How much wound science do you need to know?

Knowledge of wound healing cell biology is increasingly used to develop new wound management products and support their marketing. Understanding of the science supporting these products is required by practitioners to critically evaluate product claims and make rational decisions in selecting appropriate dressings for chronic wounds. Acquisition of an appropriate level of scientific knowledge can be challenging for the non-scientist. This article explores what that level might be and how it can be provided for practitioners in the wound care community.

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KEY WORDS
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Wound pathophysiology

This article was inspired during a late night conversation with three tissue viability nurses in a bar at a wound healing conference. Following on from a number of satellite symposia organised earlier in the day by wound healing manufacturers, the nurses, all with specialist knowledge in wound healing, unanimously supported the comment by one of them that 'the companies are trying to blind us with science'. This suggested that the nurses were not equipped with the knowledge to deal with the onslaught of scientific information that increasingly seems to be used to support wound management product marketing. It seems worthwhile therefore to attempt to identify how much scientific knowledge is needed when interpreting product marketing claims and to identify where relevant information may be sourced.

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Knowledge of cellular events during normal healing and the functional changes associated with wound chronicity has been growing over recent decades. This has been utilised by wound management manufacturers to develop new products that modulate events within the wound environment with the intention of stimulating healing. Among these may be included wound dressings with potential bioactivity (Cullen et al, 2002; Colletta et al, 2003), tissue engineered dermal replacements (Falanga, 2000), recombinant growth factors (Robson et al, 2000), protease inhibitors (Fray et al, 2003) and anti-bacterial dressings (Landsdown, 2005).

A greater diversity of available products brings with it the challenge of choosing the most appropriate management strategy for an individual wound. The manufacturers are increasingly using scientific data and claims to market their products and this is reflected in the increasing technical complexity of publications describing the use of these products in nursing journals. Increasingly this requires an understanding of the claimed mode of action combined with a knowledge of wound pathophysiology to critically appraise the value of a particular product.

Practitioners generally are not trained biochemists, cell or molecular biologists yet they need sufficient knowledge to make the best decision for the patient. To highlight some of the issues involved this article will present a brief overview of the differences between healing and chronic wounds. Then using protease inhibition as an example it will explore what knowledge would be required to understand how this product class may be utilised and where the knowledge required can be obtained.

Normal healing

The objective of this article is not to provide a comprehensive review of the healing process and the known defects within the chronic wound. Such an exercise will require a series of articles to be meaningful. This section is provided to identify the opportunities for bioactive wound therapies to exert an effect on chronic wounds.

For the purpose of discussion the sequence of cell activities leading to wound closure may be divided into the four phases of haemostasis, inflammation, granulation tissue formation and re-epithelialisation (*Figure 1*). These are followed by scar formation and remodelling of the healed dermis to restore strength to the wound. The phases are not functionally distinct in time as they overlap and events within each phase initiate and regulate those occurring in later phases. Healing is considered to be regulated by growth factors and cytokines that act as intercellular messengers. These are produced at

