

The Healing Process at Cellular Level: A Review

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THIS paper discusses the healing of soft tissue injuries from a cellular viewpoint. It explains how the cells clear away the damage and repair the injury, and it describes the influences that can help or hinder them in their work. The fundamental work in this area was done at the turn of the century; more recent research has been funded by drug companies looking for the perfect suture material for surgery (Dunphy, 1971).

Healing cannot be accelerated. But if we know the basic mechanisms of repair, we can tell patients how to avoid delayed or poor repair. The mechanisms are different at each of the three stages, which are Injury, Inflammation and Repair.

Injury

Injury is the medical term for cellular damage. In a sprain, bruise, or crush, the local network of blood vessels is damaged. Oxygenated blood can no longer reach some tissues, so the cells die. The damaged vessels bleed. So injured soft tissue consists of dead cells, extracellular substance, and extravasated blood.

Dead cells. As the cells fail to get their metabolic needs, their vital processes run down, and they die. All cells contain cytoplasmic particles called lysosomes, which contain liquefying digestive enzymes. When a cell dies, its vital processes can no longer keep the lysosome membranes intact, and their contents are released. (These enzymes help meat that is hung to become tender.) As well as breaking down dead cells, the enzymes released have a powerful effect on nearby cells and blood capillaries.

Extracellular substance. This includes fibrous tissue (collagen), elastic fibres, and fat. Its architecture is disrupted by the injury.

Extravasated blood. Blood released from damaged blood vessels consists of cells, platelets and plasma. The cells and platelets are dead owing to lack of oxygen. The red cells break down to cellular debris and haemoglobin pigment; the platelets release thrombin. This enzyme changes fibrinogen to fibrin. The fibrin deposits out as an irregular meshwork of short fibres, and the blood cells get caught up in it, forming a clot.

The network of fibrin can also prevent bacteria from spreading freely in the tissue fluid if there is infection.

Summary

Within ten or 15 minutes of an injury the damaged soft tissue contains disrupted extracellular tissues, dead and dying cells which begin to release powerful digestive enzymes, and a variable amount of blood which may be clotted. The next stage, inflammation, is the reaction of the cells of the body to this damage. It is also the reaction of the body to infection, and some characteristics of inflammation do more to help fight infection than to aid repair.

Note that the death of cells is due to the interruption in their blood supply, and though the initial damage may cause the death of many cells, any further reduction in the blood supply will cause further death of cells. In this way it is quite possible for as much damage to be done through failure to treat an injury as was caused by the original injury.

Inflammation

The cardinal signs of inflammation are *Calor*, *Rubor*, *Dolor* and *Tumor*.

Calor and Rubor. Heat and redness do not occur straight away, they take a few hours to develop. They are caused by the opening up of thousands of tiny local blood vessels, forming an increased vascular bed. The opening up of capillaries is caused by chemicals, released by the liquefying dead cells, acting directly on the local vessel walls. The blood vessels dilate, and those that were previously closed, open up. Hence the area becomes warm and pink. Inside the capillaries, the stream slows, and after a time the white cells seem to stick to the walls. By four hours after the injury, white cells are beginning to pass through the vessel walls to the damaged area.

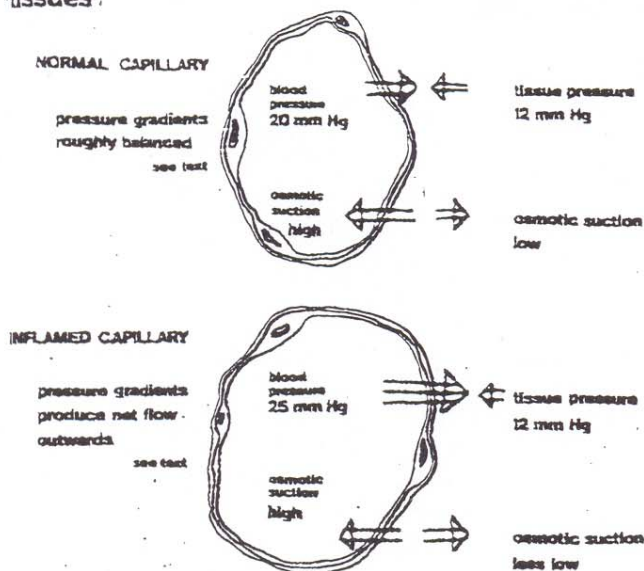
Dolor. Pain is caused by chemicals, released by damaged and dying cells, acting on the bare nerve ending of pain fibres. It can also be caused by a large rise in local tissue pressure.

