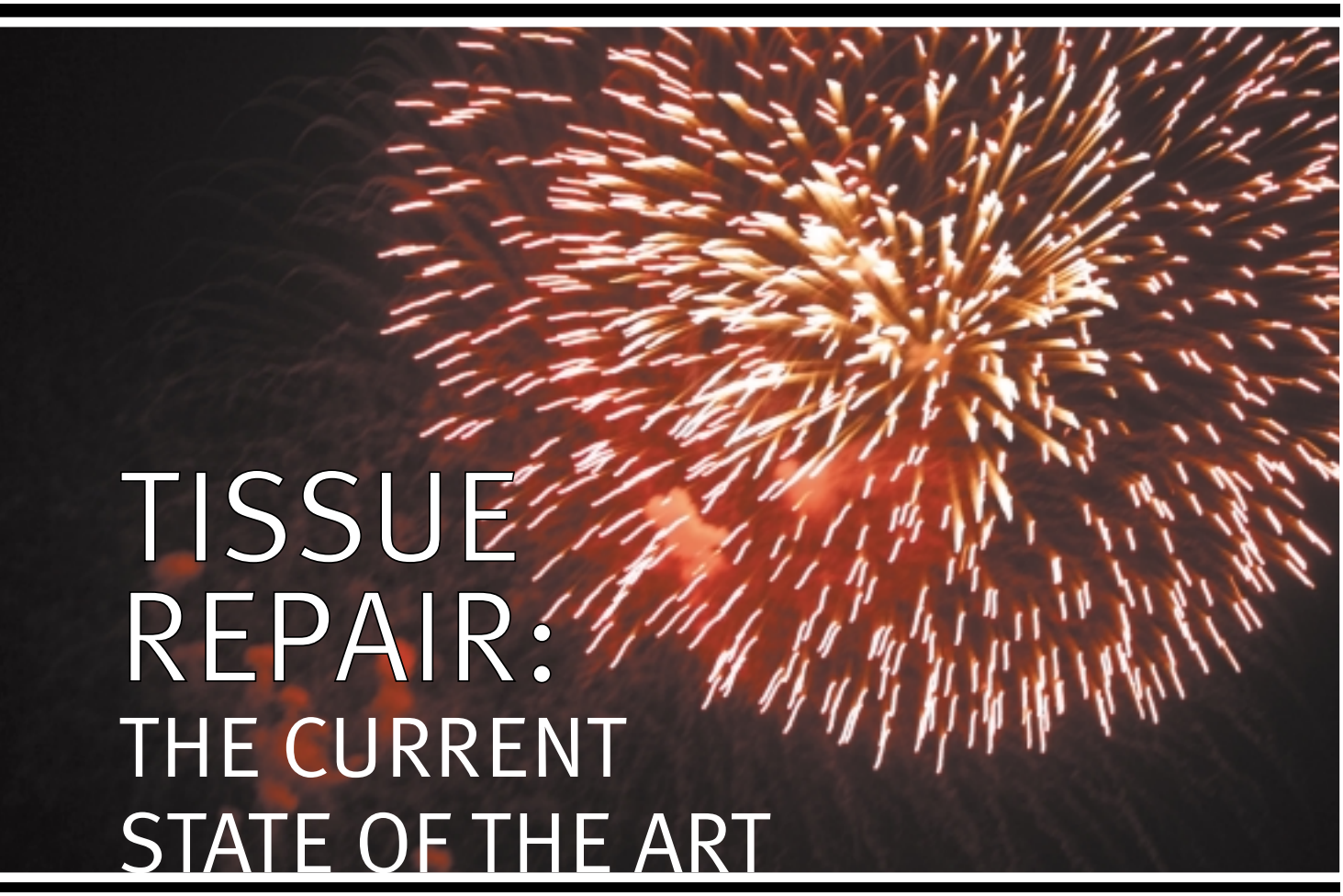

# TISSUE REPAIR: THE CURRENT STATE OF THE ART

By Professor Tim Watson, MCSP, PhD

**The aim of this paper is to summarise the salient issues in the field of soft tissue repair without claiming to provide a full review. In a subsequent paper, the capacity for different electrotherapy modalities to influence these processes will be considered. Some examples of the potential influence of manual and exercise therapies are included in this text.**

Tissue healing consists of a complex series of cellular and tissue reactions that enable the body to achieve a functional repair of tissues that have been damaged – in most cases. There are individuals for whom this process goes astray, and those that seek help for a normally presenting repair process.

