alignment of the fibres also permits the formation of cross-links which lend further stability to the new tissue.

Secondary intention

In wounds that have sustained a significant degree of tissue loss as a result of surgery or trauma, it may sometimes be undesirable or impossible to bring the edges of the wound together. In these situations the surgeon may favour leaving the wound open to heal by secondary intention. A similar decision may be taken if there is considered to be a serious risk of infection, or if there is a likelihood of subsequent wound dehiscence. It has also been found that healing by secondary intention can sometimes give better results than primary closure or split-skin grafting, where the cosmetic results of the latter method can be marred by contraction, wrinkling and pigmentation.[4-6]

Although the basic mechanisms of healing of granulating wounds are similar to those that occur in wounds that heal by primary closure, there are significant differences, particularly in the relative duration of the various stages of the healing process. Like a sutured wound, a defect that is left to heal by secondary intention first undergoes an inflammatory response. During this time the exposed tissue or defect may become covered or filled with a layer of blood or serous fluid, which is released during or soon after the initial injury.

As a result of increased capillary and venous permeability, erythrocytes, leucocytes and platelets are liberated into the wound. Neutrophils predominate during the first two to three days but as these decrease in number they are followed by macrophages, which reach their maximum level on day five or six. As in a sutured wound, macrophages are responsible for the bulk of phagocytic activity but they also produce a host of complex proteins and extracellular products including a chemotactic factor, which is thought to attract fibroblasts to the wound area. Fibroblasts appear in the base of the developing wound as early as day four or five and are responsible for the production of intracellular precursors of collagen, which are eventually made into collagen fibrils extracellularly. This process of collagen production is thought to be at least partially under macrophage control.

Around the second or third day, endothelial cells appear in the developing inflammatory tissue as capillary buds. Knighton *et al.*[7] have suggested that the low oxygen tension in the centre of the wound in some way attracts macrophages, the only cells that are able to withstand the severe hypoxia in this situation. The macrophages clear away portions of the fibrous clot and liberate growth factors which stimulate the production of a capillary network. These capillaries retain their permeable nature and thus provide a constant source of cells and fluid for the developing tissue. When the process of repair is complete the demand for oxygen is substantially reduced and much of this new vasculature is lost.

During healing, the wound becomes progressively filled with granulation tissue, which is composed of collagen and proteoglycans, a complex mixture of proteins and polysaccharides together with salts and other colloidal materials which together produce a gel-like matrix contained within the fibrous collagen network. The production of granulation tissue continues until the base of the original cavity is almost level with the surrounding skin. At this stage, the epithelium around the wound margin becomes active and begins to grow over the surface of the wound, thus restoring the integrity of the epidermis. Occasionally the production of granulation tissue continues after the wound cavity has been filled, leading to the formation of ‘hypergranulation tissue’ or ‘proud flesh’. This is sometimes associated with the use of occlusive dressings, and is often removed by the application of a caustic agent such as a silver nitrate pencil. A less traumatic method involves the short-term local application of a suitable corticosteroid cream or ointment, although this should only be done under medical supervision. Alternatively, a change to a more permeable dressing may be all that is required. The formation, causes and management of hypergranulation tissue have been reviewed previously.[8]

A further, and equally important, part of the healing process is contraction, a mechanism by which the margins of the wound are drawn towards the centre. This produces a small area of scar tissue, which may be only one-tenth of the size of the original wound. Contraction may take place in all healing wounds, but it is particularly important in large wounds that are left to heal by granulation and epithelialization. Although in many anatomical sites the process of contraction results in a wound with an acceptable cosmetic appearance, contraction of a wound on the face may result in distortion of the features due to the ‘purse string’ effect. Contraction takes place at a rate of approximately 0.6 - 0.7 mm/day and is not related to wound size, although it is known that rectangular wounds contract more rapidly than round ones. It has been shown that the contractile forces can be sufficiently powerful to cause severe loss of function,[9] and in wounds on the dorsum of the hand they have even been known to cause dislocation of the knuckles.[10]