Tumor. Swelling after soft tissue damage takes a few hours to develop. (If there is immediate swelling, it means that substantial bleeding has occurred.) The swelling of inflammation is mostly fluid, called the inflammatory exudate. It occurs because the chemicals released by the damaged tissues affect local capillaries and make them more permeable. The inflammatory exudate differs from normal tissue fluid in that it contains a large number of inflammatory cells and a very high concentration of protein.

The protein has of course come from the plasma proteins, so all the usual albumins and globulins will be there, including the gamma globulins, and fibrinogen. The gamma globulins are antibodies, and their outpouring in inflammation is part of the body's defence against infection. The network of fibrin formed from fibrinogen is also one of the body's vital defence mechanisms against the spread of infection. But if there is a large inflammatory exudate there is a lot of fibrin, which becomes organised into scar tissue. In serous cavities such as pleura, peritoneum, and synovial joints, the fibrin forms a shaggy coat on the inner lining of the cavity; the resulting scar tissue then contracts. In the pleural and peritoneal cavities, the scar tissue forms fibrinous adhesions. In synovial joints the end result is a thickened contracted joint capsule. So in physiotherapy and in surgery, a large inflammatory exudate must be prevented if at all possible.

Another difficulty arises from the large amount of protein in the inflammatory exudate, which raises the

Fig 1: Hydrostatic pressures between capillaries and tissues.



osmolarity (osmotic pressure) of the tissue fluid in the damaged area. Osmotic pressure is a suction force — it draws fluid towards high concentrations. Hence more fluid than usual is drawn out of the local capillary vessels into the tissues.

Fig 1 shows the normal pressure gradients for the flow of fluid at the middle of the capillary loop, when fluid-in and fluid-out are about balanced. However, when the vascular bed is increased (the *calor* and *ruber* stages of inflammation), there are many extra vessels, each of which is more open than usual. Local arterioles also become widened. Hence there are more capillaries, each more permeable than usual, and with higher pressure inside them.

The result of the increased vascular bed, at higher local blood pressure, plus raised tissue fluid osmotic pressure, is an outpouring of more and more inflammatory exudate. Swelling can go on increasing up to the fourth day.

We would very much like to try to decrease this outpouring of fluid with its load of fibrin. It can be done by changing the pressure gradient between the capillaries and the tissue fluid. The means will be discussed later.

The inflammatory exudate also contains leucocytes, which can engulf particles such as bacteria by phagocytosis (Greek *phagein* = I eat). They used to be called *n. trophages* and *macrophages*, according to size. They can function in quite low oxygen levels. Attracted by chemicals to the dead tissue, they begin the removal of the dead and disrupted tissues.

As phagocytic cells move, they put out arms (pseudopodia) like amoebae, and directly they make contact with a bacterium or a piece of debris they engulf it. They do this most effectively when the particle is trapped in the web of fibrin — another defensive reason for our enemy the fibrin. In plain fluid, phagocytosis is much less effective, and here it has been shown that agitation of the tissue fluid

increases the rate of phagocytosis by increasing the rate of chance contact. This may be the basis for the improvement attributable to ultrasound, Diapulse, or gentle deep massage, if applied soon after an injury (Dyson and Suckling, 1978; Patrick, 1978).

Summary

Set off by the enzymes released by damaged tissue and dead cells, inflammation is a change in the local network of capillaries that leads to an outpouring of inflammatory exudate, a fluid rich in antibodies and from which is laid down a network of fibrin. In the exudate come vast numbers of cells that begin to clear up the debris and dead cells. The inflammatory exudate may still be growing at the third or fourth day, especially if there is a large amount of damage, or more damage from continued use. Further death of tissue may prolong the phase of exudation still further (fig 2).

