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Chapter 6

Psychoneuroimmunological aspects of wound healing and the role of pain

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Key points in this chapter include:

- Physiological aspects of wound repair
- Psychoneuroimmunological factors on wound healing
- Tissue type
- Impact of gender, age and health behaviours on wound healing.

As you are reading this there is a good chance that your body is undergoing some sort of healing, be it from a superficial paper cut or a surgical procedure. Your immune system plays a well-characterised role in any healing process; as such, psychological and behavioural factors that affect immune and neuroendocrine function — from psychological stress and mood to sleep patterns — influence healing as well. The clinical importance of research in this area is striking. Along with an increasing appreciation for the impact of psychosocial and behavioural factors on wound healing has come a greater understanding of the physiological mechanisms which connect such factors to healing outcomes (Engeland and Marucha, 2009). Research in this area will help to develop better models for predicting healing trajectories, as well as novel interventions to improve healing outcomes and associated factors (e.g. pain).

Research in the field of psychoneuroimmunology has burgeoned over the past 25 years, with dramatic demonstrations of not only the role of psychosocial and behavioural factors on immune function, but also their impact on wound healing (Christian et al, 2006; Engeland and Marucha, 2009; Walburn et al, 2009). The goal of this chapter is to review key established findings in this area, while simultaneously highlighting findings in related areas that are less

well consolidated, such as interconnections between psychological factors, physical pain, immune function, and healing. We begin by reviewing the physiological aspects of wound repair that are related to psychological stress. Next, we review human studies documenting the impact of psychoneuroimmunological factors on wound healing, studies which have dealt with diverse aspects of stress, including perceived psychological stress, stressful events, depression, anxiety, and pain. Separate attention is paid to issues of tissue type (dermal versus mucosa) and wound type (acute versus chronic). Chronic wounds have received less empirical attention than acute wounds, yet represent a much larger financial burden on health care and are the focus of most intervention efforts. We also review promising and relatively recent research on the impact of individual differences (e.g. gender and age) and health behaviours (e.g. alcohol use and sleep) on the healing process. Finally, we conclude with a summary of findings in these areas and suggest avenues for future research and clinical efforts.

Physiological mechanisms of stress

Wound healing typically follows an orderly and predictable pattern comprised of three overlapping phases: an inflammatory phase (which takes hours to days) in which blood flow to the area is increased, a blood clot is formed, and the required inflammatory cells (e.g. neutrophils, monocytes) are recruited to the area; a proliferative phase (days to weeks) in which there is a dramatic increase in the recruitment and proliferation of fibroblasts, epithelial cells, and endothelial cells to begin the rebuilding process; and a remodelling phase (weeks to months) in which the connective tissue matrix begun in the previous phase is fully formed and restructured. These phases are interdependent and success in later stages depends on success earlier in the healing process (Engeland and Marucha, 2009). Psychological stress can impair healing in each of these phases. For the purpose of this chapter, psychological stress will be defined as the perception that one's resources are taxed in a manner that one is unable to cope effectively with negative events.

The perception of stress by the brain can trigger activation of two main stress pathways, both of which modulate immune functioning and wound healing. These pathways are the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS).

The hypothalamic-pituitary-adrenal axis

Activation of the HPA axis starts with the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH signals the anterior pituitary via the hypophyseal portal system, and induces the release of adrenocorticotropic hormone (ACTH). This, in turn, enters the general circulatory system and causes glucocorticoids (GCs) to be secreted from the adrenal glands. GCs down-regulate further activation of the HPA axis through a negative feedback system targeted at GC II receptors located on various brain areas, including the hypothalamus, hippocampus, and pituitary gland. Thus, the HPA axis is negatively self-regulating.

Immune cells possess GC receptors and, as a result, GCs exert effects on virtually all aspects of immunity (Chrousos, 1998). As a result, dysregulation of this axis affects wound healing. Cortisol, the primary GC in humans, has strong immunosuppressive, anti-inflammatory, and anti-mitotic properties. A single administration of GCs in humans reduces circulating lymphocytes and monocytes by 70% and 90%, respectively (Berczi, 1986). GCs have been shown to reduce neutrophil (Clark et al, 1979) and monocyte (Norris et al, 1982) recruitment to injured tissues, and to decrease both macrophage phagocytosis and bacterial killing (Fauci et al, 1976). Together, this results in impaired bacterial elimination and delayed wound debridement. Keratinocyte and fibroblast proliferation is inhibited by GCs, as is collagen production (Edwards and Dunphy, 1958; Beer et al, 2000), resulting in a thinned abnormal regeneration of the epidermis. Overall, GCs can impair bacterial clearance, compromise re-epithelialisation, reduce wound strength, and slow wound closure.

