CHAPTER 9 THE ROLE OF OEDEMA IN HEALING.

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9.1 INTRODUCTION.

At the conclusion of this presentation of the aetiology of post-surgical oedema, the clinician is faced with the question of management. Several methods of controlling oedema have been identified (as outlined in Chapter 8). Some appear to be successful (though never entirely); others are of equivocal benefit. However, the question arises, physiologically and clinically, as to whether this control is necessary or appropriate, since oedema results from processes which ultimately lead to repair of the surgical injury. Further, for the "average" oral surgical procedure, the resulting post-surgical oedema is only moderate.

Furthermore, within four days, it has significantly reduced, and has probably fully resolved after 7-10 days without any intervention. The question, "Is intervention required?" must therefore be asked, especially since the most effective method of control so far described (corticosteroid therapy) is potentially fraught with hazards, not least of which is the disruption of healing.

There are certainly some situations where the limitation of oedema is critical. The excess fluid may compromise the surgical repair of soft tissue reconstructive procedures (ZAWORSKI & NORIEGA 1978). In facial and neck surgery, it may cause respiratory embarrassment, and following neurosurgical procedures, it may raise intracranial pressure to critical levels (HONE 1977). In these and other similar circumstances, there is no question that the formation of oedema must be effectively controlled.

Furthermore, although the transudation of fluid into the injured tissues is accompanied by beneficial effects, this fluid itself may
compromise repair, even when in moderation.

Discussion of the role of inflammation and its consequent oedema is therefore the basis of this chapter. Should the clinician be concerned by the fluid accumulation? How is the patient best managed? In this context, the composition and effects of such accumulation on the injured tissues form a beginning point.

9.2 THE EFFECTS OF OEDEMA FORMATION.


As has been shown, oedema, both clinical and microscopic, is a natural consequence of tissue injury. The inflammatory exudate is chiefly composed of protein, lipids, lipoproteins, microorganisms and cellular debris and various enzymes (FLOREY 1970b; SMITH et al 1970; GLASSER & BARTH 1982). Various nutrients (such as glucose), immunoglobulins and mediators of inflammation (in active or inactive forms) are also present (SMITH et al 1970; WILLIAMS 1979). (See 4.6).

As this fluid accumulates, interstitial tissue hydrostatic pressure increases causing limitation of blood flow in an area which is already severely compromised by local vessel division and fibrin deposition. Fluid accumulation also increases intercapillary distance, thereby increasing the distance which oxygen and other vital nutrients must diffuse (CASLEY-SMITH 1973; AMIN et al 1983). (See also 6.2.1.4). It is possible that these factors contribute to local tissue ischaemia, which, through failure of the adenosine triphosphate-dependent sodium/potassium pump, may cause further swelling (COLEN et al 1979).

In post-surgical inflammation, where frank haemorrhage has occurred, numerous erythrocytes are also contained within the
interstitium. Similarly, the level of fibrin is high. The significance of the red cells lies chiefly in that they soon become effete and they must be removed by phagocytosis. Their presence therefore places additional load upon macrophages.

Fibrin is significant for similar reasons and also since its polymerisation within the interstitium dramatically reduces tissue permeability, thereby preventing dissipation of the accumulated fluid.

The development of haematoma within the wound, as a result of continued or recurrent vessel leakage, contributes to both of these aspects. It also increases the wound dead space, thereby further compromising nutrient supply and increasing the size of the ultimate scar (6.3.5).

The presence of extravascular fibrin and erythrocytes thus increases the cellular infiltrate (and hence the inflammatory response), and it delays the deposition of collagen and proteoglycans.

The combined effects of fluid accumulation and decreased tissue permeability lead to the formation of a stagnant, protein- and nutrient-rich fluid throughout the interstitium. This fluid retards tissue metabolism and may allow the proliferation of contaminating microorganisms (KAPLAN & WEINSTOCK 1967). It is therefore reported by some clinicians to delay healing (LIE et al 1967; SALISBURY & HUNTER 1972). It is unlikely however that this fluid is completely static and the presence of some flow within it may limit these effects.

On the other side of the discussion, the formation and collection of such a fluid has some advantages. Firstly, it assists with the entry and movement of leucocytes into and through the tissues (WILLIAMS 1979). Secondly, while lymphatic flow is still occurring, it
flushes the damaged tissues with plasma, diluting toxins and wastes (CATCHPOLE 1973). Thirdly, the reduced tissue permeability may aid in limiting the spread of contaminating organisms and of the inflammatory process (SILBERBERG 1979). Fourthly, it provides the reparative cells within the wound with a supply of nutrients such as glucose, amino acids (from protein lysis) and vitamins. These nutrients both supply the immediate needs of these cells and provide biological "building-blocks" for cell synthesis in the proliferative phase of repair.

These advantages are obviously outweighed if the intercapillary distance is so increased that ischaemia develops. However, some oedema does not appear to be detrimental to healing unless tissue vitality is compromised by other factors such as rough handling and tight suturing.