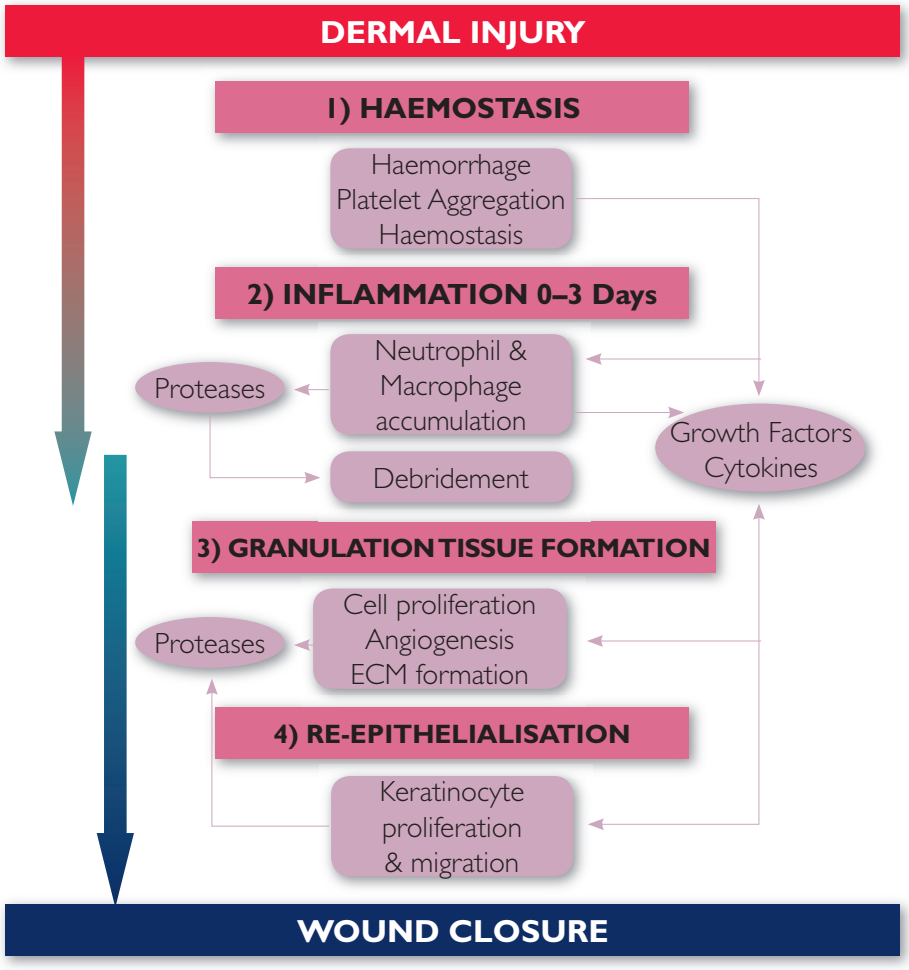

Figure 1. Normal wound healing.

the wound site and differing profiles of factors are produced by cells at each phase of healing. For a full discussion of the cell biology of normal healing see Cherry et al (2000).

The chronic wound

Cells within chronic wound tissue do not follow the normal healing trajectory and appear to be arrested in a non-resolving inflammatory state with high numbers of neutrophils and macrophages present. Although keratinocytes proliferate at the chronic wound margin, granulation tissue does not produce an intact extracellular matrix (ECM) which is required for re-epithelialisation to proceed.

Cells within chronic wound tissue do not follow the normal healing trajectory and appear to be arrested in a non-resolving inflammatory state with high numbers of neutrophils and macrophages present. In normal wounds keratinocytes at the wound margin proliferate and respond to signals provided by ECM synthesised by fibroblasts in granulation tissue. This allows them to migrate over the wound surface and successfully re-epithelialise the wound. Keratinocytes do proliferate at the margin of the non-healing chronic wound but fail to migrate over the wound bed. This is a consequence of a defective ECM that fails to provide appropriate cues to initiate keratinocyte migration and re-epithelialisation.

Inflammation

Chronic wounds are characterised by the presence of high numbers of neutrophils and macrophages that produce large amounts of inflammatory mediators and proteolytic enzymes. The mediators activate endothelial cells in capillary walls to stimulate exudate production and allow more inflammatory cells to enter the wound bed, while uncontrolled excess proteases cause tissue degradation and prevent the formation of functional ECM. The majority of chronic wounds are colonised with aerobic and anaerobic bacteria (Bowler, 2002) that can also produce more proteases and act as a continuing stimulus to activate neutrophils and macrophages to prolong the chronic inflammation seen in this wound type.

Granulation tissue formation

Multiple defects are found in chronic wound granulation tissue (*Table 1*). Growth factor profiles are modified by comparison to healing wounds (Cowin et al, 2001). Blood vessels are surrounded by fibrin cuffs that prevent oxygen diffusion into the wound tissue, trap circulating leucocytes and intensify the inflammatory response. As wound duration increases so the number of senescent fibroblasts increases. These cells produce more proteases than their non-senescent counterparts to add to those produced by macrophages and neutrophils thus contributing to the degradation of ECM and preventing the migration of keratinocytes over the wound bed.

