLEM & NORDENRAM 1973). Modern techniques using intermittent pneumatic compression of the hand are also said to significantly reduce post-operative oedema (HAZARIKA et al 1979).

Immobilization in the initial post-operative phase is also reported to be beneficial in reducing oedema (OMER & BROBECK 1971; HUFFMAN 1977), perhaps by reducing systemic blood flow and maintaining resting blood pressure, in addition to avoiding shear stresses in the wound (see 6.2.4.5). However, exercise (for example, vigorous chewing) is recommended later to prevent stiffness, stimulate blood flow and increase the mechanical forces clearing oedema (ARCHER 1975).

The use of vaseline gauze sutured around the oral commissures (in extended surgery), appears to diminish the trauma caused by instrument retraction, thereby reducing perioral oedema (WEINBERG et al 1975). Maintenance of adequate lubrication of the lips may also be benefical in reducing lip oedema and excoriation.

Pulsed electromagnetic energy has also been suggested to be of benefit as a "tissue conditioner", thereby reducing inflammation and accelerating healing (WILSON 1972; HUTCHINSON et al 1978). Originally introduced as an adjunct to physical therapy in the treatment of sporting injuries (WILSON 1972), this therapy is suggested to

depolymerise extravascular fibrin, re-establishing tissue fluid flow and permitting drainage (ARONOFSKY 1971).

ARONOFSKY (1971) reported that this therapy (given pre- and post-operatively) was more effective in reducing post-operative pain and oedema than the variety of pharmacological methods available. Other studies demonstrated some benefit though this did not reach the statistically significant level (WILSON 1972; HUTCHINSON et al 1978). However, the technique is now largely ignored for this treatment, perhaps because of the cost of equipment.

8.3.1.2 Thermal changes.

Several studies on pharmacological modification of oral surgical oedema also describe the apparently routine use of ice packs immediately following surgery (SHUTTEE 1962; HUFFMAN 1977; ARCHER 1975). These authors recommend that these cold compresses should be applied intermittently to the cheek for the first 24 hours, following which heat should be applied. A similar regimen is also recommended for early management of acute trauma (ARCHER 1975).

Cold is suggested to decrease capillary blood flow, tissue metabolism and the rate of transcapillary exchange. Application of cold is also thought to abstract heat from the region thereby lessening peripheral nerve sensitivity and relieving pain. Removal of the cold appears to be followed by a reactive hyperaemia with compensatory dilatation of superfical veins. (ARCHER 1975).

Studies on the effect of cold on oedema are few. OMER & BROBEK (1971) report that cold compresses produce minimal reduction in skin temperature and little reduction of oedema. However, patients in their series on hand surgery were more comfortable with ice packs in addition

to pressure dressings and elevation.

SHEHADI (1972) also found the post-operative application of cold to be of little benefit in reducing ecchymosis and swelling following rhinoplasty. However, intra-operative hypothermia using irrigants was effective in reducing these signs.

Local exposure to heat on the other hand, supposedly results in stimulation of vasomotor reflexes. Thus the number of open capillaries increases, metabolism is accelerated and the rate of transcapillary exchange is increased. These local increases in circulatory flow lead to an increased rate of oedema formation (hence not applied in the first 24 hours). They are also thought to accelerate healing (ARCHER 1975).

The penetration of heat applied in the form of poultices, compresses, hot water bottles or hot mouth rinses is not great (approximately 1mm); heating is by conduction (ARCHER 1975). Much greater penetration is obtained with heat from luminous sources such as sunlight and lamps. However, the rate of penetration of either method is slow, and heat is quickly dissipated through the action of circulatory reflexes. For this reason, large quantites of heat energy are required to alter tissue temperature to any depth (ARCHER 1975).

Heat and cold may be used in combination. Thus cold packs may be applied initially to reduce local blood flow and hence oedema, followed by heat to speed healing and aid resolution of any infection which may present. However, it appears that these techniques produce only slightly diminished oedema, though they may provide some relief of pain.

8.3.1.3 Surgical drains.

The use of surgical drains dates back to Hippocrates. It has without doubt withstood the test of time in surgical practice (NORA & BRANSFIELD 1972), drains being used in many branches of surgery including plastic, head and neck, orthopaedic, and perineal (ANON 1975), and being supported by a variety of textbooks of general surgery including SABISTON (1977) and HARDY (1977).

One of the major indications cited for the use of drains is to prevent haematoma formation in wounds in which there is a raw oozing area causing continued transudation or exudation (SCHILLING 1976; WHEELER & LAKHANY 1976). When in this situation, drains are reported to minimize oedema and haematoma formation (MOORE et al 1975; WHEELER & LAKHANY 1976; MITTELMAN & DOBERNECK 1982; YORDAN & BERNHARD 1982), perhaps through provision of a sinus tract which acts as a vent for continued transudation and exudation (SCHILLING 1976). However, considerable controversy exists in the general surgical literature as to the effectiveness, the site of placement, and the length of time which drains should be maintained in the wound. The wisdom of prophylactic drainage is also questioned (NORA & BRANSFIELD 1972).

Types of drainage systems.

Several types of drains have been recommended. The simplest are the corrugated strip drain (Portex) and the soft latex tube drain (Penrose) (BOURKE et al 1976). Ribbon gauze wicks impregnated with antiseptics such as bismuth iodoform paraffin paste (B.I.P.P.) have also been used, but are not now generally recommended (FLYNN et al 1983). In an effort to improve their efficacy, various modifications of the basic tube drain have been proposed: the drainage tube was incorporated into a closed system; suction was added and then a small

air vent tube (forming a sump) was added to the suction. The sump was then placed within a soft Penrose drain and later enclosed by gauze packing, ... and so on.

Effectiveness.

There is little reliable information on which to base a comparison of the various drainage techniques (VAN DER LINDEN et al 1981). However, whatever the diversity of surgical opinion concerning the use of drains, one thing is clear: if a drain is to be used, it must drain effectively (VAN DER LINDEN et al 1981). In a classic paper testing the efficiency of drains, YATES (1905, cited by GOLOVSKY & CONOLLY 1976), inserted drains into the peritoneal cavity of dogs. He showed that although serous exudation and drainage begins immediately, the drain was quickly encapsulated by fibrinous exudate. Being isolated from the wound space, the drains therefore became inoperative within 24 hours.

This paper is often cited in argument against the use of drains. However, Yates' work cannot be directly compared with the clinical post-surgical situation since he did not perform full surgical operations, merely opening the peritoneum for insertion of the drain. The additional surgical insult caused by completion of cholecystectomy (in one series) is suggested to cause persistence of drainage for over 2 days (VAN DER LINDEN et al 1981). It is however true that any drainage system will become blocked and sometimes this blockage occurs early (GOLOVSKY & CONOLLY 1976).

Attempts have been made to assess the clinical efficacy of drains. Of the studies on this topic, some give testimonial support to the effectiveness of closed suction drains (MOORE et al 1975; FARRIS & HAYS 1981). Others (BOURKE et al 1976) report that closed suction

drains are superior to closed static drains, and others (VAN DER LINDEN et al 1981) that closed static drains are better than Penrose drains for management reasons. However, FRASER et al (1982) report that Penrose and sump suction drains are equally effective.