9.2.2 Other Effects.

In surgery around the face, two other factors complicate the development of oedema. Firstly, because of the relatively thin soft tissue layer covering the face, swelling alters the individual physiognomy (POLLMANN & HILDEBRADT 1982). In addition to physical effects, such as talking and eating, this alteration also has psychological effects both for the patient and his/her family (SHINADI 1972). Secondly, swelling of maxillary soft tissues may involve the eyelids (thereby restricting vision) (HABAL & POWELL 1978) or the tissues of the neck (tending to compromise the airway).

The impact of the former can usually be minimised if the patient is prepared for these changes pre-operatively. However, restriction of vision may be severely incapacitating, though this is rare unless the surgery directly involves the orbits, or unless other complications, such as cellulitis, develop. Similarly, while the surgeon must take all
precautions regarding airway embarrassment, it is rare for a patient who has undergone elective surgery to have major problems with airway obstruction.

9.3 INFLAMMATION: DEFENCE MECHANISM OR DISEASE STATE.

Based on the observation that in some inflammatory reactions (for example, the Arthus reaction) the damage caused by the reaction itself far exceeds that of the inflammatory stimulus, some authors claim that the inflammatory processes are disease states, not defence mechanisms (THOMAS 1971; 1973). This opinion chiefly refers to the activation of host leucocytes, particularly neutrophils. That there is some basis to these remarks is echoed in comments relating to the amount of tissue damage/ extravascular clot/ microbiological contamination which is present in a wound. Most recommend that these factors should be reduced so as to minimize neutrophil infiltration and lysosomal release, and hence added tissue lysis. (See Chapter 6).

The literature generally expresses the view that some inflammation is part of the normal response of an organism to surgical trauma, and that its consequences (including oedema) are "not entirely undesirable" (QUINN 1964). This statement is almost always qualified by remarks such as "however, in certain unpredictable cases, we encounter a massive, yet localised type of oedema which tends to accentuate post-operative pain and prolong the healing period" (YOUNG 1979). (See also QUINN 1964; MAGNES 1966; MARLETTE & AMEN 1970).

Why "massive...oedema" should occur in some cases has not been established. From a review of the aetiological factors involved, it is obvious that many such factors (for example, the degree of bacterial contamination or of PMN infiltration) cannot be assessed clinically. It
is likely that the massive inflammatory response which develops in some individuals may relate to factors such as these.

Also likely to be important is the connective tissue configuration of the individual in the area of surgery. This may govern how the oedema is expressed, firstly in different individuals, and secondly in different sites in the same individual since the response to identical inflammatory stimuli injected into different sites is reportedly quite different. (The sensitivity of different sites on humans is unknown, VINEGAR 1983). These factors obviously are not apparent clinically, but they may explain the unpredictable nature of oedema in some circumstances.

It is certainly clear that the early inflammatory response is inextricably linked to coagulation and to the subsequent rate and character of repair (DUNPHY 1969; HUNT & HALLIDAY 1980) since:

i) inflammation cannot commence until haemorrhage has ceased.

ii) factors activated by the coagulation sequence stimulate inflammatory cells and initiate the activation of inflammatory mediators (1.3.4).

iii) inflammatory cells remove damaged tissue and toxins within the wound (1.4.2).

iv) these cells (particularly macrophages) release factors which are thought to stimulate reparative cells (1.5.1.1).

The effect of this linkage is seen, for example, in patients on long-term corticosteroid therapy (QUINN 1964). Steroids act primarily on inflammatory cells, inhibiting their infiltration into injured tissues and suppressing their release of inflammatory substances. The steroid-induced suppression of these cells is followed by delayed proliferation and synthesis of fibroblasts and endothelium.
Some have proposed the concept of an "ideal inflammatory response" (DUNPHY 1969). Although this has not been defined, such a response would presumably achieve the required functions of inflammation (lysis and phagocytosis of devitalised tissue cells and microorganisms) without causing additional tissue damage. Such an ideal response would depend on limiting the initiating injury, but it is also apparent that components of the inflammatory response are capable of a severe reaction which is out of proportion with the injury. Recent investigations suggest that the reactive intermediates of arachidonic acid metabolism (including oxygen radicals) (VINEGAR 1983) and those radicals generated by the "respiratory burst" of "professional phagocytes (polymorphs, monocytes, macrophages)" (ZABUCCHI et al 1980) may be the major substances responsible for the detrimental effects of inflammation.

These substances are believed to participate in oxygen-dependent microbiocidal and cytocidal activities of phagocytes either inside or outside the cell. In these activities they are generally considered beneficial. However, they can also cause significant damage both from within a cell (to the phagosome or plasma membrane) or to the surrounding tissue. They may also boost the inflammatory response by promoting further increases in microvascular permeability, generating chemotactic factors and stimulating lymphocytes (BJORK et al 1980; ZABUCCHI et al 1980). Other lysosomal constituents, particularly the neutral proteases and similar trypsin-like enzymes, are also capable of widespread tissue destruction. (See 3.3.2.3).