Re-epithelialisation

There is no shortage of keratinocytes in the chronic wound as they proliferate at the wound margin but do not migrate over the granulation tissue (Andriessen et al, 1995). This is a consequence of the degraded ECM being unable to give the appropriate signals to initiate keratinocyte migration. When an appropriate ECM is provided, re-epithelialisation is achieved (Herrick et al, 1992).

Therapeutic targets in the chronic wound

Based on our knowledge of the differences between healing and non-healing chronic wounds, features of the chronic wound can be identified (*Figure 2*) and go some way to explaining why it will not heal. The hard-to-heal chronic wound may be defined by the following characteristics:

- Bacterial critical colonisation
- Chronic inflammation
- High protease levels
- Low protease inhibitor levels

Table 1
Therapeutic targets in the chronic wound

Defects that are therapeutic targets	Possible treatment	Comment
Bacterial critical colonisation	Topical antiseptics (White et al, 2001)	How to define critical colonisation?
High protease levels	Protease inhibitor	Which one?
Degraded ECM	Supply temporary ECM	
Senescent fibroblasts	Supply non-senescent fibroblasts	From tissue engineered dermal replacement
Disordered/degraded growth factors	Supply growth factors	Which one or combinations?

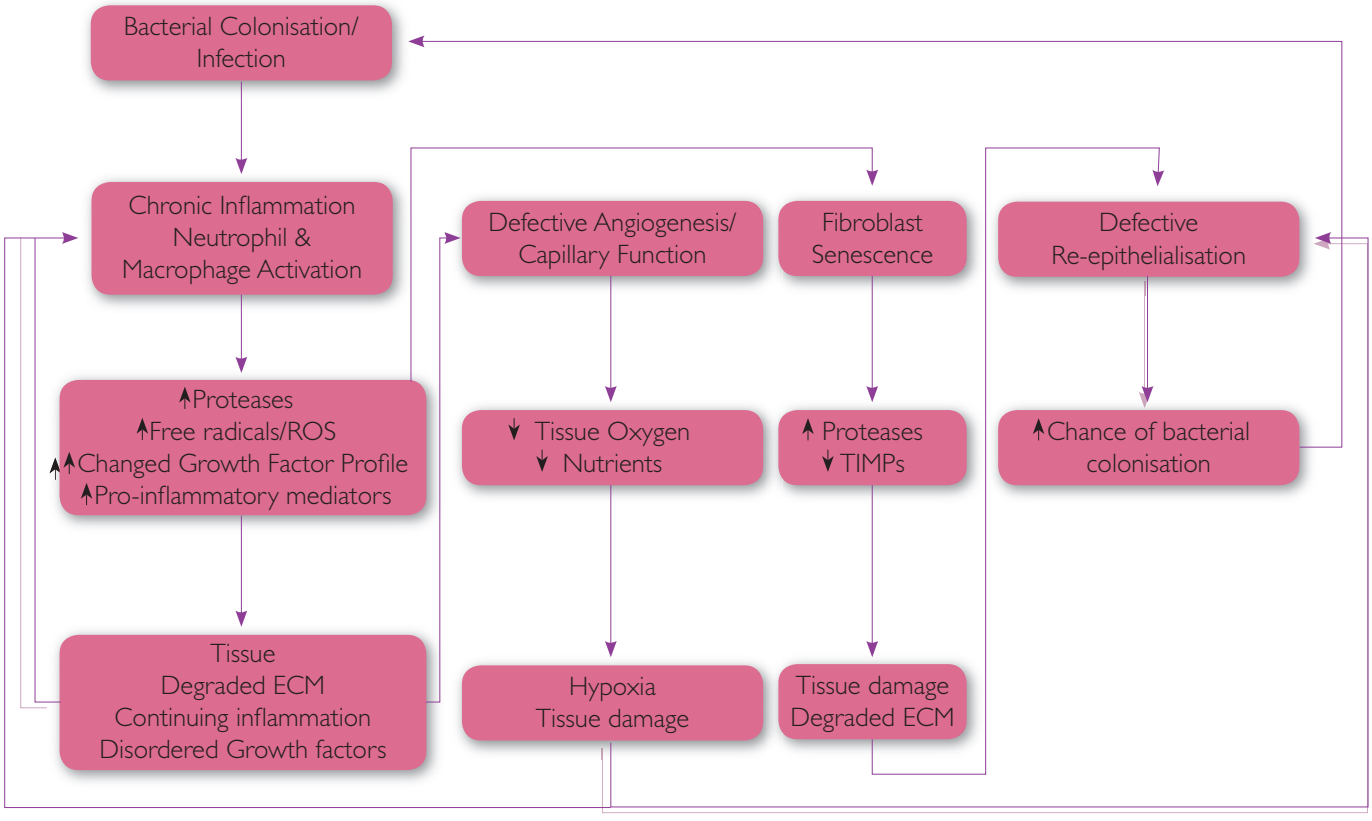

Figure 2. Features of the chronic wound contributing to non-healing.

- Degraded ECM
- Senescent fibroblasts
- Disordered/degraded growth factors.

Reversal of some of these features may break into the self-reinforcing loop whereby chronic inflammation leads to tissue damage that stimulates more inflammation. Taking this knowledge-based approach leads to a number of possible therapeutic approaches (*Table 1*). Such a therapeutic diversity raises the challenge of selecting a product that is most appropriate for a wound at a particular time point. This choice