These discrepancies may be resolved by the observation that the varied surgical situations necessitate the use of different drainage systems. For example, where there is a wound cavity, sump suction drainage is reportedly the most efficient since it aids in reducing wound dead space (GOLOVSKY & CONOLLY 1976; GUPTA et al 1978; MILSOM & GUSTAFSSON 1979). Where there is no cavity, all that is required is a pathway of least resistance to the surface: a Penrose drain is reportedly ideal (ANON 1975; GOLOVSKY & CONOLLY 1976).

However, other investigators (SPOONER et al 1970; WHEELER & LAKHANY 1976) found that drains were not effective at all in reducing oedema and haematoma, and that non-drained sites healed best (FARHA et al 1981; BUDD et al 1982). WHEELER and LAKHANY (1976) suggest that the advantage which might be expected from the facilitation of the passage of blood and exudate to the surface is possibly offset by the less effective obliteration of wound dead space, which is the inevitable consequence of drain insertion.

Length of drainage.

In principle, drainage is maintained as long as significant fluid seepage continues (NORA & BRANSFIELD 1972; EDIT. 1975; SCHILLING 1976). In a clean wound, this is about 48 hours (SCHILLING 1976). If the drain is maintained in situ for longer, it acts as a traumatic stimulus itself (VAN DER LINDEN et al 1981), and becomes a portal of entry for infection of the wound by superficial organisms (NORA & BRANSFIELD 1972). It is said that this increased risk of infection is

greater with open drains (such as Penrose and Portex) than with closed systems of drainage (BOURKE et al 1976; VAN DER LINDEN et al 1981).

Complications.

Because of the above problems, drains are sometimes reported to increase the length of hospitalisation and the incidence of post-operative fever and wound complications (such as sepsis and dehiscence) (FARHA et al 1981; BUDD et al 1982; MITTELMAN & DOBERNECK 1982). WHEELER and LAKHANY (1976) however, found no increased incidence of wound complications associated with the use of drains. Another study found that closed suction drainage actually reduced the wound infection rate in a variety of GIT surgical procedures (FARRIS & HAYS 1981), as would be theoretically expected by removal of the pooled fluid exudate (MITTELMAN & DOBERNECK 1982; YORDAN & BERNHARD 1982).

In summary, surgical drains appear to be of some value in reducing post-surgical oedema. The degree of reduction obtained is, however, debated. The use of drains may be complicated by retrograde infection and increased incidence of dehiscence, though insertion of the drain via a separate "stab" incision may minimise the latter. A difficulty in investigating the technique of drainage is the large variety of types of drains in use. These may have different applications in different wounds; which is most appropriate and effective in oral surgical wounds is however, unclear.

8.3.2 Pharmacological Methods of Control.

One of the problems with the pharmacological suppression of inflammation is the number of alternate pathways which are available for the production of inflammatory mediators (WILLOUGHBY & DI ROSA 1971). Also, some mediators appear to duplicate the action of others

(as described in Chapter 3). For these reasons, the list of pharmaceuticals which have been implicated in the modulation of inflammation continues to grow. It is noted that oedema forming as a consequence of the direct surgical injury is unlikely to be controlled pharmaceutically. This discussion therefore chiefly refers to control of the oedema which is superimposed on injury-induced oedema as a result of the action of inflammatory mediators.

A particularly confusing aspect of this area of research is that there is wide species variability and marked differences in mediation of the various experimental models of inflammation. Whilst some merit can be gained from careful examination of this information, very much more research is required using the surgical model and either human clinical trials, or animals with similar drug responses to man.

GILMORE (1976) classifies four groups of anti-inflammatory agents: non-steroidal anti-inflammatory drugs (NSAID's), corticosteroids, cytotoxics (immunosuppressives) and miscellaneous. For the purposes of this discussion, the cytotoxic group is omitted from later discussion since these drugs are generally only used in severe chronic inflammatory states. Several other classifications will be mentioned including antihistamines, antibiotics, plant and animal enzymes and the benzo-pyrone group.

The mode of action of all these agents is considered to be immunologically non-specific since they do not interfere with the reaction of antigen and antibody, or with sensitised lymphocytes (GILMORE 1976). GLENN & SEKHAR (1971) state that a central component of an effective anti-inflammatory drug must be membrane stabilization. This feature has been identified to varying degrees in most of the ab[illegible] will be seen.

In this discussion, drugs will be considered in terms of their clinical effect(s) on oedema, their postulated mode of action and any complications or side effects which may accompany their use. In many situations, the effect of these agents on the closely related post-operative signs of pain and trismus will also be mentioned. It is important to note here that it is frequently difficult to distinguish between symptomatic post-operative complaints and the action of a drug in causing side effects (YOUNG 1967). This distinction is clarified as much as possible in the ensuing discussion.

PILLER (1975) outlines four parameters within which the anti-inflammatory action of drugs should be considered:

i) their effect on the rate at which oedema forms,

ii) their effect on the maximum swelling volume,

iii) the time in which this volume is reached,

iv) their effect on the rate of resolution of oedema.

It is felt that this outline should form the basis of all discussions on the anti-inflammatory actions of pharmaceutical agents. Unfortunately, however, few authors consider more than the effect on maximal volume and rate of resolution of oedema. This may be understandable in view of the difficulty of taking recordings on human subjects at sufficient frequency to measure the other variables.

8.3.2.1 Antihistamines.

Considering the early discovery of the role of histamine as a mediator of inflammation, it is not surprising that early investigations were performed on the effect of antihistamines on inflammatory oedema. However, other than reports by CRANIN & CRANIN (1964) and SHEHADI (1972), it is generally agreed that antihistamines such as diphenhydramine and mepyramine have a negligible effect on

oedema (QUINN 1964; GALLOWAY et al 1967; ARONOFSKY 1971; ARCHER 1975; GARCIA-LEME et al 1977).

This insignificant effect is to be expected in view of more recent observations that histamine is only important in the immediate-transient phase of inflammation (3.3.2.1).

8.3.2.2 Antibiotics.

"It is both logical and experimentally well founded that therapeutic levels of effective antibiotics present at the moment and site of entry of sensitive bacteria into an organism may favourably influence the course of subsequent illnesses related to such bacteria" (POLK & LOPEZ-MAYOR 1969). In an attempt to maximally utilize this concept, many oral surgeons prescribe antibiotics to all patients undergoing surgery (JUNIPER 1972). However, in view of the serious consequences of such use (see later), it is essential to determine, clinically and experimentally, if such therapeutics are warranted.

Requirements for antibiotic therapy.

Firstly, it must be established that the drugs in common usage are capable of entering the operative field, namely alveolar bone and blood clot. That this is so has been clearly demonstrated for penicillin, doxycycline and clindamycin (JUNIPER 1972; BYSTEDT et al 1978; BYSTEDT & NORD 1980). Erythromycin also penetrates these tissues but is less effective (BYSTEDT et al 1978). (This list is not exclusive).

Interestingly, penicillin was found to enter the wound by diffusion and its rate of entry was not influenced by the age of the wound. Thus this antibiotic does not need to be present pre-operatively, though it does require continued administration to

maintain its concentration at sufficient levels (JUNIPER 1972).