Wound contraction generally begins about the end of the first week and may continue until the wound is completely closed. It is brought about by the action of a specialist cell called a myofibroblast which is formed from a normal fibroblast as a result of major structural and functional changes. Myofibroblasts show many of the properties of both fibroblasts and smooth muscle cells and will respond to agents that cause contraction or relaxation of smooth muscle tissue. The cells are joined together over the entire wound surface; when they contract they gradually pull in the edges of the wound. Some early evidence suggests that there may be a connection between the initiation of myofibroblast activity and the state of hydration (or dehydration) of the surface of the wound.[11] The process of contraction takes place most quickly if a wound is clean and free of infection and is slowed down or prevented altogether by the presence of eschar or adherent dressings.[12]

The healing of traumatic injuries, in which large areas of skin are lost, depends upon the extent of the damage. Superficial and shallow partial thickness burns, for example, heal as the surviving epidermal cells begin to grow and spread across the surface of the wound. In deep dermal burns, these epidermal cells can develop from small numbers of surviving cells present in the lower parts of hair follicles and sweat glands. These will grow up onto the surface of the wound and appear as isolated islands which gradually increase in size, eventually merging together. If a burn has been severe, the survival of these isolated areas of epidermis may be prejudiced by dehydration or an inappropriate method of treatment. In full thickness burns all epidermal elements are lost; without the application of a skin graft, resurfacing of the wound can only take place by migration of epithelial cells from the wound margins, and healing is therefore very slow.

Delayed primary closure

Less commonly used than the other methods of healing, delayed primary closure is generally carried out when, in the opinion of the surgeon, primary closure may be unsuccessful due to the presence of infection, a poor blood supply to the area, or the need for the application of excessive tension during closure. In these circumstances, the wound is left open for about three to four days before closure is effected. In these situations, sutures may be inserted at the time of the operation but left loose.

Grafting and flap formation

A skin graft is a portion of skin composed of dermis and epidermis that is removed from one anatomical site and placed onto a wound elsewhere on the body. If successful, grafting ensures that the wound will heal rapidly, thus reducing the chances of infection and the time spent in hospital. The major disadvantage of this technique is that the patient finishes up with two wounds instead of one, and it is often reported that the pain associated with the donor site is worse than that occasioned by the original injury. Most commonly used are partial thickness or split thickness grafts. These range in thickness from about 125 to 750 microns, although grafts 300 - 375 microns thick are typically employed. These are removed from a suitable donor site, such as the thigh or buttock, using a special knife which can be preset to ensure that the harvested material is of the required thickness. As elements of epidermal tissue remain in the base of sebaceous glands and hair follicles, the donor site heals rapidly, usually within 10-14 days.

For more specialist applications, such as facial reconstruction, full thickness grafts can be taken which may contain fat, hair and sebaceous glands. They have the advantages that they are cosmetically more acceptable and less likely to form severe contractures than split thickness grafts. Full thickness grafts are also used when a neurovascular bundle or cortical bone must be covered with tissue. They have the disadvantage that, in many cases, the donor site will itself require the application of a second, partial thickness graft, if the wound is too large to be closed by suture.

The success of a graft depends upon a number of factors, the most important of which is the presence of a good vascular bed to supply the metabolic needs of the transplanted tissue. Stress on the graft itself, infection, and the formation of seromas and haematomas are major causes of graft failure.

Skin flaps differ from grafts in that the relocated tissue is usually not completely separated from the body. In this technique a portion of skin and subcutaneous tissue is raised on three sides and rotated or transposed to cover an adjacent area of skin loss. In this way the entire flap continues to receive a supply of blood from its original vasculature until it becomes established elsewhere. The maximum size of the flap depends upon the anatomical site from which it is raised, and the nature and distribution of the major blood vessels. In a variation of this technique, a flap of tissue is relocated complete with its attached blood supply: this is known as a free flap transfer. A more detailed summary of the techniques of grafting and flap formation is given elsewhere.[13]

MONITORING PROGRESS TOWARDS HEALING

In both normal clinical practice, and more particularly in formal clinical trials designed to compare different forms of treatment, it is important to adopt some objective measures to monitor changes taking place within a wound to determine the effectiveness of a particular form of therapy.