may of course change over time depending on the exact status of the wound. Ideally the choice could be aided by use of an appropriate diagnostic test that might indicate the most appropriate therapy. Currently such a test does not exist although tools are being developed (Margolis et al, 2004) to identify hard-to-heal wounds that may require adjunctive treatments. In the absence of a diagnostic test, informed choice of an appropriate treatment strategy currently requires a knowledge of the relationship between the cellular causes of clinical observations combined with a knowledge of the mode of action of wound management products (Harker and Moore, 2004). This relationship can be demonstrated by consideration of the role of proteases in chronic wounds and the rationale underlying development of a protease-inhibiting wound dressing.

Management of wound protease levels

Proteins are essentially chains of amino acids linked together by peptide bonds. Proteases digest proteins by breaking the peptide bonds so that increasingly smaller chains are produced and eventually they could be reduced to single amino acids. Proteases are produced by the majority of wound

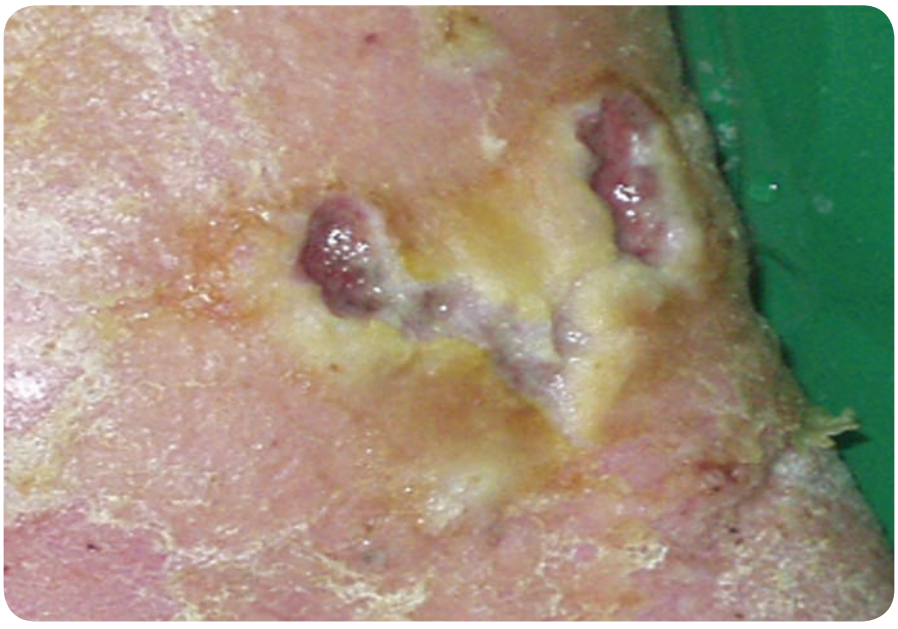

Figure 3. Venous leg ulcer demonstrating peri-ulcer skin damage caused by exposure to wound exudate containing proteases. Photograph kindly provided by Mr Keith Cutting, Buckinghamshire Chilterns University College, UK.

cells and are required for normal healing where their activity is tightly regulated. However, in chronic wounds protease levels can be 30 times higher than in healing acute wounds (Trengove et al, 1999). Such levels are generally considered detrimental to the healing process and their ability to cause tissue degradation can be seen in peri-wound skin (*Figure 3*) where excessive exudation can allow prolonged exposure to wound proteases leading to excoriation and epidermal stripping (Fletcher, 2002).