Research concerning tissue repair is published at a significant rate and there are several areas of rapid development, particularly (a) the identification of numerous growth factors that influence and control the processes and (b) the role of angiogenesis as an essential component of repair. Reference will be made to recent work in both fields. More complete and in-depth reviews can be found in references 1-9.

## BASIC TISSUE REPAIR PHASES

The process of tissue repair is complex and for most individuals, following some form of injury or tissue damage, is remarkably efficient. It would also be difficult to argue that there was any need to change the process of tissue repair. If there is an efficient system through which tissue repair is initiated and controlled, why would there be any reason to change it? The more logical approach would be to facilitate or promote the normal tissue repair process, and thereby enhance the sequence of events that take the tissues from their injured to their 'normal' state. Understanding the basic responses that occur in the tissues during the sequence of events

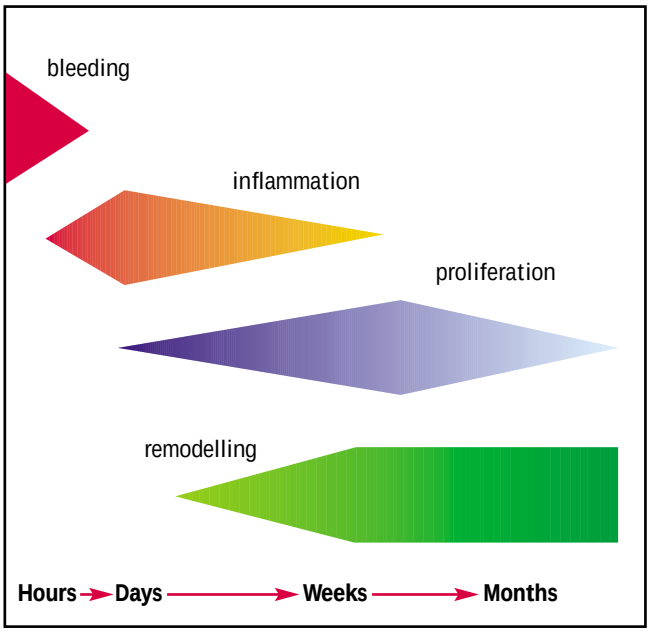


**Figure 1: The essential phases of tissue repair**

that constitutes the healing process, provides the key for effective therapy.

The division of tissue repair into phases is a way of helping to understand and deal with a complex series of events. Phasing is useful in this context, but the body effectively treats this as a series of reactions with a change in emphasis rather than a series of discrete stages or phases.

Time scales for repair cause much controversy. Any cited here will be those that relate to the average injury in the average tissue in the average patient. Some will move more swiftly and others less so, and the response of the individual should always take precedence over the supposedly 'normal' reaction

Figure 1 illustrates the overall relationship between the 'phases' of healing. They overlap, interact and are interdependent to a greater extent. The diagram time scale is not linear in that the scale shifts from hours through to months. The essential components of each phase are identified below.

## Bleeding phase

This is a relatively short lived phase, and will occur following injury, trauma or other similar insult. Clearly if there has been no overt injury, this will be of little or no importance, but following soft tissue injury, there will have been some bleeding. The normal time for bleeding to stop will vary with the nature of the injury and the nature of the tissue in question. The more vascular tissues (eg. muscle) will bleed for longer and there will be a greater escape of blood into the tissues. Less vascular tissues (eg. ligament) will bleed less (both in terms of duration and volume). It is normally cited that the interval between injury and end of bleeding is a matter of a few hours (6-8 hours is often quoted) though this of course is the average. Some tissues will continue to bleed for a significantly longer period, albeit at a significantly reduced rate. A crush type injury to a more vascular tissue – like muscle - could still be bleeding (minimally) 24 hours or more post trauma. Any intervention that has the capacity to increase local tissue blood flow during this period would be overtly inappropriate. Short duration cold treatments can be effective so long as the cold source is not left in place for sufficiently long to result in a vasodilatory response.