These typically involve a record of changes in area or volume as the wound progresses towards healing, but equally important in some instances are the changes, both positive and negative, that occur in a wound's appearance. These may be due to the removal (or formation) of sloughy or necrotic tissue, the production of granulation tissue or new epithelium, or even the development of infection. Equally important are any changes that are visible in the periwound skin as these can sometimes provide an early warning of potential wound-related problems.

Monitoring wound area

Most practitioners record some basic information on wound dimensions. In its simplest form this simply consists of a simple sketch in the patients notes sometimes annotated with rough measurements of maximum length and breadth.

A more accurate procedure involves the production of a tracing of the wound on a piece of transparent plastic which may be marked with a grid to enable an estimate of the wound area to be made by counting the number of squares enclosed within the perimeter of the wound. A variation of this technique involves cutting out and weighing the wound tracing and calculating its area using a predetermined value for the weight per unit area of the tracing medium. More recently computer based systems have been described which facilitate calculation of wound area measurements from tracings or photographs. Numerous publications are available which describe these various techniques in some detail, and in some instance provide comparisons between them.[14-26]

Most planimetry techniques only provide two dimensional information, a measure of wound area. They do not facilitate measure of wound depth, which may be particularly important in cavity wounds. Historically this problem was addressed by measuring the volume of normal saline that could be introduced into a wound - a messy and inaccurate procedure, or by making a mould of the wound using something like alginate dental impression material[27] from which the wound volume could be determined indirectly by displacement or calculated by dividing the recorded weight by the density of the alginate. This procedure was said to be particularly useful for pressure sores and other irregular lesions which were difficult to measure by alternative means.

Once again, however, computer based systems have been described that facilitate such measurements. Plassmann[28-30] developed a system using colour coded light which projected a series of lines onto the wound and surrounding skin. Using a sophisticated computer algorithm the wound volume was calculated from the observed deformation in the pattern of these lines. A laser scanning method for measuring wound volumes has been described by Smith *et al.*[31]

Measurements of wound areas and volumes are not of any particular intrinsic value; it is the changes that take place in these values which are important to the patient and clinician. These changes may either be used to compare different products in a particular population, as in a clinical trial, or compare them with previously determined standard values for a similar patient population.

Marks *et al.*,[32-33] calculated the healing rates of hundreds of healthy surgical wounds from which they have derived simple equations which could be used to predict the likely time for such a wound of a given size to heal as follows:

$$\textit{Time to heal in days} = (\textit{Wound depth in mm} \times 1.23) + 3.6$$

They suggested that similar equations can be produced other wound types for example pilonidal wounds and wounds produced following surgery for hidradenitis suppurativa. Using these equations as a base line it is possible to monitor the progress of a wound and ensure that the rate of healing does not vary significantly from the norm; for example, due to the presence of a subclinical infection.

Similar exercises have been conducted with venous leg ulcers[34] and it has been suggested that the change in wound area during the first few weeks of treatment can in some instances can provide a useful prediction of eventual healing.[35-36] Similar opportunities also said to exist with pressure ulcers.[37]

Monitoring wound appearance

As previously indicated changes in the appearance of a wound can be as important as a change in area or volume, indicating, for example, the need for, or the success of, a period of debridement or a course of antimicrobial therapy.

Most people are familiar with the basic classification system in which wounds, or various portions of their surface, are described as Black, Yellow, Red or Pink, representing in turn necrotic tissue, slough, granulation tissue and new epithelial tissue. This simple classification although far from perfect, can provide a useful starting point to treatment or the dressing selection process.