It is well documented that ECM components such as fibronectin and vitronectin are present as proteolytically degraded fragments in chronic wound fluid whereas the intact molecules are present in wound fluid taken from healing acute wounds (Grinnell et al, 1992). The observation that protease levels are lower in areas of chronic wounds that are improving (Tarlton et al, 1999) suggests that it would be beneficial to decrease the levels of proteases in chronic wounds.

The data quoted here represent the tip of an iceberg of knowledge of the role of proteases in wound physiology generated over many years. Their functions can be summarized very simply:

- Proteases digest proteins
- They are essential for normal healing
- They are present at a higher level in chronic wounds
- They are associated with growth factor and tissue degradation in chronic wounds.

Logic suggests that inhibiting protease activity in chronic wound healing may restore a tissue synthesis/degradation balance to that found in normal wounds where they are involved in autolytic debridement, cell migration and ECM remodelling. However, one does not want to achieve total inhibition as these normal processes may be affected.

Wound management products that target excess protease activity

Three possible approaches are available to decrease overall wound protease activity:

Direct inhibition/absorption by wound contact dressings

A dressing composed of a mixture of freeze dried cellulose and oxidised regenerated cellulose (Cullen et al, 2002) is currently widely advertised and claims to 'speed healing by rebalancing protease levels and protecting growth factors' (Advertisement, 2005). This product has been the subject of a major marketing campaign and advertisements are extensively supported by published references and information on the manufacturer's website (Johnson & Johnson, 2005). Data on the proposed mode of action are presented along with articles describing clinical evidence and review articles on chronic wound pathology and management.

The concept of using wound contact dressings to inhibit protease activity is not unique and other dressing formulations such as cotton gauze/alginate-containing protease inhibitors have been developed (Edwards et al, 2003).

Modulation of the wound environment

An interesting alternative approach is to modify the wound environment so that protease activity is diminished. All enzymes tend to work most efficiently at a defined optimum pH that differs from enzyme to enzyme. Proteases of the type found in chronic wounds digest proteins most efficiently at a neutral (7) to slightly alkaline (8) pH (Greener et al, 2005). This is said to be the pH found in chronic wounds and it has been suggested that making the wound environment acid by decreasing the pH to 4 may help control protease activity (Schultz et al, 2005). This has been proposed as the potential mode of action for a topically applied ointment that controls pH levels in the wound to modulate protease activity (Anon, 2005).

Pharmacological inhibition of protease activity

While not currently available in the clinic it is worth mentioning that efforts have been made to develop compounds that will specifically inhibit individual proteases. The advantage over the previous two approaches which will non-specifically inhibit the majority of proteases present in the wound, is that this approach can be targeted for individual enzymes. We know that some protease activity is required for healing to proceed and that a blanket suppression of protease activity by non-specific inhibitors can actually inhibit healing (Mirastschijski et al, 2004). Using a specific protease inhibitor that only affects matrix metalloprotease-

3 (MMP-3) activity has produced positive results in a model of a chronic dermal ulcer. Specific inhibition of this enzyme protects the ECM from degradation and allows the proteases involved in keratinocyte migration to function in allowing keratinocytes to migrate over the now intact ECM and re-epithelialise the ulcer (Fray et al, 2003). More candidates for specific protease inhibition are likely to become available for chronic wound management because of the high level of interest in their development for prevention of cancer metastasis (Ikejiri et al, 2005).