Secondly, the selected antibiotic must be effective against the organisms which are present. Based on the sensitivity of the oral microflora, penicillin is the drug of choice in the mouth (BYSTEDT & NORD 1980; DORNBUSCH 1980). Clindamycin, doxycycline and erythromycin also appear to be effective (DE MARCO & KLUTH 1972; BYSTEDT & NORD 1980). (Again, other antibiotics are also undoubtedly effective).

Effectiveness.

A major problem in the testing of clinical effectiveness of antibiotics is that many investigations are poorly constructed. Thus the massive study of RUD et al (1963), which supported the use of sulphonamide cones in extraction sockets, is unfounded since it lacked adequate controls. Later investigations (MACGREGOR & HUTCHINSON 1975) found that although this treatment was better than the placebo, it was no better or worse than leaving the socket alone.

Concerning systemically administered antibiotics, BYSTEDT et al (1981) found that tinidazole reduced post-operative swelling but the difference was not statistically significant. Similarly with penicillin and lincomycin (HELLEM & NORDENRAM 1973). Doxycycline is reported to reduce oedema on day 2 and day 5 post-operatively but not on other days. The other antibiotics tested (penicillin, erythromycin and clindamycin) had no effect on oedema (BYSTEDT et al 1980). They are, however, reported to reduce trismus (MACGREGOR & ADDY 1980), necrosis of the flap margin (DE MARCO & KLUTH 1972; BYSTEDT et al 1980), and pain (BYSTEDT & NORD 1980).

The picture is therefore not clear, though it appears that antibiotics do not generally offer significant reduction of oedema.

Further carefully constructed studies are needed for clarification. It would be expected that any antibiotic effect on post-surgical oedema would occur by destruction of microbial contaminants, thus lessening the inflammatory response.

Another aspect of the question of antibiotic use is whether the incidence of post-operative infection is sufficiently high to warrant antibiotic therapy and whether antibiotics actually lower this rate of infection. Surprisingly, the incidence of infection in a contaminated environment such as the mouth is reported to be low (VAN GOOL et al 1977).

Also surprisingly, though some reduction is reported in 'contaminated' general surgery (POLK & LOPEZ-MAYOR 1969; POLK 1974), PATERSON et al (1970) found that routine prophylactic antibiotics have not lowered the incidence of infection in oral surgery. This survey reviewed trauma, elective 'clean' and 'clean-contaminated' wounds and found that antibiotic prophylaxis was even associated in some situations with raised incidence rates! This observation raises serious questions as to the value of prophylactic antibiotics. However, further investigation is necessary.

Limitations of antibiotic therapy.

The growing area of concern with antibiotic use relates to the danger of such therapy to the patient and the community. These dangers arise from sensitisation of the patient to the antibiotic, from the inherent toxicity of the antibiotic concerned, and from the emergence of resistant strains of micro-organisms (PULASKI 1961; MARLETTE & AMEN 1970; MACLEAN 1975). In addition there is the possibility of encouraging the growth of resistant, possibly pathogenic strains leading to secondary bacterial or fungal infection. The high cost of

these drugs must also be considered (PATERSON et al 1970). Further, some have suggested that antibiotics lead to impaired wound healing by the suppression of protein synthesis, thus leading to increased dehiscence. However, this was not found to be so in a study using tetracycline (MANN & BEDNAR 1977).

However, it is difficult, on the basis of these complications, to condone indiscriminate routine use, particularly in view of the dubious value of antibiotic therapy. While various proposals for the use of prophylactic antibiotics have been outlined for general surgery (See HUNT (Ed.) 1980), it is important that the role of antibiotic therapy be thoroughly clarified for surgery in the oral environment (as stated by MACGREGOR & ADDY 1980). It appears that antibiotics have little effect on post-surgical oedema, but that they do improve flap vitality.

8.3.2.3 Plant and animal enzymes.

Since MARTIN et al (1953) demonstrated that proteolytic enzymes have an anti-oedema effect in rats, many such products have been marketed (cited by GYLLING et al 1966). Most of these are of animal origin (such as trypsin and chymoral) and are commonly administered by parenteral injection at the site of injury (GYLLING et al 1966). Similar substances have also been extracted from vegetable sources including papase (derived from Carica papaya, POLLACK 1962) and bromelain (derived from pineapple, GYLLING et al 1966). These are effective following per-oral administration (GYLLING et al 1966). Also included in this category must be the streptokinase-streptodornase agents which are of microbial origin, derived from Lancefield Group C strains of streptococci.

Mechanism of action.

The significant feature of all these agents is that they are variously active proteolytic enzymes. It is generally supposed that they exert their effect by increasing the lysis of fibrin thereby increasing tissue permeability and allowing diffusion of the inflammatory exudate out of the region of trauma (POLLACK 1962; QUINN 1964; GYLLING et al 1966; GALLOWAY et al 1967; KORBEL 1970; ARONOFSKY 1971; SALISBURY & HUNTER 1972; GRAFF-RADFORD et al 1979-80).

The exact mechanism of how such fibrinolysis is achieved is however not clear. It is difficult to explain a direct fibrinolytic action since serum contains enzymatic inhibitors of these enzymes (DE N'YEURT 1972). While some claim that the individual variability of the quantity of enzymatic inhibitor(s) produced after administration of the enzyme may explain the clinical variability in effectiveness (MARLEITE & AMEN (1970), but this remains unproven.

It has been shown that these agents are able to be absorbed (KORBEL 1970; DE N'YEURT 1972). However, they then appear to become bound to proteins of some kind; therefore, how do they exert their effect? DE N'YEURT (1972) suggested that naturally occurring proteolytic enzymes at the site of inflammation (such as plasmin and lysosomal hydrolases) may release the active enzyme, which is then suggested to activate additional plasmin, producing fibrinolytic effects (POLLACK 1962; QUINN 1964).

Alternatively, YOUNG (1967) suggested that the administration of proteolytic enzymes led to increased serum esterase levels. Increased serum esterase was then thought to inhibit inflammation by increased hydrolytic degradation of the inflammatory peptides.

However, these concepts remain speculation and the true mechanism of action of these agents remains unknown (BREYTENBACH 1976; SMITH & FORD-HUTCHINSON 1979).

Effectiveness.

The effect of proteolytic enzymes on oedema and other post-operative sequelae is also controversial. Many authors (MAGNES 1966; GALLOWAY et al 1967; LIE et al 1967; YOUNG 1967; HUMPHRIES 1969;1974; KOBEL 1970; MARLETTE & AMEN 1970; ARONOFSKY 1971; DE N'YEURT 1972; McCUE et al 1972; YOUNG 1979) report that these enzyme preparations are effective in reducing oedema and other post-operative sequelae following vasectomy, and various foot, hand and oral surgical procedures. However, many of these evaluations are merely "testimonials" and others use relatively subjective measures of effectiveness.

Other authors (GYLLING et al 1966; HUNTSINGER & LEBHERZ 1966; SALISBURY & HUNTER 1972; SHEHADI 1972; BREYTENBACH 1976; CACI & GLUCK 1976; CAMERON 1980), generally using more objective measures of efficacy, found proteolytic enzymes to be of no benefit in reducing oedema across a similar range of surgery, although some (SHEHADI 1972; CACI & GLUCK 1976; CAMERON 1980) did report relief of pain and trismus, and/or diminished ecchymosis.