The release of these substances appears to relate to the level of cell (particulary PMN) activation. Where bacterial contamination is significant (perhaps particular microorganisms more than others),
neutrophil activation is high with massive release of oxygen radicals, hydrolytic enzymes and so on. Local tissue destruction in such areas is severe (ARPORS 1983). This picture is confused by observations that massive neutrophil activation may also occur in response to insignificant stimuli (VINEGAR 1983). This is perhaps a form of hypersensitivity to cell/microorganism fragments.

Despite this apparently uncontrolled behaviour, several autoregulatory mechanisms are evident throughout the processes of inflammation:

1) The chief proposed mediators of inflammation (kinins, acidic lipids, complement by-products) are rapidly converted to inactive metabolites (see 3.3.1.2); inflammation therefore is dependent upon the continued activation of these substances, not on their long-term action.

2) The metabolism of membrane fatty acids contains several inter-linking negative feedback mechanisms such that the generation of metabolites serves to limit further synthesis (see 3.3.2.2).

3) Several enzyme inhibitors of various inflammatory sequences are present in the plasma, for example, Cl esterase inhibitor (3.3).

4) The cyclic nucleotides (cAMP/cGMP) appear to exist in a dynamic intracellular balance; the degree of activity of the cell depends upon which is dominant (3.3.2.5). Therefore biochemical variations in the local environment (particularly changes in concentration or concentration gradients) are significant in modifying cell function, and perhaps in altering the effect of individual substances such as hormones, mediators (3.4).

5) The "2 series" acidic lipids (those chiefly involved in inflammation) are suggested to be controlled through negative feedback mechanisms by the "1 series" (HORROBIN 1980).
6) Through its release of lysozyme, neutrophil phagocytosis may limit further accumulation and phagocytosis (3.4).

7) Hormones with non-specific action (such as corticosteroids and insulin) may modify the overall response (suppress or boost respectively) depending upon whole body needs/conditions (GARCIA-LEME 1981b).

Further, in view of the oral environment and therefore the significant presence of contaminating microorganisms in the surgical wound, some inflammatory response involving PMNs must be considered appropriate. WILLOUGHBY (1977) made a similar observation on the role of inflammation in the mouth, suggesting that mouth ulcers occurring as side-effects of the newer anti-rheumatoid drugs may signify excessive suppression of such normal oral defence mechanisms.

9.4 CONCLUSION.

It must therefore be concluded that an inflammatory response is essential to healing. However, healing may be delayed or impaired by either an insufficient or an excessive response. This gives rise, in theory, to the difficult concept of an "ideal inflammatory response". Certainly, features of inflammation have been identified as detrimental (especially the various oxygen radicals derived during PG synthesis and by the phagocyte "respiratory burst") (see above); however, even these have beneficial effects, and so far, no inflammatory models have been identified in which an "ideal response" occurs.

The picture concerning oedema is similarly complex. Although its formation has benefit through its provision of nutrients to the wound space and through its assistance of leucocyte movement through the injured tissue, the collection of fluid may cause tissue ischaemia, it
potentially provides an excellent medium for the proliferation of microorganisms and it causes lowered tissue permeability following fibrin polymerisation. Nevertheless, in the absence of additional anatomical considerations such as airway maintenance, moderate oedema generally appears to cause little biological harm, although bacterial proliferation is an important area of concern in large areas of oedematous tissue.

From the patient's viewpoint, pain is to some extent related to the relative size of the oedema, with greater distension causing more discomfort (MACGREOR & HART 1969; TEN BOSCH & VAN GOOL 1977). There is a similar correlation with functions such as talking and eating. The psychological effects of the altered physiognomy are also significant to a person following surgery; the size of the swelling, the patient's preparation for the changes and his/her ability to cope with stress determine how relevant this factor is.

The surgeon is therefore faced with the situation where, on the one hand, inflammation and its consequent oedema are normal responses which are generally appropriate and essential to wound repair, and on the other, the patient experiences pain and limitation of some functions as a result of the surgery and oedema. The "simple" solution to the management of a patient following oral surgery might therefore be merely to provide adequate control of pain. The addition of appropriate antibiotics as prophylaxis against the proliferation of contaminating microorganisms within the accumulated fluid might also be advantageous, though studies showing that the incidence of post-operative infection is not altered whether or not antibiotics are used (8.3.2.2) would deny this. The whole question of antibiotic therapy following oral surgery requires further investigation.
However, the occasional patient who develops "massive" oedema presents a problem since most agents reportedly capable of limiting oedema must be present at the initiation of the inflammatory response or earlier. The literature points to several clinical factors which are most likely to cause such increased oedema. These are ranked in some order of significance. (It is important to note however that situations where oedema is "massive" may indicate the presence of additional factors, for example the development of infection).

1. Reflection of the periosteum: increasing the size of the mucoperiosteal flap increases the oedema, particularly if muscle lateral to the external oblique ridge is elevated. (This statement must be correlated with #2.) (6.3.1).

2. Surgical trauma: increasing trauma produces increased oedema (6.3.6).

3. Operating time: increasing the length of surgery produces increased oedema (perhaps in association with #2.) (6.3.4).

4. Haemorrhage/haematoma: prolonged haemorrhage (either proceeding from the wound or developing into a haematoma) is accompanied by markedly increased oedema (6.3.5).