### KEY POINT

**Recently, an increased emphasis has been placed on the capacity of cold therapies to reduce the amount of secondary cell death due to local hypoxia, and it may transpire that this is a more important aspect of the use of cold than the vascular effects that have been emphasised hitherto (10).**

## Inflammatory phase

The inflammatory phase is an essential component of the tissue repair process and is best regarded in this way rather than as an 'inappropriate reaction' to injury. The inflammatory phase has a rapid onset (few hours) and swiftly increases in magnitude to its maximal reaction (2-3 days) before gradually resolving (over the next couple of weeks). It can result in several outcomes but in terms of tissue repair, it is normal and essential.

The complex chemically mediated amplification cascade that is responsible for both the initiation and control of the inflammatory response can be initiated by numerous events, one of which is trauma. Mechanical irritation, thermal or chemical insult, and a wide variety of immune responses are some of the alternative initiators, and for a wide range of patients experiencing an inflammatory response in the musculoskeletal tissues, these are more readily identified causes. Although the 'inflammation following injury' sequence will be addressed in this paper, other routes can be substituted as appropriate.

There are two essential elements to the inflammatory events, namely the vascular and cellular cascades. Importantly, these occur in parallel and are significantly interlinked. Figure 2 summarises the essential elements of the inflammatory cascade. The chemical mediators that make an active contribution to this process are myriad. In recent years, the identification of numerous 'growth factors' had led to several important discoveries and potential new treatment lines (11). Some of these mediators directly contribute to the pain experienced at the injury site eg. interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) released by macrophages (12). An inter-

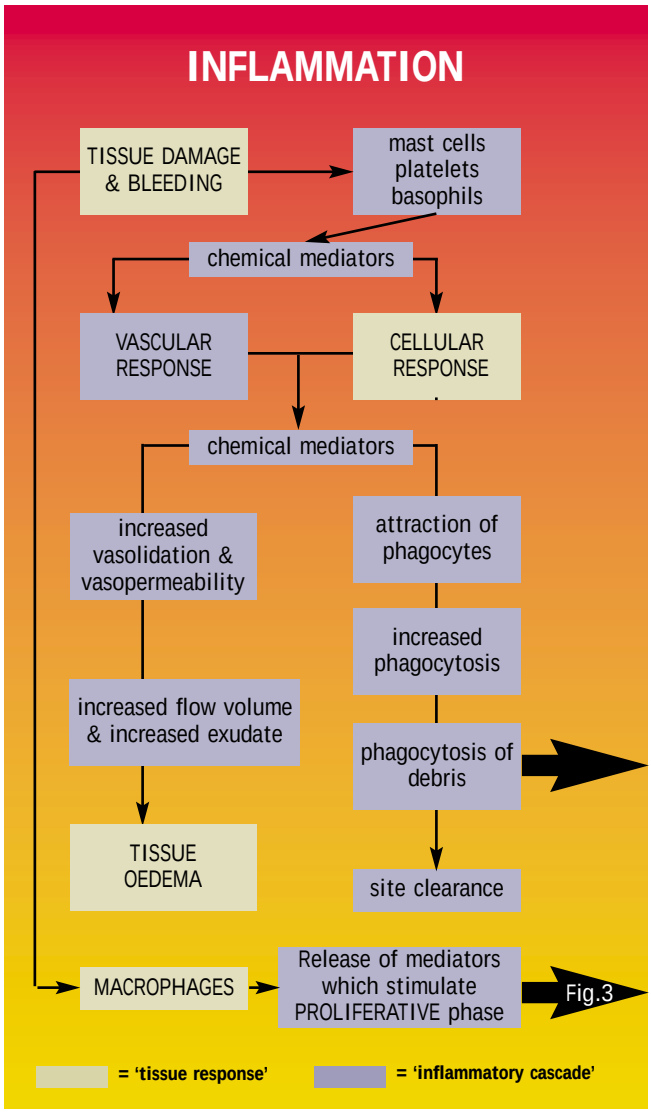


**Figure 2: The major components of the inflammatory events**

esting recent study (13) demonstrated the relationship between mechanical stretching and the production of various mediators – leukotriene B4 and prostaglandin E2 – in human tendon fibroblasts.