While the empirical use of many such drugs in man has not been severely jeopardised by a lack of knowledge of their modes of action, carefully designed investigations are needed to determine whether these agents do in fact produce more benefit than alternative treatment modalities (SMITH & FORD-HUTCHINSON 1979), or than no treatment at all. At this point, these agents do not appear to offer significant benefit. It is further noted that many (particularly animal products) may also

produce a wide range of side effects including fever, pain and allergic/sensitivity reactions (GALLOWAY et al 1967; ARONOFSKY 1971).

8.3.2.4 Non-steroidal anti-inflammatory drugs (NSAID's).

"The early history of anti-inflammatory drug therapy belongs to analgesics and salicylates" (HOLT 1979). In recent times, these drugs have been loosely grouped under the classification of "non-steroidal anti-inflammatory drugs" (abbreviated to "NSAID's"). As will be seen, considerable variations in efficacy and mode of action are evident in comparisons of these drugs.

Mode of action.

Perhaps the most significant advance in understanding the action of these drugs was the discovery in three different experimental systems that the generation of PG's was inhibited by aspirin-like drugs ("aspirin-like" in action, not structure) (VANE 1971, cited by FERREIRA & VANE 1979). It has since become obvious that, for many such agents, this action is their primary (but not sole) pharmacological action (FERREIRA & VANE 1979; GRYGLEWSKI 1979; SATO et al 1980).

This inhibition of PG synthesis by aspirin occurs by acetylation of the enzyme, cyclo-oxygenase, which is responsible for catalysing the conversion of arachidonic acid to the labile endoperoxide - PGG2 (GRYGLEWSKI 1979; SHEN 1979; KUEHL & EGAN 1980) (see TEXT-FIGURE 3.4). However, the mechanism of the inhibition of PG synthesis by NSAID's is complex and may differ for different drugs in this group (GRYGLEWSKI 1979).

It is widely reported that there is good correlation between the capacity of a NSAID to inhibit PG synthesis in vitro and its ability to suppress inflammation in rat paw oedema (BRUNE et al 1979; SHEN 1979;

KUEHL & EGAN 1980). Thus NSAID's which cause little or no inhibition of PG synthesis (such as phenacetin and paracetamol) (VINEGAR et al 1978; PENN 1980, p193), have limited anti-inflammatory action.

This inhibition of PG synthesis markedly inhibits the second phase of platelet aggregation (see 1.3.2.2). Similarly, inhibition of leucocyte mobilization is also reported (VINEGAR et al 1978; DI ROSA 1979; GRYGLEWSKI 1979). Since oedema formation in at least a few experimental models is closely associated with neutrophil margination and emigration (VINEGAR et al 1973; 1978; 1981; WEDMORE & WILLIAMS 1981; ISSEKUTZ & MOVAT 1982), administration of NSAID's is likely to reduce exudation. The work of GARCIA-LEME et al (1977) and GARCIA-LEME (1981b) alsc suggests direct leucocyte inhibition.

The nechanism of action however remains disputed. Some suggest that NSAID's act <u>in vivo</u> by releasing an endogenous anti-inflammatory substance (such as endogenous glucocorticoid) rather than by directly blocking the action or release of inflammatory mediator(s). The endogenous substance would then be responsible for effects such as the suppression of leucocyte function. A similar indirect action may result from a "counter-irritant" action of the NSAID (VINEGAR et al 1978; FERREIRA & VANE 1979).

In summary, while the most obvious mode of action of NSAID's in the reduction of oedema and erythema may be blocking of prostaglandin synthesis, this effect may indeed result from more complicated processes, possibly also involving oxygen-derived radicals (VAN DE STADT 1982). NSAID's have no known effect on fluid-phase mediators such as kinins. This narrow range of action may explain the observation that although these agents do reduce inflammation, they are seldom entirely effective <u>in vivo</u> (GILMORE 1976) (see below).

Effectiveness.

Despite the controversy over the mode of action of NSAI drugs, it is agreed that oral ingestion of these agents ameliorates at least part of the four cardinal signs of inflammation (GLENN & SEKHAR 1971; VAN DE STADT 1982). The phenylalkanoic acid derivative, ibuprofen (Brufen (R)), is reported to be up to 32 times more potent in animals than acetylsalicylic acid with respect to anti-inflammatory, analgesic and antipyretic actions. However, there is some divergence of opinion about its anti-inflammatory efficacy in man, particularly as related to acute inflammatory conditions (LOKKEN et al 1975). Whilst it is reported to be of value in sport injuries (LOKKEN et al 1975; BOURNE 1980), and in reducing post-surgical pain (and thus perhaps indirectly trismus), this drug produced only slight reduction in swelling (not statistically significant) (LOKKEN et al 1975; VAN DER ZWAN 1982).

Indomethacin (another phenylalkanoic acid derivative) is also widely used in the treatment of chronic inflammatory joint and muscular disorders. In addition to its action on the cyclo-oxygenase pathway, indomethacin is also thought to inhibit lysosomal enzyme release and superoxide generation (VAN DE STADT 1982).

Again, experimental evidence attributes this drug with marked anti-inflammatory efficacy, inhibiting carrageenin-induced oedema (MONCADA et al 1973) and post-surgical oedema (AMIN et al 1983) in rats following IM injection. In its action on carrageenin paw oedema, indomethacin is reported to be more potent than phenylbutazone (SENA et al 1981) and equipotent to the steroids in rats (AMIN et al 1983).

However, trials investigating the clinical efficacy of indomethacin have found only slight (not statistically significant) reduction of oedema (PETERSEN 1975; VAN DER ZWAN et al 1982). The use

of this drug was therefore not recommended for routine use in oral surgery, particulary in view of its complications (see later) (PETERSEN 1975).

The picture with pyrazole derivatives such as phenylbutazone is similar. Phenylbutazone and its active metabolite, oxyphenbutazone (Tanderil (R)) are reported to have powerful anti-inflammatory actions and some analgesic and antipyretic effects (PENN 1980, p194). Its main therapeutic usage is again a variety of rheumatic and chronic inflammatory conditions (BREYTENBACH 1976).

These drugs are reported to effect significant reductions in pain and trismus but only non-significant reduction of post-surgical oedema (BREYTENBACH 1976; BYSTEDT 1976). Slight reduction in ecchymosis is also reported (BYSTEDT 1976).

Aspirin itself is generally not regarded as having major anti-inflammatory effects, at least in acute inflammation, although it is active in blocking PG synthesis, thereby relieving pain (PENN 1980, p190f). Little clinical investigation has been made of its use to reduce swelling following surgery.

Interestingly, the clinical efficacy of some NSAID's is reported to show seasonal variation. For example, aspirin is less effective in inhibiting mononuclear infiltration and in reducing oedema in summer months than in winter. Indomethacin on the other hand was effective at all times of the year. It is speculated that perhaps seasonally fluctuating endogenous adrenocorticoids may be involved (WARNE & WEST 1980).

Side effects.