The amounts of necrotic or sloughy tissue present in a wound are frequently determined in clinical trials involving debriding agents and so methods are required for determining these values with reasonable accuracy. Once again the simplest technique involves a visual estimate of the proportion of the total surface of the wound surface covered with necrotic material, but a more accurate value can be obtained using planimetry as previously described. Using this approach the amount of each tissue type present within the wound is individually recorded and calculated separately. Alternatively it is possible to photograph the wounds and determine the colour distribution by digital analysis[38-39]

Digital photographs themselves represent a useful method for recording changes in wound appearance, but it is important to produce these under standard conditions to maximise their value in this regard.[40]

PROBLEMS ASSOCIATED WITH WOUND HEALING

Delayed wound healing

Although the majority of wounds heal uneventfully, problems do sometimes occur. In most instances these are associated with delayed healing or scar formation. Some wounds, particularly those associated with malignant disease may never heal, and in such situations optimum control of exudate and odour may be all than can be offered to provide the best possible quality of life to the patient.

Infection

The isolation of microorganisms from a wound is not, of itself, an indication of the presence of an infection, as wounds of all types can rapidly acquire bacteria from any one of a number of sources. Such contamination may result from contact with infected or contaminated objects, the ingress of dirt or dust, either at the time of injury or later, or from the patient's own skin or gastro-intestinal tract. For example, it has been found that, unless effective measures are taken to prevent contamination, virtually all burns become colonized by bacteria within 12 to 24 hours.[41]

The consequences of bacterial contamination of a wound will depend upon a number of factors: these include the number of organisms, their pathogenicity (potential to cause disease), and the ability of the patient's own defence system to combat any possible infection. This in turn may depend upon the patient's age, general health and nutritional status, and other factors such as the administration of immunosuppressive drugs, which may inhibit the production of leucocytes.

Many wounds will yield a variety of organisms upon microbiological investigation but may never show the classical symptoms of infection - redness and swelling with heat and pain, which were described by Celsus nearly two thousand years ago. Indeed the presence of a whole host of different organisms is virtually inevitable in dirty or sloughy wounds such as leg ulcers or sacral pressure areas (particularly in patients who are doubly incontinent). However, a similar pattern of infection in a major burn could, if untreated, rapidly develop into a life-threatening septicaemia. Signs that a previously healthy wound may be developing an unacceptably high bioburden include a change in colour or odour, or an increase in exudate production. If adequate measures are not taken to control the infection, it may lead eventually to the formation of cellulitis and ultimately bacteraemia and septicaemia.

Lawrence, in a series of publications on the effects of bacteria on burns[42] and wound healing,[43-44] described the techniques available for detecting and quantifying the number of bacteria present in a wound, and outlined changes in the types of organism that have been isolated from infected wounds over a thirty-year period. The most common pathogen to be isolated from wounds of all types is *Staphylococcus aureus*.

This organism, which is found in the nose of 20-30% of normal persons, may be isolated from approximately one-third of all infected wounds. Other organisms that can cause serious wound infections include *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, and some Proteus, Clostridium and coliform species. Gilliland *et al.* showed that the presence preoperatively of Pseudomonas sp. and *S. aureus* significantly reduced skin graft healing; they also demonstrated that in 16 ulcers which were slow to heal or which recurred after discharge, 15 (94%) contained *S. aureus*.[45]

The types of organism present in a given wound may not remain constant but vary as the condition of the wound itself changes.[41] Burns covered with a wet slough frequently contain an abundance of Gram-negative bacilli - including *P. aeruginosa, Proteus mirabilis*, Klebsiella spp., and *Escherichia coli* - together with *Streptococcus faecalis*, *S. aureus* and *S. pyogenes*. As the slough separates, however, the numbers of Gram-negative organisms decrease and the Gram-positive bacteria predominate. Of all these organisms, Lowbury and Cason[41] identified *S. pyogenes* and *P. aeruginosa* as being amongst the most serious pathogens in a burn. *S. pyogenes* will cause the total failure of a skin graft if present at the time of operation and *P. aeruginosa* has been found to be an important cause of systemic infections in patients with severe burns, although other organisms may also cause serious problems from time to time.

The number of organisms that might be considered to constitute an infection in a wound was discussed by Lawrence,[44] who considered that the level of 10^5 per gram suggested by Pruitt,[46] formed a useful guide - provided it was recognised that the bacteriological picture of a wound could change from day to day.