**Vascular events**

The vascular events involve an essential combination of a vasodilatory response with increased flow volume (although at a lower velocity) and a vasopermeability (increased leakiness) of the vessels. These processes are initiated and controlled by a wide array of cytokines and mediators released in cascades. The combined events result in an increase in local flow, production of exudates and a stabilisation of the area. As we know, the external signs of the inflammatory process are largely a result of these events (heat, redness, swelling, pain).

The flow and pressure changes in the vessels allows fluid and the smaller solutes to pass into the tissue spaces as the vessels show a marked increase in permeability to plasma proteins (14,15).

The effect of the exudate is to dilute any irritant substances in the damaged area. Due to the high fibrinogen content of the fluid, a fibrin clot can also form, providing an initial union between the surrounding intact tissues and a meshwork which can trap foreign particles and debris. The meshwork also serves as an aid to phagocytic activity (see Figure 2). Mast cells in the damaged region release hyaluronic acid and other proteoglycans which bind with the exudate fluid and create a gel which limits local fluid flow, and further traps various particles and debris (16).

**Cellular events**

The early cellular response in the damaged tissue is the attraction and stimulation of a range of phagocytic white blood cells (PMNs). There are a wide range of mediators that initiate and control these events. The role of these cells is essentially debris removal (assuming that there is no infection) - to remove the debris and enable the construction of a repair onto a sound foundation rather than build the scar on top of the debris.

Dead and dying cells, fibrin mesh and clot residue all need to be removed. As a 'bonus', one of the chemicals released as an end product of phagocytosis is lactic acid which is one of the stimulants of proliferation – the next sequence of events in the repair process.

**KEY POINT**

**There is scope for the relationship between exercise, lactate production and stimulation of proliferative events to be explored further.**

The inflammatory events therefore result in a vascular response, a cellular and fluid exudate, with resulting oedema and phagocytic activation. The complex interaction of the chemical mediators not only stimulates various components of the inflammatory phase, but also stimulates the proliferative phase that follows. The course of the inflammatory response will depend upon the number of cells destroyed, the original cause of the process and the tissue condition at the time of insult. Much as the process has been considered to be disadvantageous, it is in fact both essential and a normal component of repair. The evidence would suggest that without it, repair itself will progress less efficiently, and inhibition of the inflammatory events can lead to inhibition of the repair stages to follow (17-19).

Several recent papers have considered the role of inflammation in relation to tendon injury, tendinopathy and associated problems (20-22). The conflicting views on whether there is (or is not) an inflammatory event in this tissue are well considered in these papers.

## Proliferation phase

The proliferative phase essentially involves the generation of the repair material, which for the majority of musculoskeletal injuries, involves the production of scar (collagen) material. The proliferative phase has a rapid onset (24-48 hours) but takes considerably longer to reach its peak reactivity, which is usually between 2-3 weeks post injury (21) - the more vascular the tissue, the shorter the time taken to reach peak production. This peak in activity does not represent the time at which scar production is complete, but the time phase during which the bulk of the scar material is formed. The production of a high quality and functional scar is not achieved until later in the overall repair process. In general terms it is usually considered that proliferation runs from the first day or two post-injury through to its peak at 2-3 weeks and decreases thereafter through to a matter of several months post-trauma.

The repair process restores tissue continuity by the initial deposition of granulation tissue which matures to form scar tissue. Repair tissue is a connective tissue, distinct right from the onset in several ways from the connective tissue native to the site (23). Interesting recent developments have identified that in muscle there is a degree of regenerative activity post-trauma, linked to the activation of a mechanosensitive growth factor and subsequent activation of muscle satellite (stem) cells (5). A range of growth factors have been identified as being active in the processes of proliferation, leading again to some new potential treatments (24).