5. Suturing: excessive suturing to achieve full primary closure appears to retain fluid within the tissues, thereby increasing oedema (6.3.7; 6.3.8).

6. Bacterial contamination: increasing the contamination leads to increased oedema. Debridement however, reduces the number of contaminating organisms to low levels (6.2.3).

7. The patient's age: increased age is associated with a mild increase in oedema (5.2.1).

8. The patient's sex: females tend to have greater oedematous responses than males, more so at times when oestrogen levels peak
(puberty, ovulation, the last trimester of pregnancy) (5.2.3).

Unfortunately, this list is not yet complete, nor is it fully confirmed, even though many of the comments appear obvious. However, on the basis of the present information, its assumptions appear reasonable. In the presence of these factors, the oedema is likely to be aggravated. Appropriate control measures may therefore be instituted.

However, there is still the problem of being unable to assess key microscopic factors which may also dramatically modify the oedematous response. Not least of these factors is the microscopic extent of the injury itself. Despite these difficulties in predicting which patients will develop a severe inflammatory response to surgery, it seems unreasonable that anti-oedematous agents should be prescribed routinely. The implications of these questions are considered in the concluding chapter.
Following surgical incision, some degree of tissue damage occurs - a "wound" is formed. Whilst it is the body, not the surgeon, which achieves the repair through a sequential series of processes (some occurring simultaneously), the surgeon must always aim to provide circumstances which are the most conducive to prompt, uncomplicated healing with minimal functional disturbance. He therefore must be fully cognisant of the cellular and biochemical processes involved. Central to this understanding is that reparative tissue functions to some extent as an organ in its own right. This intimate, ecological co-operative of new blood vessels, macrophages, granulocytes and fibroblasts which forms is designated as the "wound module" (1.1).

A significant aspect in this response of an organism to injury is its characteristic stereotyped pattern which is collectively termed "inflammation". This pattern depends more upon the species or the individual than upon the nature of the damaging agent. Physical, chemical or biological stimuli of sufficient intensity will all evoke a similar response. Structural features peculiar to the tissue or organ involved may mould its form, but the pattern is essentially the same (GARCIA-LEME 1981b).

In considering the aetiology and management of post-surgical oedema, a review of this response as a whole was considered vital. Not disputing the stereotype, it was found that inflammation subsequent to surgery involved complexities not described by the major experimental models used to investigate this field. These complexities arise principally from the direct effect of the surgery itself.
Vessels - both blood and lymphatic - are sectioned, torn and stretched: an area of hypoxia is created; pathways of fluid drainage are disrupted. The tissue framework is crushed and distended by retraction and surgical manipulation; some tissue is devitalised and some destroyed. The vessel injury is plugged through the mechanisms of haemostasis: the fibrin clot further impedes flow and may enlarge wound space, further compromising tissue vitality. In addition, its removal occupies reparative cells, and time is required before new tissue can be laid down. Further, the incision breeches the mucosal barrier, admitting microorganisms deep into the tissues.

Since the reaction seen in acute inflammation is chiefly vascular, the damage to blood and lymphatic vessels is particularly significant in creating and exacerbating the fluid/protein exudation, and in thwarting its removal by the lymphatics. Such severe direct injury precipitates a very particular pattern of leakage from all damaged blood vessels. Such leakage commences immediately, rapidly reaches a plateau, and then continues until damaged vessels are repaired or plugged (3.2.1.3). Peripheral to this area of severe injury, tissue damage is more moderate; the inflammatory reaction here more closely resembles the stereotype, with immediate and delayed leakage responses (3.2.1.3; 3.2.1.5).

A fundamental consideration in the understanding of the tissue response to injury, and the subsequent gross leakage of protein and fluid is the microvascular framework of the tissue operated on and its normal physiological function. An examination of this area reveals that there is normally a finely-tuned dynamic balance between osmotic and hydrostatic pressures across the capillary (Starling's forces) which allows fluid to leave the arterial capillary and mostly be reabsorbed.
at the venous end of the microcirculation. The small but significant amount of plasma protein which also forms part of the outflow from the arterial capillary is removed with the remainder of the fluid by the lymphatics and by tissue proteolysis. Remarkably, this system is able to rapidly adapt to gross alterations of one or more components of this balance so as to maintain the hydration of the interstitium at a fairly static level (2.3.3; 4.2).

Also important in this balance is the configuration of the connective tissue matrix. This matrix consists of two phases. The first, a fixed system composed essentially of a network of interconnecting fibres to which various complex proteoglycans are attached (the "colloid-rich"/"water-poor" phase). The other is a labile, diffusible system which is essentially an aqueous solution of salts, metabolites and polymers filling the interstitium. This phase also forms a fluctuating network of aqueous channels which facilitate protein, cell and fluid movement through the interstitium (2.4; 4.3).