As with their therapeutic effects, the pattern of side effects which these drugs induce is similar. In acute usage, prolongation of bleeding time (due to impaired platelet thromboxane production, SCHERBEL & WILKE 1981), CNS disturbances such as dizziness, headache and vertigo, and, most common, gastric mucosal lesions are all well-known complications. The nephrotoxicity which is consequent to long-term use of NSAID's is also well documented (PETERSEN 1975; BYSTEDT 1976; SCHERBEL & WILKE 1981; VAN DE STADT 1982). When it is observed that this chemically-diverse group of substances share similar therapeutic actions and side-effects, a common mechanism of action is likely to underlie both.

Evidence seems to be accumulating in support of this hypothesis; altered prostaglandin synthesis appears to be central. For example, in stomach, kidney and brain, prostaglandins are important in autoregulatory functions, and pharmaceutical inhibition of their synthesis therefore causes toxic effects (DODGE et al 1979; FERREIRA & VANE 1979; SCHERBEL & WILKE 1981; VAN DE STADT 1982).

Drugs such as indomethacin and phenylbutazone are generally reported to have a high incidence of side-effects (particularly gastric and CNS) and are often poorly tolerated by patients (PETERSEN 1975; DODGE et al 1979; PENN 1980, p195; VAN DER ZWAN et al 1982). Phenylbutazone is potentially very toxic and may cause agranulocytosis and other blood dyscrasias. Regular peripheral blood examinations are therefore mandatory for any patients given medium to long-term therapy.

It is interesting to note that AMIN et al (1983) recommend the use of indomethacin over steroids. These authors (having found significant improvement in post-surgical sequelae) believe that the

side-effects which may accompany indomethacin, though common and undesirable, are of less biological effect than the widespread alterations which steroid therapy produces.

The overall belief however is that NSAID's are disappointing in their ability to reduce post-operative sequelae, particularly oedema in the clinical setting. It must be remembered that inflammation is multifactorial and this finding in relation to NSAID efficacy emphasises that prostaglandins are not the sole mediators of inflammation (see also FERREIRA & VANE 1979; BONNET et al 1981).

8.3.2.5 Corticosteroids.

The adrenal cortex secretes a large number of hormones which are steroidal in structure. These are divided for convenience into three groups:

i) those predominately effecting carbohydrate, protein and fat metabolism, as well as exerting potent anti-inflammatory action (glucocorticoids).

ii) those which principally control fluid electrolyte homeostasis (mineralocorticoids), and

iii) the sex hormones (PENN 1980, p106).

Collectively, the glucocorticoids and mineralocorticoids are known as "corticosteroids". The distinction between them is somewhat arbitary since each has some actions of the other (PENN 1980, p106). Therapeutic interest has however been directed towards the glucocorticoids (cortisone and hydrocortisone) more so than the mineralocorticoids (deoxycorticosterone) (GREENFIELD & CARUSO 1976).

The physiologic functions and pharmacologic actions of these substances are numerous and diverse. In addition to influencing the

metabolism of protein, carbohydrate and fat, and the fluid and electrolyte balance, these substances also contribute to the maintenance of functions in the cardiovascular and nervous systems, and in the kidney and other organs and tissues. Corticosteroids also impart to the body its capacity to resist stressful stimuli of all types. It is because of this diversity of physiologic functioning that these substances are considered to be a fundamental component of body homeostasis (WILLIAMSON et al 1980). The glucocorticoids also exert anti-inflammatory effects which will be discussed later.

The glucocorticoids are 21-carbon steroidal molecules synthesised from cholesterol under the influence of corticotrophin (PENN 1980, p107f; WILLIAMSON et al 1980). (See SCHLAGEL (1972) and JASANI (1979) for detailed description of the structure of these hormones). Cortisol (hydrocortisone) is the principle circulating glucocorticoid in man. It is important to note that relatively small differences in structure of these steroid molecules may cause distinct differences in potency and duration of action (WILLIAMSON et al 1980).

This has been the basis of research into the development of synthetic analogues such as prednisolone and prednisone. In the development of these, and particularly of the newer steroids (methylprednisolone, paramethasone, betamethasone, triamcinolone and dexamethasone), research has aimed at minimizing mineralocorticoid activity and increasing anti-inflammatory potency (GREENFIELD & CARUSO 1976). However, other glucocorticoid actions (such as inhibition of protein synthesis and glucose uptake by the tissues, and mobilization of stored free fatty acids) are retained (see JASANI (1979) for detailed discussion of these effects). Inhibition of protein synthesis is of particular importance to this discussion, as will be shown.

Since their isolation in the early 1940's, the naturally occuring steroids have been known to exert significant anti-inflammatory/immunosuppressive effects, such as the suppression of increased permeability (GREENFIELD & CARUSO 1976). This action appears to be produced by vasoconstriction and by the reduction of vascular hyperactivity. (GILMORE 1976; WILLIAMSON et al 1980). Other anti-inflammatory effects include suppression of leukotaxine and histamine release, stabilisation of cell membranes and connective tissue structure (WILLIAMSON et al 1980), generalized suppression of leucocyte numbers and functions, and increased resistance of the vascular endothelium to cell adherence (GILMORE 1976).

Mode of action.

When the steroidal and non-steroidal anti-inflammatory drugs are considered in relation to inflammation, two facts emerge. Firstly, each of the NSAID's is effective against only one or a few mediators or phasic components of inflammation. Steroids on the other hand, while not directly effective against fluid-phase components (GILMORE 1976), are non-specific in action and thus effectively moderate nearly all aspects of the inflammatory reaction (SCHLAGEL 1972). Secondly, all inflamed tissues are hyperactive with appreciably accelerated metabolism. Corticosteroids are primarily inhibitory when present at pharmacological concentrations (SCHLAGEL 1972). Taken together, these points suggest a single, primary mode of action.

It is thus hypothesised that steroids effect some conformational or functional change in receptor/membranes (both cellular and subcellular) which blocks the access of other molecules (such as fluid-phase mediators) to receptor sites. This action is particularly evident in the stabilizing actions of steroids on vascular permeability and

leucocyte adherence to endothelium (SCHLAGEL 1972; FAUCI 1976).

Three hypotheses have been presented (from FAUCI 1976):

i) that steroids directly interact with cell/lysosome membranes thereby altering either their stability or surface configuration,

ii) that corticosteroids react with a cytoplasmic receptor, migrate to the cell nucleus and there induce new protein synthesis by affecting transcription and/or translation of nucleic acids. (At the same time, synthesis of normal proteins (for example, collagen) and of DNA/RNA is depressed (FINE et al 1977)),

iii) that corticosteroids activate cyclic AMP and so modulate cell functions.

Importantly, it is not felt that these hypotheses are mutually exclusive (FAUCI 1976) and thus all three could be in operation together, thereby accounting for the various changes which are consequential to steroid therapy.

i) Direct membrane interaction.

As was described in 3.3.2.5 (cyclic nucleotides), it is now becoming apparent that many cellular enzymatic reactions occur at the interface between the cell membrane and the external milieu (U. RYAN 1983). Direct steroid-induced physiocochemical modifications of the cellular membrane may establish rate-limiting steps or blocks in such reactions.