**KEY POINT**

**Blaney Davidson et al (25) have identified for example that there is a relationship between a growth factor (TGF-β) and the capacity of cartilage to repair, and that it is associated (in an animal model at least) with aging whilst Molloy et al (9) have provided a useful review of the role of various growth factors following tendon injury.**

Two fundamental processes involved in the repair are fibroplasia and angiogenesis (Figure 3). The function of the fibroblast is to repair the connective tissue (26). Fibroblasts appear to migrate to the area from surrounding tissue. Fibroblastic activation is chemically mediated, and a wide range of such mediators have been identified, including various factors released from the macrophages (eg. MDGFs) during the inflammatory stage. Fibroblasts migrate into the wounded area and proliferate within the first few days after the tissue damage. Fibroblastic production of new collagen required to effect the repair is oxygen dependent and low tissue oxygenation will limit the efficacy of the process. Fibroblasts not only produce the required collagen, but also the glycosaminoglycans and proteoglycans needed for the 'ground substance'. The bonding of the triple helix collagen molecules and their relative lubrication will influence

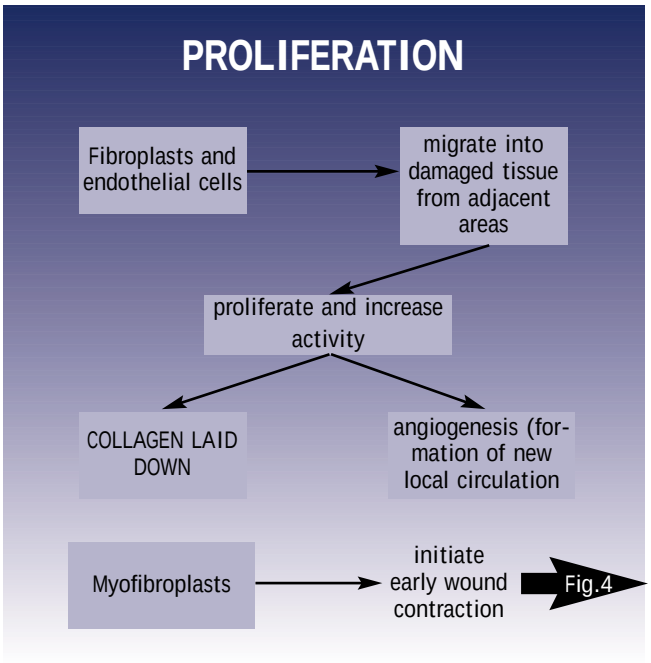


**Figure 3: The major components of the proliferative events**

## KEY POINT

**The result of various therapies on these combined effects requires further investigation, but immobilisation effectively inhibits this process while early movement will encourage quality scar material production. Immobilisation has significant effects on collagen structure and behavioural characteristics, and the effects of early immobilisation may still be influential at this stage and in relation to long term outcomes (27,28).**

the mobility and extensibility of the scar tissue.

The angiogenenic response that occurs alongside the fibroblastic activity is receiving a deal of attention at the present time (29-32). Angiogenesis (the formation of new local blood vessels in the injured area) is essential in that the production of collagen by the fibroblasts is inhibited in low oxygen environments. The angiogenesis results in increased local flow and thus an increased availability of oxygen, enabling the fibroblasts to generate their product. A wide range of mediators have been shown to exert an influence on these events, and interestingly a range of stimulants (including ultrasound, electrical stimulation and exercise) have been shown to stimulate this normal reaction (33-36).

Myofibroblasts are derived from fibroblasts activated by a variety of chemical mediators, and are responsible for wound contraction and the early strength of the repair. They draw the edges of the wound together, particularly in skin lesions, thus reducing the size of the final scar (7,16,37,38).

Scar/granulation tissue matures with lymphatic development (in much the same way as capillary development), nerve fibre ingrowth and mast cell invasion. Collagen fibres are oriented in response to local stress thus providing tensile strength in the required directions (see Figure 4). As the granulation tissue matures, there is a process of devascularisation with obliteration of the lumen of the vessels.

