PAPERS

Wound healing

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SUMMARY

The majority of wounds encountered in the accident and emergency department are superficial in nature and a consequence of accidental trauma or the elective surgical incision of infected foci. The techniques of management of such cases have undergone few changes in recent years, and any advances of a practical or therapeutic nature have been comparatively modest. On the other hand, many major advances have occurred in our understanding of the factors involved in the basic pathophysiology of wound repair. This paper is a summary of our present concept of the process of repair in soft tissues.

Connective tissue formation

All wounds of soft tissues, whether they be incised, sutured incisions or gaping, excised defects, heal by the formation of connective tissue and a fibrous scar. Connective tissue is composed of collagen fibrils, elastin, and an amorphous extracellular matrix known as the ground substance, and it is helpful to our understanding of wound repair if we consider the normal mechanisms of connective tissue formation.

Collagen

The fibroblast cell is responsible for the synthesis of collagen (Ross & Benditt, 1965; Bornstein & Ehrlich, 1973) and the molecule is synthesized from three peptide chains which are bonded together in a triple-helical configuration. The peptide chains, known as alpha chains, differ in their amino acid constituents and four different types of collagen have been identified based on the composition of these chains. The alpha chains are rich in the amino acids proline and lysine, and these are converted to hydroxyproline and hydroxylysine during collagen synthesis (Goldberg & Green, 1969). This process requires the presence of ferrous iron, a reducing substance such as ascorbic acid, alpha ketoglutarate, and oxygen. Absence or deficiency of any one factor

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prevents collagen synthesis in vitro, and it has been suggested that this vital step in collagen synthesis accounts for the adverse effects of ascorbic acid deficiency and tissue hypoxia on wound healing in man.

New collagen is extruded from the fibroblast cell and deposited as extracellular fibrils. These fibrils mature rapidly by forming cross-links with adjacent collagen molecules, and this more mature form of collagen provides mechanical strength to the wounded tissue. The cross-links are attributable to the presence of aldehyde-containing amino acids formed by the oxidative deamination of lysyl and hydroxylysyl residues in the collagen molecule, a reaction which is known as aldol condensation, and the product of the reaction is known as a Schiff base (Tanzer, 1973). Certain substances such as penicillamine and beta-amino-propionitrile (contained in the sweet pea, Lathyrus odoratus) can interfere with collagen maturation by blocking the formation of Schiff bases.

Radioisotope studies have demonstrated that there is a constant turnover of tissue collagen, and the rate of collagen synthesis varies in different tissues. Collagen is broken down by enzymes known as collagenases found in various tissues including the epithelial cells and dermal layer of the skin, synovial fluid, the mucosal cells of the colon, and in polymorphonuclear leucocytes and tissue macrophages (Grillo & Gross, 1964; Lazarus et al., 1968; Hawley, 1969; Leibovitch & Weiss, 1971; Wahl et al., 1975; Bauer et al., 1975). Collagenolytic activity is increased after wounding, and it is greatly exaggerated in the presence of wound sepsis (Hawley, 1969).

The normal pattern of collagen measurements in an incised sutured wound is shown in Fig. 1. A real reduction in the collagen content of the wound edges may occur during the first few days of healing due to collagenolysis. This is followed by a sharp increase in wound collagen as synthesis is established during the second week of repair. The collagen content of the wound may fall again during the later stages of healing but this is not associated with weakening of the wound repair. Indeed, the mechanical strength of the wound becomes progressively greater due to maturation and remodelling of the wound collagen (Fig. 2). This process of remodelling probably continues indefinitely, and the rate of collagen synthesis and lysis remains greater than that of unwounded tissue (Riley & Peacock, 1967; Madden & Peacock, 1968).

![Fig. 1](http://emj.bmj.com/) Measurements of collagen in healing wounds. The early reduction in wound collagen is due to collagenolysis in the wound edges; and the late reduction is due to remodelling of mature collagen fibrils. (From Irwin (1981) Wound Healing, Principles and Practice, with kind permission of the publisher, Chapman and Hall.)
Fig. 2 Measurements of the mechanical strength of the sutured surgical wound. Note the correlation between these changes and the measurements of wound collagen (Fig. 1). (From Irwin (1981) Wound Healing, Principles and Practice, with kind permission of the publisher, Chapman and Hall.)

**Ground substance**

The ground substance contains water, electrolytes, glycoproteins, and a specific class of compounds known as proteoglycans. All connective tissues contain varying amounts of ground substance between the cells and collagen fibres but the functions of this material and its method of formation remain rather obscure.