With the fixed network tending to resist expansion from the resting state and contributing to definition of tissue compliance (4.2.2.1), and the fluid partition between the colloid-rich and colloid-poor phases providing an osmotic buffer limiting excessive fluid movement between the phases and into the interstitium, tissues generally have a fairly high degree of resistance to fluid accumulation. The physiological balance of forces governing fluid movement also resists its accumulation. This resistance varies directly with tissue density (4.4).

Notwithstanding this resistance, the circumstances which develop as part of the post-surgical inflammatory response, in addition to the injury itself, produce plasma exudation of such dimensions that the
dynamic equilibrium provided in normal function is grossly overwhelmed. It is also noted that this resistance itself is lessened by the activation of various proteolytic enzymes as a consequence of inflammatory sequences. There is therefore a considerable shift of fluid, and, more importantly, plasma protein into the interstitium.

Although both the lymphatic and tissue proteolytic systems increase their activity several fold, these mechanisms are unable to cope, particularly because of the direct damage they themselves sustain at surgery. The function of the lymphatics is further impaired by the formation of fibrin thrombi within the inflammatory exudate and within their lumen. Such thrombi superimpose acute lymphoedema upon the oedema developing as a result of the wound (4.7; 4.8).

A continuing feature of surgical wounds is the gradual degeneration of surgically damaged cells. The degree to which this degeneration progresses is determined by the severity and duration of the injury, by the nutrient supply and by the particular vulnerability of different cell types (WRIGHT 1955; BOYD 1970). Some cells, for example, those in the line of the incision (VAN LANCKER 1977) are destroyed immediately; others will later develop degenerative changes which ultimately progress to cell necrosis. Some cells will show degenerative changes up to a point, and then these will reverse, and the cell recover (see 3.2.1.3).

Those cells which die subsequently undergo autolysis due to the disorganisation of intracellular enzyme systems and their indiscriminate action (WRIGHT 1955; HESLOP 1981). Ultimately, the cell disintegrates, and the enzymes are released into the environment where they may act on other tissue (WRIGHT 1955), although plasma inhibitors may limit this in the sites closest to a functioning circulation (BOYD
Within the centre of the wound these changes are likely to contribute to further cell necrosis, thereby potentiating the oedema. This will occur particularly when it is endothelial cells which are degenerating, causing gaping of the intercellular junctions. In well vascularised tissues such as those of the oral mucosa (especially supraperiosteally), there is likely to be a significant incidence of prolonged vessel leakage as a result of such endothelial damage. The discharge of polymorph lysosomal enzymes is also likely to contribute to endothelial and connective tissue cell damage.

An important question therefore concerning post-surgical inflammation is the role of these cells (PMNs). It is known that they are chiefly responsible for the elimination of contaminating organisms and in this their role is clear. However, they are also able to readily inflict severe tissue damage through release of activated cytoplasmic constituents, particularly oxygen radicals. It is not yet clear what factors initiate neutrophils to adopt the more aggressive, damaging role, apparently releasing these bacteriocidal agents indiscriminately. Bacteria or bacterial products may be involved (3.4; 9.3). The extent of this activation in surgical wounds has not been determined.

The surgical wound thus contains two sources of oedema. In addition to the effects of cell degeneration and necrosis as a direct result of surgery (described above), it is likely that plasma and cellular chemical mediators are also active in increasing vessel permeability (see 3.3; 3.4). The quantitative effect of each has not been described, though it would seem that the surgical effects predominate because of the prolonged nature of the oedematous response. It is likely however, that there is some degree of continuous
activation or renewed activation of mediators as the reaction progresses, and particularly as cells degenerate, releasing intracellular enzymes.

Some attempt has been made to draw together all these factors in **TABLE 10.1**, thereby providing some description of the post-surgical oedematous response against a very approximate time scale based on the observation (described earlier, 5.1) of maximum post-surgical oedema occurring at 24-36 hours. Presentation of such an outline is based upon the similar concept of VINEGAR et al (1982). It is complicated by the fact that the surgical insult is not a single injury, but a series of injuries proceeding until the surgery is complete. It must be admitted that major deficiencies are present in this schema, and much is conjecture, particularly aspects of the time scale. These problems could be corrected by careful experimental investigation. Nevertheless, it was felt that presenting such an outline at least provided some definition of the post-surgical response and clearly summarised the major factors involved in its aetiology.

**TABLE 10.1 SCHEME REPRESENTING THE ONSET, DEVELOPMENT AND DECAY OF POST-SURGICAL OEDEMA.**
(The removal of the mandibular third molar tooth).