The membranes would therefore become less responsive to exogenous and endogenous chemical mediators of inflammation, which is likely to explain the effect of steroids on microvessel permeability and dilatation (SCHLAGEL 1972).

This direct membrane action is also probably a significant component in the suppression of lysosome discharge in inflammatory cells. However, whether or not such suppression occurs is somewhat controversial. Although many authors report it (WILLOUGHBY & DI ROSA 1971; HELLEM & NORDENRAM 1973; HOWE 1977; COLEN et al 1979; GRYGLEWSKI 1979; YAMADA et al 1979; KUEHL & EGAN 1980), others believe that lysosomal release is only inhibited with excessive concentrations of steroid and therefore not at in vivo doses (GILMORE 1976). Further investigation with careful monitoring of steroid dosage is required to clarify this discrepancy.

ii) Specific cytoplasmic receptor.

The supposed interaction of steroid with a specific cytoplasmic receptor and the subsequent alteration of cell functions, such as protein synthesis, may possibly produce a host of effects. Among these is the synthesis of a specific protein (only apparent in the presence of steroid) which is thought to inhibit phospholipidase A2 and thus prostaglandin synthesis (both cyclo-oxygenase and lipoxygenase pathways) (FINE et al 1977; HIGGS et al 1979; JASANI 1979; KUEHL & EGAN 1980; VAN DE STADT 1982). As a consequence of this hypothesis, seriously damaged tissues or cells, or systems which contain an excess of free arachidonic acid, are relatively resistant to the inhibitory action of glucocorticosteroids (VAN DE STADT 1982).

iii) Cyclic nucleotides.

Steroid-induced alterations in the intracellular cyclic nucleotide ratio (by elevation of AMP levels) are also likely to be significant. Elevation of cyclic AMP levels, is generally believed to inhibit cell functions such as migration, adherence and phagocytosis and lysosomal enzyme release (GOLDSTEIN 1977; BONNETT et al 1981).

Interactions between steroids and cAMP thus provides another pathway of pharmacological action for these agents.

Anti-inflammatory effects of steroid therapy.

Whatever the mode of action, steroids affect leucocytes in two ways. Firstly, they affect the traffic, circulation and availability of these cell populations to and from various tissue compartments. Secondly, they affect leucocyte function, both in the circulation and after their migration into various sites, such as inflammatory loci (FAUCI 1976).

These effects are expressed differently in the various leucocyte populations. For example, the infiltration of granulocytes into inflammatory sites is depressed, though their functions are not appreciably altered. On the other hand, steroids induce a monocytopenia and diminish monocyte infiltration, as well as impairing monocyte phagocytic and bacteri cidal activity (FAUCI 1976; GILMORE 1976; SALMELA & AHONEN 1981).

On the lymphocyte series, the effect of glucocorticoids depends on the animal species. In so-called "steroid-susceptible" animals (rabbit, rat and mouse), steroids cause lympholysis, decreasing the number of both T and B cells and reducing circulating levels of their products (for example, lymphokines and antibodies). Lymphocytes are also redistributed so that more are held within the bone marrow (GARCIA-LEME et al 1977; DANNENBERG 1979; GARCIA-LEME 1981).

In "steroid-resistant" animals (man, monkey and guinea pig), steroids cause little or no lympholysis: overall lymphocyte function is not profoundly affected. Nonetheless, fewer lymphocytes enter the blood and inflammatory sites, and thus they are essentially unable to

participate in the inflammatory response (FAUCI 1976; GILMORE 1976; DANNENBERG 1979).

In summary, the result of steroid therapy is a delayed and reduced inflammatory cell infiltration (HUNT 1976b; SCHILLER & DE SILVA 1979; SALMELA et al 1980b). It is commonly held that this suppression is the major anti-inflammatory action of these drugs (FAUCI 1976; SCHILLER & DE SILVA 1979).

Steroids also contribute to the maintenance of vascular tone (GILMORE 1976; FERREIRA & VANE 1979), probably through causing release of noradrenaline, or by alteration of blood vessel proteins (SCHILLER & DE SILVA 1979). Inhibition of prostaglandin synthesis may also contribute to the maintenance of normal blood flow. Steroids also enhance the resistance of cells to lysis, and of endothelium to leucocyte adherence (FAUCI 1976; GILMORE 1976).

In view of these wide ranging effects which steroid administration achieves, it would be expected that significant inhibition of the early inflammatory response would be present, should appropriate levels of steroid be present. That this is so has been extensively reported in both experimental (COLEN et al 1979; KUEHL & EGAN 1980; ZAREM & SODERBERG 1982) and clinical studies (HOOLEY & FRANCIS 1969; MARLETTE & AMEN 1970; PAPANGALOU 1972; HOOLEY & HOHL 1974; CORBOY 1976; HUFFMAN 1977; GREENFIELD & CARUSO 1976; HABAL & POWELL 1978; YAMADA et al 1979; VAN DER ZWAN et al 1982). Only one study, to this author's knowledge, failed to find evidence of significantly reduced post-operative swelling with prednisolone therapy (CACI & GLUCK 1976).

Thus, therapy with glucocorticoids, particularly the synthetic analogues (PENN 1980, p108) is generally regarded as being highly efficacious in reducing post-surgical inflammation and oedema. Furthermore, one thorough study comparing various NSAID's with betamethasone (VAN DER ZWAN et al 1982) found that betamethasone was the only agent which significantly reduced oedema formation. The supremacy of the steroids over all other anti-inflammatory agents is also supported by other investigators (KUEHL & EGAN 1980), though these effects only occur if steroid therapy is commenced soon following surgery (SALMELA et al 1980b; SHAMBERGER et al 1981).

However, some confusion results from the variety of experimental dosages used. These are sometimes well in excess of <u>in vivo</u> therapeutic levels , and the results of such studies thus show exaggerated effects, both advantageous and disadvantageous. Nevertheless, many authors state that the routine use of glucocorticoids should be avoided because of the possible adverse effects of these preparations (ARONOFSKY 1971; PETERSEN 1975; HUNT 1975; 1976b; COLEN et al 1979; KUEHL & EGAN 1980; SALMELA 1981b). These questions are further considered later.

Side effects.

It appears that the side effects accompanying the administration of steroids are likely to be a direct result of their pharmacological action (in a similar manner to the side effects of the NSAI drugs). For example, steroid-induced suppression of leucocyte involvement in the inflammatory response reduces inflammation, however, it therefore also prolongs resolution of this phase, with subsequent delay of repair. These effects are especially seen in relation to the suppression of macrophage and fibroblast activity.

GREEN (1965), in an early clinical study, reported that steroid therapy given before and at the time of operation exerted an unfavorable effect on the healing of the surgical wound, with increased incidence of dehiscence. Since this time, many studies have reported delayed or impaired healing following steroid treatment (NEWCOMBE 1972; SCHILLING 1976; FINE et al 1977; AHONEN et al 1980; GOFORTH & GUDAS 1980; GOLAN et al 1980; SALMELA et al 1980a;b; SALMELA 1981b; SALMELA & AHONEN 1981; SHAMBERGER et al 1981; HOLUND et al 1982). This risk is increased where wounds are 'contaminated' (AHONEN et al 1980).