Decisions, decisions, decisions

Let us move forward a few years, and assume that there are three types of product available for protease inhibition in the chronic wound — a dressing that non-specifically inhibits proteases, an ointment that lowers wound pH and one or more specific protease inhibitors. How is it decided which product, if any, is most appropriate for a particular wound? The possibility exists that a diagnostic test may be available to make the decision in an objective way. From our present knowledge base this seems unlikely and practitioners will have to rely on their own judgement to identify a wound management strategy.

The initial decision to use a protease inhibitor may be based on clinical experience, knowledge of the relationship between clinical observation and wound pathophysiology (Harker and Moore, 2004), and possibly by using a decision-making framework leading to wound bed preparation (Schultz et al, 2005). This would indicate using a protease inhibitor where there is a high bacterial count or prolonged inflammation.

Having made the decision to use a protease inhibitor the next choice will be — which one? This is possibly more difficult as each will have a different mode of action that may not be applicable to all wounds. The non-specific inhibitor probably will inhibit all proteases to some extent, lowering wound pH makes the assumption that the wound under treatment is not already at an acid pH, and the specific inhibitor will only affect individual enzymes. If its target enzyme is not responsible for the observed clinical features it will have little beneficial effect.

Of course each manufacturer will provide supporting information relating to their particular product; sometimes in great depth. To the non-scientist this may well be seen as obfuscation — hence the comment 'trying to blind us with science'. To determine whether this is the case and help make a rational decision the practitioner probably does require some knowledge of wound pathophysiology, biochemistry and cell biology. The problem is how much and where to obtain it?

Discussion: nurses and bioscience

In order to understand the science underpinning wound management products, a basic knowledge of cell biology and biochemistry at least is required. This is demonstrated in the simplified outline of chronic wound biology

presented above where it was not possible to avoid using scientific terms that assume some knowledge of cell biology. Even if one were not interested in the science it is essential to understand the methodological and statistical significance of case studies, case series and the various varieties of comparative clinical studies that are used in product promotion. For each case study presenting a positive outcome how many unsuccessful outcomes remain unreported? As scientists we are taught a healthy cynicism and to disbelieve anything until the case is proven evidentially.

It appears that biological science education is a problem for nursing students especially if they have no previous experience in the subject (McKee, 2002). This has been attributed to a number of diverse reasons (Jordan et al, 1999) such as:

- Teachers of science face an image problem
- Student nurses aspire to be 'ministering angels' rather than competent and knowledgeable technicians
- Science may be viewed as 'non-caring'.

The idea of acquiring wound healing knowledge at a postgraduate level is particularly daunting because many of the current concepts relating to chronic wound pathophysiology remain theories with supporting data. As such they are not 'facts' and remain liable to change over time and interpretation to suit a particular objective. This requires some knowledge in order to challenge such interpretations.

Wound healing knowledge is available from a variety of sources including structured postgraduate courses (Wound Healing Research Unit, 2005), a diverse variety of unstructured internet sources, text books and articles in nursing journals. Postgraduate courses offer an excellent solution but demand commitment and time. No alternative single, independent and comprehensive resource exists that can be accessed on demand to offer information suitable for individuals with differing levels of background knowledge in wound science. To return to the protease inhibitor example; it would be of value if a series of articles were available for the practitioner to delve into at the depth they required or desired. This would provide unbiased information to allow evaluation of product claims and relevance to the clinical challenge being addressed. A single text book would be of biblical proportions to encompass such a diverse range of subjects. The ideal solution may be an internet-based resource that can take advantage of hyperlinks between the different basic science and clinical practice subject areas. This could be supported by a series of hard copy articles that build to form a reference work in an appropriate journal.

Such a solution could prevent the situation arising where the gains of bioscience knowledge are unapplied or misapplied in wound healing with development of a theory–practice gap (Jordan, 1994). WUK

Key Points

- Knowledge of the biology of normal and chronic wound healing is increasing in complexity.
- The increased knowledge base is being utilised to develop and market new wound management products.
- Some knowledge of the science underpinning wound management products is required to evaluate and apply appropriate treatment strategies.
- Apart from formal postgraduate courses no single, comprehensive and comprehensible, readily accessible source of wound science information is available on demand.
- The requirement for wound science information may be provided to practitioners by an appropriately structured, dedicated website in concert with published hard copy material.

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