<table>
<thead>
<tr>
<th>Onset.</th>
</tr>
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<tbody>
<tr>
<td>Step 1. Surgical injury (?leading to altered tissue protein)</td>
</tr>
<tr>
<td>- vessels divided - frank haemorrhage</td>
</tr>
<tr>
<td>- tissues compressed and stretched</td>
</tr>
<tr>
<td>- cells devitalised</td>
</tr>
<tr>
<td>- histamine released from mast cells</td>
</tr>
<tr>
<td>- entry of microorganisms (3.2.1.3; 3.3.2.1)</td>
</tr>
<tr>
<td><strong>Step 2.</strong> Haemostasis - begins the moment of incision, but although normally complete within minutes, the continued surgical insult disrupts early attempts and creates additional injury. (1.3)</td>
</tr>
<tr>
<td><strong>Step 3.</strong> Activation of Hageman Factor and dependent systems. (3.3.1.4)</td>
</tr>
<tr>
<td><strong>Step 4.</strong> Kinin and plasmin released. (3.3.1.1; 3.3.1.2)</td>
</tr>
<tr>
<td>? activation of complement. (3.3.1.3)</td>
</tr>
</tbody>
</table>

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Step 5. Increased blood flow and vessel permeability. (3.2.1.5)


Step 7. Leucocyte chemotaxis (particularly PMNs) and adherence to vessels at inflammatory site. (3.2.2.1; 3.2.2.4)

Step 8. PMN diapedesis into the injured interstitium. (3.2.2.2)

Step 9. Biosynthesis of prostaglandins and activation of leucocyte lysosomal contents. (3.3.2.2; 3.3.2.3)

Step 10. (Limited) release of vasoactive prostaglandins, oxygen radicals and active lysosomal contents.


Step 12. Phagocytosis of bacteria and necrotic cells/cell fragments.

Step 13. Some leucocytes damaged/destroyed during encounter with microorganisms.

Step 14. Some "leakage" of active lysosomal enzymes into the interstitium during phagocytosis and following leucocyte injury. (3.2.2.6)

Step 15. Enzyme-induced tissue damage causing:
- tissue devitalisation
- membrane perturbations — PG synthesis.

Step 16. Major phase of prolonged vasodilatation commences. (3.2.1.5)

Step 17. Vascular permeability further increased.

Step 18. Efferent lymphatics obstructed by fibrin deposition. (4.8)

Development.


Step 20. Death of tissue and inflammatory cells at centre of wound due to hypoxia and surgical injury (?time). (3.2.1.3)

Step 21. Release of an agent chemotactic for monocytes from injured and phagocytosing PMNs. (3.2.2.5)

Step 22. Emigration of monocytes into the injured site. (3.2.2.3)

Step 23. Monocyte-neutrophil interaction.

Step 24. Cytoplasmic injury from activated enzymes in cytoplasm and lysosomes of damaged PMNs. (3.3.2.4)
Step 25. Enzymatic injury to PMN plasma membrane.


Step 27. Further enzyme-induced tissue damage and lysis.

Step 28. Autolysis of damaged/hypoxic tissue cells (including endothelial cells).

Step 29. Further release of intracellular enzymes.

Step 30. Enzyme-induced increase in vessel permeability.

Step 31. Loss of endothelial cells causing additional increased permeability.

12th hr Step 32. Early phagocytosis of neutrophils by monocytes. (3.2.2.5)

15th to Step 33. Reduction in the rate of exudate formation.

18th hrs

Decay.

18th to Step 34. Continued monocyte phagocytosis as monocyte infiltration peaks. (3.2.3)

24th hrs Step 35. Migration of endothelium to replace lost cells. (1.5.1.1)

24-36 hrs Step 36. Cessation of exudate formation. (5.1)


Step 38. Proliferation of reparative tissue. (1.5)


3 to Step 40. Restitution of flow in non-sectioned lymphatics.

5 days Step 41. Epithelial migration. (1.5.1.2)

Step 42. Collagen deposition. (1.5.2)

7-10 days Step 42. Complete resolution of oedema.

Importantly, it should be noted that this schematized postsurgical oedematous response may be significantly altered by various physiological effects and pathological states. Whilst these are too varied to reiterate here, some general principles are evident.
Firstly, it is the hypothesis of this author that any circumstances which delay the deposition of collagen and proteoglycans in the wound also lead to a prolonged and perhaps enhanced inflammatory response. This is because the oral wound cannot be fully immobilised, and early movement across the wound will shear the newly formed vessels, renewing increased vessel permeability, and possibly reinstituting wound haemorrhage, (6.2.5.5). Such conditions may occur in nutrient deficiency states (for example, zinc, vitamin A and C, protein and carbohydrate deficiencies), though these deficiencies would normally have to be chronic and fairly severe for such effects to be clinically evident (6.2.1). The ultimate effect of the continued operation of shear forces in the weakened wound is wound dehiscence.

Secondly, similar effects may result where the inflammatory response itself is heightened or prolonged since significant deposition of collagen does not normally occur until resolution of the inflammatory phase is well under way. This effect may be seen where the pathosis increases tissue hypoxia, as in obesity (5.3.6), some anaemias (5.3.2.2) and cardiovascular disease (5.3.3). Enhanced inflammatory responses are probably also seen during the female sexual cycle when hormone levels peak (5.2.3.1), and in association with chronic skin disease (5.3.5).

Conditions seen in diabetes may also contribute to tissue hypoxia through vessel disease. This plus the other factors associated with diabetes (including defective insulin levels or responses) may produce severe depression of all aspects of healing in the uncontrolled diabetic (5.3.1). Leucocyte disorders in which cell function is depressed also lead to prolonged inflammatory responses, in addition to reducing body resistance to contaminating microorganisms. This commonly
leads to wound sepsis in severe cases (5.3.2.1).