Through its effects on inflammation, stress has been shown to play a role in the onset, pathogenesis, and severity of numerous inflammatory diseases such as rheumatoid arthritis, inflammatory bowel syndrome, hypertension, and asthma (Black and Berman, 1999).The effects of stress on inflammation are of particular importance for healing. Through the release of GCs, stress can alter inflammatory responses by multiple mechanisms. The release of proinflammatory cytokines (IL-1ß, IL-6, TNF-a) during tissue repair is reduced by GCs (Hinz, 2007), and prolonged exposure to circulating GCs reduces the sensitivity of some cells to the inflammatory effects of these molecules (Hubner et al, 1996; Mastorakos et al, 1999). Chronic (unremitting or frequent) stress can disrupt the circadian rhythm of cortisol and may also cause low grade systemic inflammation to occur (Hawkley et al, 2005). These changes,

in turn, dysregulate the immune system and hinder the formation of appropriate inflammatory responses when needed. Although stress can alter many aspects of wound healing, its strongest negative effects are likely to occur through the modulation of inflammation by GCs. In addition, stress also activates the sympathetic nervous system, which modulates wound healing in a different manner.

The sympathetic nervous system

In addition to causing ACTH release, CRH stimulates the locus coeruleus to release norepinephrine (NE) from sympathetic nerve endings. The adrenal glands are similarly stimulated to release epinephrine (Epi; also known as adrenalin). Thus, activation of the SNS results in plasma increases in both NE and Epi which can alter cell function and blood flow.

NE and Epi activate alpha-adrenergic receptors and cause vasoconstriction (Ahlquist, 1976). Thus, stress-induced activation of the SNS reduces peripheral blood flow. This results in slower cell recruitment as well as reduced oxygen and nutrient availability to healing tissues. Due to a disruption of blood supply and the influx of cells with high oxygen demands (e.g. neutrophils), injured tissue is typically hypoxic. Stress drives tissue oxygen levels lower again, which can negatively affect wound healing. For instance, the infusion of Epi reduces wound oxygen levels by 45% (Jensen et al, 1985).

Multiple studies have shown that reduced circulating oxygen levels are detrimental to tissue repair. Oxygen positively influences collagen synthesis, angiogenesis, and the bacterial killing capability of neutrophils (Whitney, 1989), and oxygen tension significantly alters the revascularisation and re-epithelialisation of wounds (Pai and Hunt, 1972). Not surprisingly, lower oxygen levels have been associated with increased wound infection in surgical patients (Hopf et al, 1997), and a local injection of Epi during vaginal hysterectomies has been associated with increased rates of infection (England et al, 1983). In addition to affecting oxygen, NE has been shown to alter inflammation, as it reduces proinflammatory cytokines by increasing C-AMP levels (Sanders and Straub, 2002). Thus, similar to GCs, stress-induced catecholamines (NE, Epi) can negatively affect wound healing through multiple mechanisms.

To summarise, activation of the HPA axis has strong immunosuppressive actions and is potently anti-inflammatory, which

can negatively affect healing. SNS activation reduces oxygen availability to tissues through vasoconstriction. This, in turn, hinders bacterial clearance and re-epithelialisation. Simultaneous inhibition of both the HPA axis and the SNS may be a good therapeutic target for preventing/reducing healing deficits in chronically stressed individuals (Marucha and Engeland, 2007; Engeland and Marucha, 2009).

Effects of psychological stress on wound healing

A number of studies have demonstrated that psychological stress can negatively affect healing and this has recently become a generally accepted notion. The mechanisms underlying this phenomenon, however, are still being investigated. In 1995, Kiecolt-Glaser et al reported on a wound healing study with female Alzheimer's caregivers, who experience chronic stress as part of the caregiving process. The caregivers healed dermal biopsy wounds 24% more slowly than age-matched controls (n=13/group). Immune responsiveness in these individuals was also altered, as whole blood produced less IL-1ß mRNA in caregivers compared to controls when stimulated with LPS. These findings suggest that chronic stress impairs the early inflammatory response, resulting in delayed wound healing.

In a follow-up study, skin blisters were induced by aspiration on the forearms of 36 women and the wound milieu was examined. Women with lower levels of IL-1ß and IL-8 in the wound site 24 hours after wounding had greater self-reported stress and negative affects, and higher levels of salivary cortisol than women with higher cytokine levels (Glaser et al, 1999). Stress was again associated with reduced inflammatory responses, this time directly at the wound site. These effects may have been mediated by the anti-inflammatory actions of cortisol.