Treatment in the Inflammatory Stage

To decrease the early bleeding. Elevation will lower the pressure in the local blood vessels; cooling will have the same effect by causing local capillaries to narrow.

To decrease pain (if caused by very high tissue pressure). Elevation and gentle deep massage will help disperse the fluid through lymphatic drainage.

To decrease the inflammatory exudate. Cooling will narrow the arteriolar capillaries, and will therefore lower the blood pressure at the point of injury. External compression will raise tissue pressure moderately, but must not be so much as to squash the capillaries and provoke further ischaemia. Elevation will increase drainage of the exudate through lymph vessels. Gentle muscle contractions will promote both lymphatic and venous drainage. All these are widely advocated for the early treatment of burns, crush injuries, and sports injuries (Nicholas, 1977; Hales, 1977; Williams, 1978; Williams and Sperryn, 1979). Clinical experience indicates that chymoral forte helps in the absorption of oedema and the dispersal of bruising, though the literature on this is rather specialised (De N'Yeurt, 1972; Soule *et al.*, 1966). Decreasing the inflammatory exudate will decrease fibrin production, and chymoral possibly also helps to break up fibrin.

To help phagocytosis. Anything that produces tissue fluid agitation, such as gentle muscle movements, low intensity ultrasound, Diapulse, or gentle deep massage.

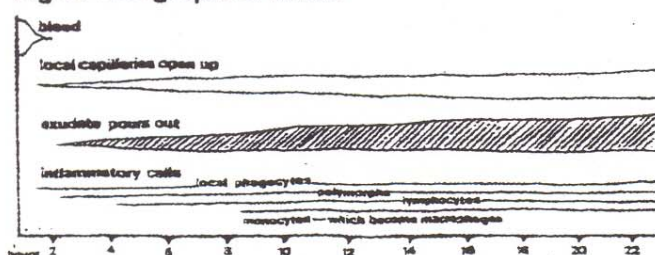
These treatments can be summed up in the classic trio: I for ice; C for compression; E for elevation. Modern experience would add an M, for gentle muscle movements. Perhaps the classic ICE should be ICEM, or even MICE!

A Note on Cortisone

The most active steroid derivative is cortisol. The action of cortisol at the cellular level is said to be to increase the resistance of the lysosome membrane of the dead cells (Boyd, 1970). It should be most effective when delivered by injection to the site of injury; its best time of action is early, in the first three or four days after injury. The increased resistance of the lysosome membrane delays the release of digestive enzymes. Thus there will be less inflammatory effect on the local blood vessels, fewer phagocytic cells, less exudate, and finally, less fibrin.

But cortisol also has a direct action on living cells, as the following quotations from Little (1973) show: 'Cortisol ... is active in reducing the mobility of fibroblast surfaces and

Fig 2: The graph of hours



inhibiting cell division. There is a noticeable decrease in proliferation of connective tissue cells. Wound healing is hindered. . . . And also: 'The permeability of . . . vessel walls to the fluids which collect during the inflammatory process is decreased.' And again: 'Dougherty and Berliner have suggested that . . . all the inflammatory actions of the corticosteroids can be explained by the stabilising of cell membranes', see Dougherty *et al* (1961).

Repair or Regeneration?

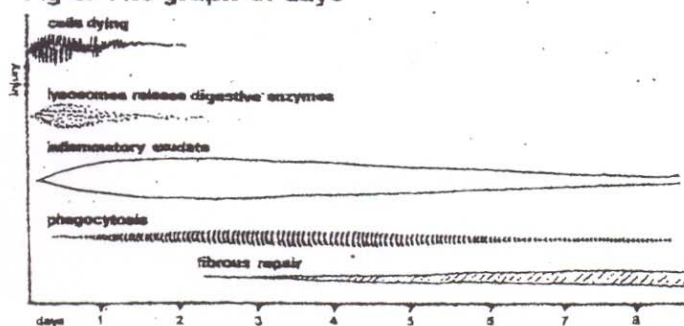
After an injury, the healed tissue is never the same as it was before. Epithelia such as skin do regenerate, but the specialised parts, the hair and the sweat glands, do not. Fibrous connective tissue such as ligament or joint capsule will be replaced, but it will not have the same structure or properties as the original. Moreover the nerve end-organs do not regenerate. Damaged muscles do not regenerate, they heal with a scar of fibrous tissue. Serous membranes like synovial joint linings, being epithelia, heal well; but if there is a lot of exudate in the joint the fibrin may eventually form a capsular thickening.