NEWCOMBE (1972) found scanty, fragile, disordered capillaries and small widely-scattered fibroblasts, (some dying) in the presence of therapeutic levels of steroids. Epithelialization, dissolution of the coagulum and wound contraction are reportedly delayed (SHAMBERGER et al 1981), and collagen and proteoglycan synthesis is said to be diminished (SALMELA et al 1980a). Thus all aspects of repair are retarded or impaired, perhaps leading to wound breakdown.

In addition, the suppression of leucocyte accumulation and function may increase the susceptibility to microbial infection (FAUCI 1976; DANNENBERG 1979; JASANI 1979). Further, the signs which characterise the onset of infection are camouflaged so that infection may be quite severe before it is apparent (CACI & GLUCK 1976).

Other reported side-effects include psychosis, peptic ulceration and abnormalities of sex hormone control (PENN 1980, p111f).

In these effects, the type of steriod used is significant. For example, synthetic preparations exert less mineralocorticoid activity than natural steroids; however, they have much more potent anti-inflammatory action and therefore produce greater suppression of

healing (GOLAN et al 980).

Dosage is also critical (HOLUND et al 1982). Thus SCHILLING (1976) reports that healing is retarded with pharmacologic but not physiologic doses. This attitude is reflected by many clinicians who report that short-term therapy is "safe" (GREENFIELD & CARUSO 1976) and that there is little effect on healing with low doses (NEWCOMBE 1972; SMALES 1978). Several other clinicians also report that steroid therapy caused no significant wound complications (HOOLEY & FRANCIS 1969: PAPANGALOU 1972; CORBOY 1976).

It is difficult to resolve the contrasting opinions of wound biologists and clinicians on this question. Corticosteroid therapy must be considered to have the potential to impair healing, but whether it does so at doses which reduce inflammation and oedema is not clear. However, an understanding of the repair processes would seem to indicate that any agent which caused the wide-spread cellular suppression of which steroids are reportedly capable, must also disrupt healing.

HPA suppression.

Perhaps an even more significant area of concern in regard to steroid therapy has been its affect on the hypothalamic-pituitary-adrenal (HPA) axis. The production of cortisol by the adrenal cortex is directly regulated by the anterior pituitary and indirectly by the hypothalamus. Under normal circumstances, adrenocorticotrophic hormone (ACTH) shows a diurnal rhythm (5.2.5) with higher plasma levels in the morning than late in the day. ACTH secretion is controlled by the hypothalamic corticotrophin-releasing factor (CRF). Stressful stimuli cause increased release of CRF above the normal periodic pattern (WILLIAMSON et al 1980).

This entire system (the so-caled "HPA axis") is monitored by a negative feedback mechanism in which increasing plasma levels of cortisol result in decreased output of ACTH. Supplementation of natural glucocorticoids with synthetic analogues similarly suppresses ACTH release, and thus depresses the natural production of cortisol (WILLIAMSON et al 1980).

Early in the history of therapeutic use of glucocorticoids, cases of severe shock, attributed to adrenocortical insufficency were reported (WILLIAMSON et al 1980). Although such shock is now uncommon (due to more careful monitoring of adrenal function and appropriate supplementation), it has been demonstrated that even short-term steroid therapy causes suppression of the HPA axis.

GREENFIELD and CARUSO (1976) report that a three-day course of dexamethasone produces significant suppression of plasma cortisol levels, which may take up to four days to disappear after cessation of therapy. The amount of suppression is said to depend on the duration of treatment and the dose administered (WILLIAMSON et al 1980). It is noteworthy that although the HPA axis is suppressed by dexamethasone administration, therapeutic levels of steroid are present at a cellular level thereby preventing any manifestations of adrenal insufficiency (WILLIAMSON et al 1980).

FAUCI (1976) reports that a single dose of a short-acting glucocorticoid given in the morning has fewer side effects (including suppression of the HPA axis) than either the same total dose of the identical agent given in divided doses throughout the day, or the equivalent anti-inflammatory dose of a long-acting agent. It is believed that this is because the morning dose more closely simulates the normal endogenous cortisol peak (see also WILLIAMSON et al 1980).

It must therefore be stated that steroids must be used with care, with remembrance both of the possible side-effects and the relative and absolute contraindications to their use (see HOOLEY & FRANCIS 1969; HOOLEY & HOHL 1974; GREENFIELD & CARUSO 1976). When such caution is used, it appears that the suppression which steroids induce in the HPA axis is of small clinical importance since, in normal individuals, stressful stimuli of sufficient magnitude can overcome the effects of the inbuilt negative feedback mechanisms (see WILLIAMSON et al 1980).

Summary.

The use of glucocorticoids is widely reported to be effective in markedly depressing the cardinal signs of inflammation, including oedema. In particular, vascular permeability and blood flow tend towards normal and leucocyte infiltration and some cell functions are depressed. The degree of this effectiveness is seen in that some authors claim that these drugs are the only clinically effective anti-inflammatory agents (VAN DER ZWAN et al 1982). However, steroids also cause suppression of collagen and proteoglycan synthesis due to impaired fibroblast function and delayed resolution of devitalized tissue and extravascular clot. The suppression of leucocytes also causes increased susceptibility to infection. The clinical effect of such alterations is disputed.

In addition, the therapeutic supplementation of natural steroids leads to some suppression of the normal regulatory mechanisms of steroid secretion. However, whilst with long-term therapy these effects are highly significant, there does not appear to be great clinical effect from short-term therapy.

These questions are considered further in 8.4.

8.3.2.6 Benzopyrones.

Recently, a new group of drugs has been added to the pharmacological armamentarium of the surgeon in the control of oedema. Termed benzopyrones since they contain a benzopyrone component, this group of drugs includes coumarin, rutin and derivatives.

Mode of action.

These drugs are said to be effective in reducing all forms of high protein oedema (FOLDI & CASLEY-SMITH 1978). However, they do not appear to act by reducing protein leakage from damaged vessels (FOLDI & CASLEY-SMITH 1978). In fact, they may actually increase vascular permeability at sites of injury (perhaps through histamine release) (CASLEY-SMITH 1976c).

Rather, it appears that the major action of these drugs is the marked increase in tissue lysis of accumulated protein (PILLER 1975; FOLDI & CASLEY-SMITH 1978). The resulting fragments, being small, are readily able to diffuse out of the tissues, thus releasing the accumulated fluid to be reabsorbed in the "venous limb" or drained via the lymphatics (PILLER 1975).

Although there is some increase in the activity of acid proteases in the free oedema fluid, serum and extracellular compartment of skin (PILLER 1976), this increased proteolysis is chiefly dependent upon macrophages. Benzopyrones increase the number of these cells in the inflammatory site (PILLER 1975) perhaps by non-immune activation of complement, thereby producing chemotactic factors (FOLDI & CASLEY-SMITH 1978). They also increase macrophage proteolytic functioning (PILLER 1975; FOLDI & CASLEY-SMITH 1978). Benzopyrones may increase PMN and fibroblast proteolytic activity as well (PILLER 1976; FOLDI & CASLEY-

SMITH 1978); however this is less significant.

These agents also appear to increase lymphatic functioning, but this can only occur where such function is not already maximal (FOLDI & CASLEY-SMITH 1978). This effect is therefore not likely to be apparent in post-surgical oedema.