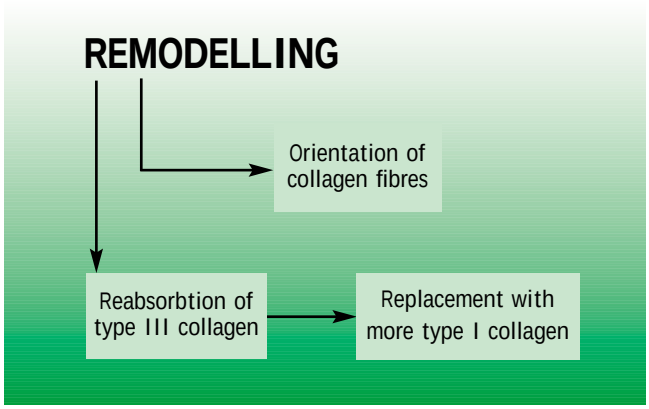


**Figure 4: The major components of the remodelling events**

### Remodelling phase

The remodelling phase is an essential component of tissue repair and is often overlooked in terms of its importance. It is neither swift nor highly reactive, but does result in an organised and functional scar which is capable of behaving in a similar way to the parent tissue (that which it is repairing). The remodelling phase has a more extensive overlap with the proliferative phase than has been previously thought, and it is now considered to start in the first week following injury – the scar is remodelled as it is constructed rather than after the event (21).

The remodelling phase primarily involves the newly deposited collagen and its associated extracellular matrix. The initial deposition of collagen produces relatively weak fibrils with random orientation. With maturity, the collagen becomes more obviously oriented in line with local stresses (39,40). A proportion of the original fine (Type III) collagen is reabsorbed (due to the action of collagenases) and is replaced with Type I collagen with more cross links and greater tensile strength (23,26). Collagen synthesis and lysis both occur at a greater rate in a normal wound compared with non-wounded tissue as old fibrous tissue is removed and new scar tissue is laid down. The maturing scar is therefore a dynamic system rather than a static one. There are several influential factors during this long phase, including physical stress (6,27,33,41). Final remodelling may continue for months, and possibly over a year beyond the obvious healing of the damage. See Hardy (16) for a comprehensive consideration of collagen behaviour in remodelling and Culav (39) for an excellent review of collagen and its roles. Frank et al (42) have provided a very useful paper with regards the optimisation of soft tissue repair.

### Cytokines, growth factors and future potential

The volume of literature published over recent years that concern the influence of a significant range of cytokines and growth factors on various aspects of the repair process is considerable. It is well beyond the scope of this paper to even begin to touch on this work, but it is expected that this field will continue to expand in the coming years, and the relationship between therapies, including exercise, manual therapy and electrotherapy and various cytokines is likely to be become more important and better understood. The possibility remains that future treatments (eg. various electrotherapies, manual therapy and exercise) will be overtly employed in order to influence these mediators and hence influence the repair process.

## SUMMARY AND CONCLUSIONS

The most likely final outcome of these combined events is that the damaged tissue will be repaired with a scar which is not a 'like for like' replacement of the original, but does provide a functional, long term 'mend' which is capable of enabling quality recovery from injury. For most patients, this is a process that will occur without the need for drugs, therapy or other intervention. It is designed to happen, and for those patients in whom problems are realised, or in whom that magnitude of the damage is sufficient, some 'help' may be required in order to facilitate the process. The help – or therapy – provided should facilitate the repair events rather than be inhibitory and although it would be difficult to argue that therapy is 'essential' it can be beneficial if applied appropriately. The body has an intricately complex and balanced mechanism through which these events are controlled and playing to the strengths of this system seems much more logical than trying to change them.

If the tissue responses in a particular patient are not progressing 'normally', then bringing them back on track will certainly help. Ensuring the right events happen even in the normally responding tissue will be beneficial. Trying to make something different happen is a difficult stance to support from the evidence.

THE AUTHOR

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*For more information about Prof Watson's work visit www.electrotherapy.org*

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