Thirdly, disorders in which haemostasis is depressed (for example, thrombocytopenia) may lead to persistence of haemorrhagic oozing, particularly at wound edges. This noticeably delays the institution of an effective inflammatory response, and therefore delays subsequent healing (5.3.2.3). Persistent oozing may also lead to the development of a haematoma within the wound, or between adjacent tissue planes. This further increases the inflammatory response, both through the continued activation of plasma mediators and the liberation of vasoactive substances by cells, and also because of the large mass of fibrin which must later be phagocytosed (6.3.5). Of course, in the presence of severe disorders of haemostasis, haemorrhage itself is the more significant clinical concern.

Underlying all these and other factors, it is likely that the connective tissue framework and genetically-determined constitution exert a significant influence over the expression of oedema. This would account for differences seen between different tissues, and is likely to be significant in explaining why different individuals develop different responses to similar surgery (5.2.6). The vascularity of the particular area and hence the extent of vessel damage is also significant (see 2.7). Microbial (6.2.3) and salivary factors (6.2.4) are important, specifically oral components of the inflammatory response.

Unfortunately, many aspects of inflammation as it pertains to oral surgical wounds remain unclear. Much information has to be extrapolated from skin wounds, and while this is a commencing point, many areas would be well served by research which is particularly directed to the intraoral wound. Nevertheless, on the basis of
comparisons of vascular supply, tissue structure and so on (2.7.4), it appears that there are many similarities with skin healing, and therefore that it is reasonable to base discussion upon such wound healing research. Important differences occur in the plane and rate of epithelial migration and the rate of connective tissue healing; mucosal wounds generally heal more rapidly (TEN CATE 1966; SCIUBBA et al 1978; BOTTOMLEY 1979).

Interestingly, the small pilot study using ultrasonography to examine the internal topography of the oedematous tissues suggested that oedema resulting from the removal of mandibular third molars was primarily within masseteric fascia. The factors which direct such collection have not been fully clarified though these findings would suggest that the chief surgical injury is closely related to this region.

Having discovered that post-surgical inflammation and oedema is chiefly the response to surgical injury, the clinician must arrive at the question of its biological significance. It must be agreed that not all of the inflammatory response is beneficial; some components in fact cause significant tissue injury. While quantitative studies have not been undertaken, it is likely that some of these components (for example, activated PMN lysosomal contents) are active in post-surgical inflammation. However, it would seem that the accumulated fluid in moderation is generally advantageous or at least not harmful, biologically speaking (9.2.1).

The patient however may not agree, both because of the discomfort (some of which is attributable to the fluid distension), and because of their altered countenance and limitation of functions such as talking and eating. Importantly however, the major cause of these
problems is probably more closely linked to the surgical wound itself, the associated neural excitation and so on, rather than more peripheral events such as fluid collection in surrounding tissues. In any case, some early limitation of function is beneficial to wound repair. The prescription of effective analgesics and rest may be all that is required. This approach of course assumes that oedema is not so excessive as to limit vital functions or structures such as the airway. It also assumes that the accumulated fluid is not pooled to such an extent that the supply of nutrients such as oxygen falls below critical levels (6.2.1.4).

Whilst such assumptions are in most cases accurate, there is always the exception. As raised in 9.3, the patient whose inflammatory response is excessive becomes a difficult management problem since all agents and therapies which assist in limiting the formation of oedema must be present immediately after surgery or earlier. It is certainly not reasonable that all patients should receive treatment to reduce the development of oedema. More so since no therapies or agents so far discovered completely prevent oedema formation (though the synthetic corticosteroids come closest). This observation would be expected from an understanding of the aetiology of the post-surgical response, since the major portion of the oedema is a direct result of the surgical injury, with the remainder being mediated by a wide variety of inflammatory substances including kinins, prostaglandins and complement. It is likely that anti-inflammatory agents only modify the release and activation of these substances, although the membrane stabilisation attributed to steroids may serve to protect damaged cells from degeneration (Chapter 8).
The relative merit of the various agents in the post-surgical situation is discussed in 8.4. In summary, antibiotics may improve flap vitality but do not appear to significantly alter the oedematous response (8.3.2.2). Plant and animal enzymes (8.3.2.3) and antihistamines (8.3.2.1) are generally considered ineffective against oedema though they may ameliorate the discomfort. The non-steroidal anti-inflammatory drugs appear to provide some limitation of inflammation and oedema, probably through suppression of the cyclooxygenase pathway of prostaglandin synthesis; this mode of action also appears to frequently lead to the development of side-effects (8.3.2.4). The corticosteroids are undoubtedly the most widely used and most clinically and experimentally effective anti-oedema agents. However, the wide base of their action leads to significant suppression or modification of many tissue functions. Not least of these is suppression of leucocyte function, which must increase the susceptibility to infection (particularly in oral wounds) and suppression of healing overall. While it may be that the side-effects of their short-term usage are of minimal clinical significance, this has not been confirmed in wound healing studies. Until this has been done, their usage must remain potentially hazardous (8.3.2.5).