So the general method of healing of soft tissue injuries is by fibrous repair. Repeated injuries to a joint capsule will not only mean it will be thickened and contracted, but also cause extensive loss of the proprioceptive nerve endings.

Healing and Repair

The processes of inflammation may continue for five days or more, though in a small injury they may be finished in three days. The next stage is called Repair, and it is signalled by the presence of a new set of phenomena. These may be seen around the third day, while the inflammatory reaction is still continuing (fig 3).

Fig 3: The graph of days



At the beginning of the repair phase the injured area contains a loose mesh of fibrin, plus the debris of dead cells from the injured tissue and some extravasated blood, all being phagocytosed by macrophages and polymorphs. The stage of repair has begun when nearby cells, previously dormant, begin actively to divide. The initiating factor is not known, though it must be a chemical. But the factors that delay healing are well known, and must never be forgotten.

Factors Retarding Healing

General Causes

Old age, low serum protein (starvation), lack of Vitamin C (scurvy).

Local Causes

1. *Ischaemia*. Apart from poor local blood supply, ischaemia can be caused by very high tissue pressure, absolute immobilisation, or dense scar tissue.
2. *Irritation*. A technical term meaning anything that provokes the continuation of the inflammatory reaction. Examples are infection and haematoma.

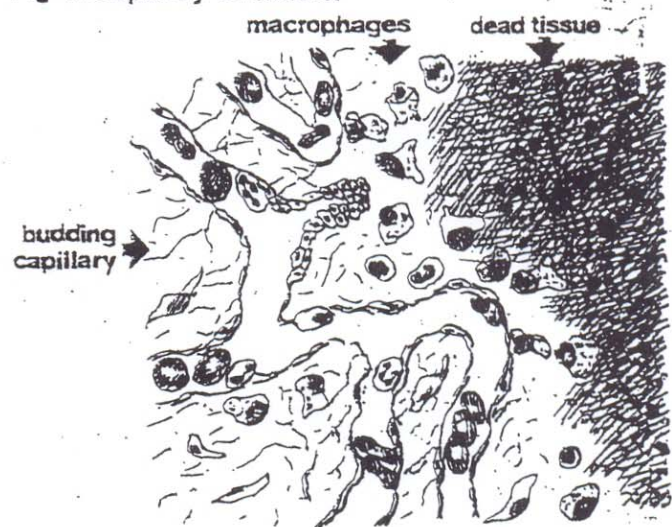
Factors Improving Healing

Ultra-violet light is said to improve the healing of skin and is used for this in many centres, especially for pressure sores. Ultrasound is said to improve fibroblastic repair (Dyson and Suckling, 1978).

Granulation tissue. In the middle of the injured area, one can imagine a twilight world like a deserted, bombed-out town, with the structural remains of the soft tissue in a sea of debris. Nothing moves here, because there is not enough oxygen to support life. On the periphery the macrophages and the polymorphs are working because they can tolerate low oxygen tension. But the cells that carry out the process of repair need plenty of oxygen and good nutrition. This requirement is fulfilled by new capillaries that grow towards the clot of debris, 'invading' it.

This process starts about 12 hours after the injury, when mitoses are seen in the cells of surrounding capillaries. Over the next three days cell division continues, forming solid capillary buds which grow towards the place where the concentration of oxygen is low. They then canalise, and form loops, and blood begins to flow round the loops, which approach the injured area (fig 4).