The proteoglycans are large protein-polysaccharide complexes, and they are heterogeneous substances: the chains of polysaccharides may have more than one type of disaccharide unit; the protein core may be heterogeneous; there may be more than one type of polysaccharide attached to the protein; and seven different types of polysaccharide have been identified in proteoglycan molecules (Table 1). Proteoglycans are synthesized by fibroblasts (Curran & Kennedy, 1955; Berenson et al., 1959), and it appears that the molecules are involved in the extracellular formation of collagen fibrils and in collagen maturation, although the precise mechanisms are obscure (Hightberger et al., 1951; Watts et al., 1964; Jackson, 1970).

The polymorphic glycoprotein, fibronectin, is a major component of the ground substance, and it appears to have an important role in cell-to-cell and cell-matrix adhesion in tissues. These processes probably involve a complex interaction between fibronectin and the proteoglycans of ground substance (Culp et al., 1979). Fibronectin is synthesized by fibroblasts and it exists as a relatively immobile network along with

**Table 1** Acid mucopolysaccharide fractions of proteoglycan molecules present in the ground substance of connective tissue

<table>
<thead>
<tr>
<th>Chondroitin</th>
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<tr>
<td>Chondroitin-4-sulphate</td>
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<tr>
<td>Chondroitin-6-sulphate</td>
</tr>
<tr>
<td>Dermatan sulphate</td>
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<td>Heparan sulphate</td>
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<td>Keratan sulphate</td>
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<td>Hyaluronic acid</td>
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collagen on the surface of fibroblasts and other connective tissue cells (Bornstein & Ash, 1977). The glycoprotein has two binding sites, one for collagen, and another for cell surfaces (Ruoslahtie & Hayman, 1979), and there is evidence that it influences the migration and orientation of fibroblast cells (Hughes et al., 1980).

**Pathogenesis of connective tissue repair**

There are three phases of wound repair demonstrable by microscopy, and these are summarized in Table 2.

**First phase**

The first phase is a vascular response to wounding; vasoconstriction is followed by vasodilation and slowing of the tissue blood flow; gaps develop between the endothelial cells constituting the walls of capillaries; and plasma, white cells and, to a lesser extent, red blood cells migrate into the fibrin coagulum which unites the wound edges. It appears that several chemical mediators are responsible for this response. The early phase of vasodilation may be caused by the release of histamine from platelets and tissue mast cells (DiRosa et al., 1971a) but other mediators including serotonin, bradykinin, kallidin and prostaglandins are involved in the later stages and in the increased vascular permeability which is evident in this phase (DiRosa et al., 1971b; Vane, 1972).

The cellular infiltrate in the early phase of wound repair has been documented in electron microscopic studies by Ross & Odland (1968). Most cells appearing during the first 48 hours after wounding are polymorphonuclear leucocytes but many of these cells undergo lysis and, contrary to the traditional concept, very few are actively engaged in phagocytosis. A few monocytic cells are present within 24 hours, and their numbers increase during the next few days until they are the dominant cells in the wound by the fifth day. These mononuclear macrophages are actively engaged in phagocytosis.

There is evidence that several humoral and chemical mediators have chemotactic effects resulting in the emigration of leucocytes into wounds. The serum complement

<table>
<thead>
<tr>
<th><strong>First phase (days 1–3 approx.)</strong></th>
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<tbody>
<tr>
<td>Vascular dilatation</td>
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<tr>
<td>Slowing of capillary blood flow</td>
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<tr>
<td>Emigration of neutrophil polymorphs into wound space</td>
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<tr>
<th><strong>Second phase (days 4–12 approx.)</strong></th>
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<tr>
<td>Reduced numbers of polymorphs</td>
</tr>
<tr>
<td>Increasing numbers of macrophages</td>
</tr>
<tr>
<td>Presence of fibroblasts, endothelial buds and collagen fibrils</td>
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<tr>
<th><strong>Third phase (after second week)</strong></th>
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<tr>
<td>Progressive loss of cells and blood vessels from wound</td>
</tr>
<tr>
<td>Collagen becomes increasingly dense</td>
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<tr>
<td>Final result is an avascular and relatively acellular scar</td>
</tr>
</tbody>
</table>

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**Table 2** The three phases of wound repair demonstrable on microscopy of an incised sutured wound
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system provides protein substrates for the enzymatic generation of at least three different chemotactic factors for neutrophils (Snyderman et al., 1971; Muller-Eberhard et al., 1972; Ward, 1972); several bacterial factors have chemotactic properties; and it has been suggested that kallikrein and prostaglandins are important mediators of leucocyte emigration (DiRosa et al., 1971b; Turner et al., 1973).