These drugs affect oedematous tissues preferentially since they depend upon the natural accumulation and activation of the cells through which their action is effected (CASLEY-SMITH 1976c). Binding of the drug to extravascular protein which is then phagocytosed presumably carries it to its site of action, the lysosome (PILLER 1976).

Effectiveness.

Several double-blind studies cited by CASLEY-SMITH (1982/1983) report marked reductions in oedema following a number of surgical procedures including GIT anastomoses, tonsillectomy, episiotomy and facial plastic surgery when benzopyrone agents are administered orally. These drugs are similarly reported to be highly effective in reducing oedema following oral surgical procedures, including osteotomy (DIECKMANN 1973; CASLEY-SMITH 1982/1983). Most commonly used is the combination of coumarin and rutin, the combination being better than using either drug alone. Higher doses are reported to be more effective (CASLEY-SMITH 1982/1983).

DIECKMANN (1973) found this combination to be significantly more effective than oxyphenbutazone in reducing pain and oedema following oral surgery.

Side-effects.

The literature suggests that these drugs may probably be used in very high doses with virtually no toxic effects (CASLEY-SMITH 1976c;

1982/1983). In the large cross-section of studies cited by CASLEY-SMITH (1982/1983), the incidence of side-effects was only 0.5%. These included slight dizziness, headache and gastrointestinal symptoms.

In summary, it would seem that the benzopyrones deserve careful investigation, since they may provide a very useful adjunct to the post-operative care of patients. They are reported to be effective in reducing all forms of high protein oedema, and appear to be almost free of side-effects. Present research suggests that they are transported to the site of inflammation bound to plasma protein and thus they act preferentially at such sites. It is thought that they act by stimulating macrophage chemotaxis and proteolysis, thereby reducing the amount of protein retained within the tissues.

8.3.2.7 Other pharmalcologic agents.

Hyaluronidase.

Hyaluronidase is a unique enzyme which depolymarises and hydrolyses the hyaluronic acid molecule. Such molecular breakdown lowers the viscosity of the interstitium, and thus hyaluronidase temporarily permits freer passage of fluid through the tissues (SHUTTEE 1962; QUINN 1964; MEYER & SILBERBERG 1977). Localised collections of fluid therefore rapidly dissipate into the surrounding tissues (SHUTTEE 1962). Of itself, hyaluronidase lacks propulsive action and it must therefore be injected under pressure into the oedematous tissue (SHUTTEE 1962). It is reported to achieve significant reductions in oedema and trismus (QUINN 1964), particularly at 48 and 96 hours (SHUTTEE 1962).

The major side-effect of hyaluronidase therapy is that its increase of tissue permeability also allows spread of microorganisms.

It is therefore recommended that this enzyme not be used in the presence of infection (MARLETTE & AMEN 1970). This does limit its use in oral surgery since all intraoral wounds are "contaminated" and therapeutic hyaluronidase may allow these contaminating organisms to proliferate more extensively. Hyaluronidase is therefore seldom used in current clinical practice.

Systemic haemostatics.

While there is no substitute for good surgical haemostatic techniques, several drugs have been claimed to be effective in promoting haemostasis. These include carbazochrome salicylate (Adrenosem (R)), conjugated oestrogens (premarin) and koagamin. It is assumed that improving haemostasis may prevent the formation of haematomata. However, double-blind studies have not demonstrated any advantage to their use (QUINN 1964).

Likewise, vitamin K (phytonadione, mephyton) has also been suggested to be beneficial in aiding haemostasis. This substance is certainly highly efficacious in patients with prothrombin deficiency, however, it is of no benefit under normal conditions (QUINN 1964).

8.4 CONCLUSION.

This chapter sets out to describe the various physical and pharmacological therapies which have been used to alleviate the sequelae which follow oral and other surgery. These techniques and drugs continue to increase in number. Disappointingly however, most appear to be only marginally effective.

A major difficulty in assessment and comparison of these therapies is the finding of a suitable technique of measuring facial

dimensions. Ideally, such a technique should be reproducible, easy to use and inexpensive.

Though physical therapies avoid the administration of toxic agents, little work has investigated their effectiveness. Nonetheless, ice packs are empirically used by some surgeons in an effort to reduce post-operative complaints. They appear however to be only of slight benefit in reducing oedema, though pain is lessened.

Surgical drains are widely used in many branches of surgery for a variety of reasons. In the context of this thesis, their significance lies in that they are said to minimise oedema and haematoma formation, perhaps by acting as a vent for the drainage of transuate/exudate. The many different types of drainage systems appear to have some differences in application. While all become nonfunctional sooner or later due to their isolation from the wound environment by a fibrin capsule, most current studies seem to find closed suction drainage systems to provide the most effective reduction of clinical oedema. Further studies are required to compare these results with the commonly recommended pharmacological therapies.

As far as therapeutic agents are concerned, some (such as antihistamines) are universally regarded as being ineffectual. Reports concerning the benefit of others (including antibiotics and various plant and animal enzymes) are divided, but do not generally find them beneficial, though they may ameliorate pain and trismus. The routine use of antibiotics, particularly, is questionable because of the individual and community effects of such therapy. Further investigation of these agents is required.

The non-steroidal anti-inflammatory drugs may have some effect in reducing oedema, though the literature is again divided. The reduction achieved does not appear to be great and significant side-effects (especially GIT irritation) are commonly reported with their use in the concentrations required to achieve anti-inflammatory effects.

The most widely used and most clinically and experimentally effective drugs in minimising oedema are the synthetic glucocorticoids. However, the serious metabolic effects of their therapeutic use, even short-term, cannot be disregarded. Also significant is the metabolic inhibition of leucocytes, which is a major aspect of their therapeutic effectiveness. Such inhibition increases the susceptibility to infection and produces significant delays in experimental wound repair. This is especially critical to the intraoral wound. However, the question of steroid-induced wound complications is not yet clear since many clinicians report no difficulties from their short-term use. Nonetheless, many authors advise against their routine use in the management of oedema because of these potential complications.

Of the drugs mentioned, the benzopyrone group deserves particular attention for several reasons. Firstly, research to date suggests that they are effective. Secondly, their use appears to cause virtually no side-effects. Thirdly, their mode of action appears to involve enhancement of normal physiological mechanisms for the resolution of oedema. Further research may find these drugs to be beneficial.

In considering these methods of control of post-surgical oedema, it is essential to evaluate just how important oedema control is for the surgery concerned and thus to assess if its control is worth the

risk of drug-induced complications and side-effects. Further clinical and experimental research is necessary before these questions can be fully answered. It is also important to remember that much of the oedematous response due to surgery occurs as a direct result of this injury. It is unlikely that pharmaceuticals will reduce this component though they may limit that oedema resulting from the action of inflammatory mediators (see Chapter 9).

All research in this field must be carefully constructed, and use reliable, objective methods of assessment in a double-blind framework where possible. Researchers must aim at objectivity in their evaluation of the reported benefits.

The principle question yet to receive attention relates to the effect of inflammatory oedema on the tissues, and whether its development is physiological or pathological. This question, which must govern the clinician's response to surgical oedema, is addressed in the following chapter.