One of the newer anti-oedema agents is the group of drugs known as the benzo-pyrones. The few studies so far performed on their action suggests that they are effective, though perhaps more in obtaining earlier resolution of oedema than in restricting its maximal development. A positive aspect to their use is that they appear to act by accelerating normal physiological mechanisms. Further, side-effects are almost non-existent. While additional investigation is required to confirm their clinical and experimental efficacy, these drugs appear to offer a useful addition to the future surgeon's armamentarium for
dealing with this difficult area (8.3.2.6).

Since no agent or therapy has full clinical and experimental acceptance in reducing oedema formation, the problem remains as to how post-surgical oedema following oral surgical procedures should be managed? The initial answer to this question must be an assessment of the major clinical factors postulated to be involved with the aetiology of this oedema (9.3). Foremost in this must be the degree of surgical trauma. With this as the baseline, it is uncommon for the patient who has undergone minor oral surgery (normally including the surgical removal of impacted teeth), to encounter severe problems with facial oedema (excluding haemorrhage and infection, by definition), particularly if the outline described in the previous chapter is carefully attended to. There would therefore appear to be no need to be concerned with oedema in such circumstances, except that the patient should be warned about it and its consequences.

In the case of major oral and maxillofacial surgery, respiratory obstruction is a significant risk. While the use of corticosteroids is considered justified by many surgeons in such circumstances, this author does not accept that the safety of their use has been adequately documented, particularly with regard to their suppression of healing and increased susceptibility to infection. Some of the older techniques of oedema control (such as drainage) may be preferable until research has clarified the picture concerning steroids or other, less damaging agents have been found. Such drains should preferably be closed suction systems exiting from a separate stab incision so as to avoid problems with retrograde infection (8.3.1.3).
This management protocol does not deny that oedema may be associated with complications, particularly when there is an extreme response. However, it would appear that these situations are mostly associated with either the formation of a large haematoma or the early development of cellulitis. The difficulty in assessing these factors, particularly the latter, is determining whether the oedema-induced tissue changes promoted the development or spread of the causal organisms, or whether it merely represents the concurrent presentation of two separate conditions. The answer is probably a little of both, since it is likely that massive oedema will to some extent compromise tissue function, thereby allowing microorganisms to proliferate more readily. It would therefore seem advisable that appropriate antibiotics be prescribed in situations where the inflammatory reaction is likely to be severe.

With the obvious presence of numerous unsolved issues throughout this presentation, there are many areas towards which future investigations could be directed.

For the oral surgeon, many gaps remain in the understanding of the ultrastructure and physiology of oral tissues and in their response to trauma. This information is important not only to describe the oral response to injury; it also may shed light on a number of other pathological processes which are expressed intraorally. Actual definition of the biological, cellular damage caused by surgery is vital. It is continually stated that damage occurs and that it is repaired by a particular series of events. However, the damage itself is poorly defined. The clinician is therefore making judgements about surgical techniques and various aspects of management without the benefit of information regarding the microscopic changes involved. This
kind of information may allow increased control of the extent of the cellular injury.

On a similar line, the function of PMN leucocytes in the oral surgical wound and the level of their activation need to be more closely described. Understanding here in the future may allow the surgeon some degree of control of the action of these cells, thereby limiting the extent of their destruction of viable tissue. Associated with this question is more data on the level of bacterial contamination in the surgical wound, the effect of the debridement on this level, and how the contaminating organisms affect the inflammatory response. Consideration of particular organisms would also be important here.

Concerning the therapeutic control of oedema, it would seem that two groups require further investigation and development. Firstly, the synthetic steroids: research into their mode of action is continuing and this is important in defining their effects. However, there are relatively few studies of their biological effects, particularly those detrimental to healing. The continued development of new agents may enable the synthesis of agents with more specific anti-inflammatory action and therefore less side-effects. However, it would seem that their high level of efficacy is at least partly due to their widespread basis of action.

Secondly, the benzopyrones: little information is yet available as to their use in situations of acute inflammation; further clinical and experimental investigation of their action and effectiveness will aid in clarifying their place.

Following on from the small experimental component of this thesis, the use of ultrasonography in the assessment of facial, and
possibly lingual, swelling deserves further investigation. The initial difficulty is the definition of the normal sonographic appearance of these tissues, however, the technique has proved beneficial in examining this region, and may be useful in the assessment and diagnosis of facial swelling of various types.

In summary, this thesis has examined the biological basis of the surgical insult and its repair, particularly as it relates to the intraoral wound. This basis has then provided the context for a detailed examination of the aetiology of the oedema which is subsequent to this injury. The aim in providing this profile of post-surgical oedema has been:

i) to clarify both clinical and microscopic factors in its aetiology and to set these out in a sequential schema,

ii) to set post-surgical oedema in its perspective and therefore divest it of some of the empirical assessment with which it has been regarded,

iii) to suggest an appropriate management protocol.

It is hoped that this may allow a more rational approach for clinicians to this common phenomenon.
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