Second phase

The second phase of repair is established by the fourth or fifth day, and increasing numbers of fibroblasts become apparent within the wound. These cells are closely followed by the endothelial buds of new capillaries and, when this phase is fully established, the wound is filled with vascular granulation tissue comprising capillaries, fibroblasts, macrophages and mast cells. Collagen fibrils are also in evidence within the wound space, and the increasing collagen content of the wound is accompanied by a sharp increase in wound strength (Figs 1 and 2).

Several recent studies have helped to determine the functions of the cells which are involved in the first and second phases of wound repair. The intracellular contents of neutrophil polymorphs (including collagenase, prostaglandins of the E series, and various proteolytic enzymes) are important in the first phase of repair (Ross & Odland, 1968) but these cells are not essential for wound healing, and studies of neutropenic animals have shown that the proliferative phase of wound repair proceeds normally in the absence of these cells (Ross, 1972). However, blood platelets released into the wound space have a key role in initiating the process of repair, probably as a consequence of a factor or factors released from these cells (Ross et al., 1974; Rutherford & Ross, 1976; Ross, 1980). Mononuclear macrophages also have an important role in initiating wound repair: studies in animals given anti-macrophage serum have shown that inhibition of these cells is followed by delayed wound repair (Leibovich & Ross, 1975). There is also evidence that macrophages determine the rate of ingrowth of new vascular endothelium due to the presence of an ‘angiogenesis factor’ which stimulates the migration and proliferation of endothelial cells (Polverini et al., 1977).

The physical environment of the wound may also determine the success of the repair process. The wound space is a rather acidic and hypoxic environment during the early phase of repair (Silver, 1980), and it has been suggested that this may act as a stimulus to the repair process (Henkind, 1973; Schaper, 1979). However, adequate oxygenation of the wound is essential during the second phase of repair; several elegant studies have shown that the process of repair is highly susceptible to hypovolaemia and other disorders which cause increasing wound hypoxia (Lundgren & Zederfeldt, 1969; Niinikoski et al., 1972).

Third phase

There is a gradual transition between the second and third phases of wound repair: the numbers of fibroblasts and macrophages decrease; the wound becomes less vascular; and extensive remodelling of the wound collagen is accompanied by a fall in the collagen content of the wound (Fig. 1). This process of involution is of variable duration and
generally takes longer in excised wounds containing larger amounts of granulation tissue. The factors which determine these changes are largely unknown but the wound scar remains a relatively weak and inelastic structure although remodelling of the collagen may continue indefinitely (Madden & Peacock, 1968; Harrison et al., 1975).

Wound contraction

Excised wounds or wounds accompanied by loss of tissue heal by a combined process of contraction and epithelial migration, and recent studies have shown that wound contraction is caused by specialized contractile cells within the granulation tissue. These cells are called myofibroblasts; their appearance is similar to that of smooth muscle cells, they synthesize actomyosin, and immunofluorescent studies have shown that they stain with human anti-smooth muscle sera (Majno et al., 1971; Gabbiani et al., 1973). However, it appears that they are derived from fibroblasts rather than smooth muscle cells (Gabbiani et al., 1973), and they are not confined to wounds. Myofibroblasts have also been demonstrated in various diseases associated with tissue fibrosis, including the carpal tunnel syndrome, Dupuytren's contracture, hepatic cirrhosis, sarcoidosis of the lung, and certain types of sarcoma (Bhathal, 1972; Madden, 1973; Judd et al., 1975; Madden et al., 1975; Chung & Kahn, 1977).

CONCLUSION

The fact that most wounds in clinical practice tend to heal in a simple, uncomplicated fashion belies the complexity of the underlying basic process of wound repair. It is a process which involves a complex interrelationship between multiple chemical, humoral, physical and cellular factors, and it is perhaps surprising that complications of wound repair are not encountered more often. Recent studies have provided a logical and scientific explanation for the adverse effects of certain clinical variables on wound healing; thus, we now understand why hypoxia and hypovolaemia have deleterious effects, why ascorbic acid deficiency may affect wound healing and why infection is such a serious complication in wounds. Wound healing has become a major subject of scientific study and, as our knowledge increases, we may look forward to benefits of a more practical nature in the management of healing wounds.

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