The management of an infected wound usually consists of a combined systemic and local approach, including the use of antibiotics where appropriate and the application of a suitable dressing, which may itself possess inherent antibacterial activity. The use of topical antibiotics is not generally encouraged, as it may cause sensitivity reactions or lead to the emergence of antibiotic-resistant strains of bacteria.

Metabolic factors

Metabolic changes, an imbalance between proteolytic enzymes and their inhibitors, and the presence of senescent cells can have a marked effect on the healing of chronic wounds.[47] Reduced or inadequate levels of growth factors may also be important, which is why much research activity has been focused on this subject in recent years

Another area that has attracted considerable interest is the excessive proteinase activity often encountered in non-healing or indolent wounds such as leg ulcers. This is believed to result from an over-expression of matrix metalloproteinases (MMPs) which are zinc-dependent endopeptidases.

Along with other similar enzymes, MMPs are capable of modifying the structure and therefore the activity of a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors and cytokine activation and inactivation. They are also thought to play a major role in cell behaviour, determining proliferation, migration, differentiation, angiogenesis, apoptosis and host defence mechanisms. In the context of wound dressings, one of their most important actions may be that of degrading all kinds of extracellular matrix proteins and causing excoriation of periwound skin, effectively extending the size of an existing wound. For this reason, considerable attention has been focussed upon dressings which are described as ‘protease modulators’ that in some way ‘mop-up’, destroy or otherwise inactivate these important molecules.

Miscellaneous factors

A number of other local and systemic factors are well recognized causes of delayed or impaired wound healing. Foreign bodies introduced deep into a wound at the time of injury can, if not removed, cause a chronic inflammatory response and delay healing or lead to the formation of a granuloma or abscess. Long-standing wounds that heal by epithelialization, such as burns and leg ulcers, may develop Marjolin’s ulcer, an uncommon slow-growing squamous cell carcinoma. Other major factors that have an important effect upon the rate of healing include the age and nutritional status of the patient, underlying metabolic disorders such as diabetes or anaemia, the administration of drugs that suppress the inflammatory process, radiotherapy, arterial disease which may be aggravated by smoking and the presence of slough and necrotic tissue.

Scar formation

Another long-term problem sometimes associated with wound healing is the formation of hypertrophic or keloid scars. These unsightly areas result from excess collagen production but the reason for their formation is not fully understood; they are most likely to occur in Negroes and in young people around puberty. Hypertrophic scars are limited to the site of the original injury but keloid scars may continue to grow and spread into the surrounding tissue for a number of years. The histological, epidemiological and aetiological characteristics of both types of conditions have been comprehensively described by Munro,[48] and a series of surgical techniques that may help to minimize scar formation were described by Pape.[49] Topical treatments that have been developed to treat or prevent hypertrophic scar formation are described in Chapter 18.

Wound pain

According to evidence reviewed by Price *et al.*,[50-51] six out of ten patients with chronic wounds suffer from persistent wound pain.

Many patients with acute wounds of all types can also experience significant pain, which is often associated with the removal or replacement of a dressing.[52-53] This problem can be particularly acute with burns and donor sites, where the application of an inappropriate dressing can cause serious discomfort or even significant rewounding upon removal as described in latter chapters.

Chronic wound pain can lead to depression and the feeling of constant tiredness. For this reason, prevention and treatment of wound-related pain should be a major priority when designing wound treatment plans for it has been suggested that unless wound pain is optimally managed, patient suffering and costs to health care systems will increase. To this end, a ‘Wound Pain Management Model’ has been described[51] that involves the proper assessment and recording of patients' experiences of pain based on six critical dimensions of the pain experience: location, duration, intensity, quality, onset and impact on activities of daily living.

This model recommends strategies for preventing and treating pain in a variety of wound types encompassing wound cleansing strategies, the use of compression or other measures to facilitate vascular flow, the use of appropriate dressings and various types of non-pharmacological and pharmacological and treatments including the use of the WHO Clinical Ladder for the control of pain originally derived for patients with cancer.

In 2007 a foam dressing containing a non-steroidal analgesic, ibuprofen, was introduced specifically to address the problems of localized wound pain and this is discussed in more detail in Chapter 10.

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