Fig 4: Capillary formation



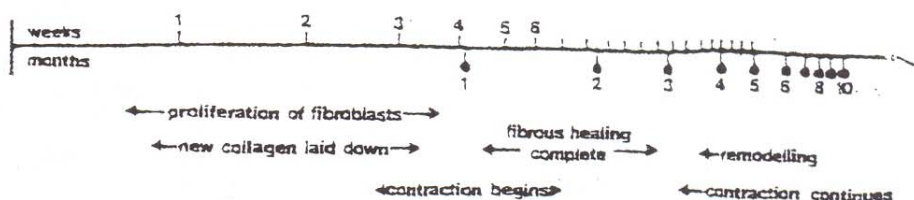
Thus all round the injury there develops a wall of capillary loops filled with blood. This begins at two days, and becomes easily visible (in a surface wound) three or four days after the injury. The new capillary tissue, or granulation tissue, looks granular and is red with blood; it bleeds easily when touched. Its vessels have highly permeable walls from which pour out plasma proteins, cells and fluid. Oxygen also diffuses from the red cells to the surrounding tissues. As these essentials of life appear around the injury, so the cells of phagocytosis and repair can extend their work where previously no cell could live.

Fibroblasts

At about the same time as the cells of the capillary walls begin to grow (about 12 to 24 hours), there is a similar change in nearby fibrocytes. These cells, normally thin and dormant, begin to fatten up and move towards the injury. Soon they start to multiply, and by the fifth day they begin to lay down fibrils of collagen in the ground substance. This process cannot happen if there is a serious deficiency of Vitamin C. The fibroblasts produce more and more fibrils, which lie parallel to each cell. The fibrils gradually polymerise to become bundles of collagen. This collagen is the fibrous tissue of the repair phase and of the healed injury.

Collagen has the property of gradually shortening when

Fig 5: Collagen timescale



week to the sixth month. New scar tissue will always shorten unless it is repeatedly stretched (see fig 5).

Factors that Affect Fibrous Tissue Healing

If the tissue being healed is kept absolutely immobile, the resultant fibrous repair is weak. When there are no natural forces on the healing tissue collagen is laid down haphazardly. It may be plentiful, but it is poorly engineered. Fibrous healing is stronger if natural movements are encouraged — it seems that the fibroblasts need to know which way to lay their collagen fibres. Gentle normal movements provide natural tensions in the healing tissue, and the resulting fibrous healing is much stronger (Mason and Allan, 1941; Stearns, 1940).

Fibrous healing will be poor if there is continued inflammation — from infection, from buried suture materials, or from a haematoma. Healing also requires a good blood supply, both to support the phagocytes and to supply oxygen and nutrients to the worker cells.

The Scientific Basis of Managing Healing Tissue

No injury can be made to heal faster than its natural speed. The tools of healing — thousands of cells getting on with their jobs — cannot be improved. All that can be done is to make sure that no contrary influences are allowed, and that all possible favourable conditions are encouraged (fig 6).

Repair is hindered by low serum protein, significantly low plasma vitamin C, and poor blood supply. The first two are not usually a problem, but anyone concerned with soft tissue injuries can advise four steps to avoid delaying the repair process through ischaemia. The injured part should be elevated to avoid high tissue pressure; gentle movement should be encouraged for venous drainage; drainage of a haematoma will avoid continued irritation; and prevention or rapid reduction of the inflammatory exudate will avoid dense scar tissue.

To encourage good quality repair, gentle natural motion should be transmitted to the new collagen bundles as they are laid down, to ensure correct architectural line-up. These movements are usually appropriate from the fifth day, and should be progressively graded until final healing. Remodelling of new collagen continues for six months or so.

If the injury is in a place where the contraction of new collagen would be a disadvantage, the repaired tissue must often be extended to maximum length. This means a full warm-up and full stretch of healed torn muscles, for up

to a year — some say for the rest of the patient's life. The same applies to healed strains and tears of synovial joint capsules, which should frequently be passively stretched to the end of range of the joint (Williams and Sperry, 1979).

Conclusion

With a good knowledge of the cellular mechanisms of inflammation and repair, the remedial professions can be sure of the basis of the advice and treatment they offer to patients who have soft tissue injuries. Moreover this knowledge should be used to eliminate treatments that do not help the cells of inflammation and repair. All treatments and advice should be judged on how they help these fundamental processes of healing.

ACKNOWLEDGMENTS

Many thanks to the following physiotherapists who helped with criticisms of this paper: Fiona Anderson, Beryl Gravelling, Sandra Mitchell, and Jenny Thompson, all of Norwich; and Jennifer Sils from the Queen Elizabeth School, Birmingham.

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Fig 6: The graph of months