In 2004, Ebrecht et al similarly demonstrated a relationship between stress, cortisol and wound healing rates. Twenty-four healthy young men received a 4mm dermal punch biopsy and healing was monitored using high-resolution ultrasound scanning. This method allows for the measurement of width at the base of the wound and provides a more accurate assessment of wound healing than surface photography (Ebrecht et al, 2004). Wound healing rates were negatively correlated with perceived stress and positively correlated with perceived optimism. Furthermore, when a median split was performed to subdivide slow

and fast healers, slow healers had significantly higher stress levels, lower trait optimism, and higher cortisol levels to awakening. These findings further confirm links among stress, anti-inflammatory stress hormones, and healing times.

The effects of stress on the healing of non-dermal tissues have also been examined, most notably on mucosal tissues in the mouth. It is well accepted that stress affects mucosal inflammation and stress is a known risk factor for periodontal disease (Boyapati and Wang, 2007). To assess the effects of a commonplace stressor on wound healing, 11 dental students received a 3.5mm punch biopsy wound on the oral hard palate at two different time points: just before examinations or during summer holidays. Students took 40% longer to heal during the examination period, and no student healed as rapidly as during the holiday (Marucha et al, 1998). It is notable that an event as benign as university examinations can significantly impair wound healing, and does so in healthy young adults who are experienced students.

The effects of examination stress have also been studied in the dermis. It was reported that examination stress increased the time to heal from experimental blister wounds. Further, this stress had an overall suppressive effect on the neutrophil transcriptome (Roy et al, 2005). This suggests the stress associated with university examinations delays healing, at least in part, by altering neutrophil function.

Clinical depression has been shown to negatively affect immune functioning in numerous studies (Kiecolt-Glaser and Glaser, 2002), which suggests depression may impede wound healing. In a study of 183 young healthy adults, individuals with higher depressive scores (assessed by the Beck Depression Inventory) were shown to heal oral mucosal wounds more slowly, even when correcting for gender, age, ethnicity, and health behaviours. None of these subjects were clinically depressed or on antidepressants; they were simply placed further along the depressive spectrum. Thus, even sub-clinical depression (dysphoria) is robust enough to affect immunity and delay wound healing.

Stress, depression and clinical outcomes

Preoperative stress relates to post-surgical reductions in lymphocyte blood counts, lymphocyte responses (Linn et al, 1988), and natural killer (NK) cell activity (Koga et al, 2001; Starkweather et al, 2006). Broadbent et al (2003) assessed the effects of preoperative stress on post-surgical wound repair. Scores on the Perceived Stress Scale (PSS)

were obtained for 47 patients before they underwent an open incisional hernia operation. Wound fluid was collected from 36 participants over the first 20 hours following surgery. Higher stress levels predicted lower levels of IL-1ß, and greater worry about the operation predicted a more painful and slower recovery. Greater worry also predicted lower levels of matrix metalloproteinase (MMP)-9 in wound fluid. MMP-9 facilitates cellular migration within the wound, and is important for tissue remodelling and wound architecture. Thus, preoperative stress appears to alter inflammatory and matrix remodelling processes, resulting in a poorer healing outcome.

Following coronary bypass surgery in 72 patients, higher depressive symptoms at discharge predicted infection, impaired wound healing, and poor emotional and physical recovery. These patients were 3.7 times more likely to experience wound infections and healing problems six weeks after discharge (Doering et al, 2005). In a similar study involving 309 patients, higher optimism predicted a lower rate of re-hospitalisation and better recovery for the first six months after coronary bypass surgery (Scheier et al, 1999).

In a study of burn patients, having a pre-existing psychiatric illness (i.e. psychosis [n=8] or depression [n=9]) related to poorer healing outcomes. Control subjects (n=33) were matched for gender, age, burn severity, type of burn, depth, and location. Patients with a pre-burn psychiatric diagnosis took longer to heal and were in hospital significantly longer than matched burn patients without psychiatric illness. Patients with psychosis healed particularly poorly (Tarrier et al, 2005).

Both experimental and clinical studies clearly demonstrate that stress and depression can impair the healing process, and factors such as optimism may be beneficial. Other factors related to stress and depression (such as mood, hostility, anger, and social interactions) can also influence healing, and are reviewed below.

Effects of behavioural constructs and interventions on wound healing

On separate days, 42 married couples engaged in either a 30-minute conflictive discussion (on topics of disagreement between them), or a relatively neutral and non-conflictive discussion. Following the conflictive interaction, experimental dermal blister wounds healed more slowly, and with lower levels of proinflammatory cytokines

(IL-1ß, IL-6, TNF-a) in the wound fluid than following the non-conflictive interaction. Moreover, high-hostile couples healed at only 60% the rate of low-hostile couples (Kiecolt-Glaser et al, 2005). Using the same blister wound model, individuals who exhibited lower levels of anger control were categorised as slower healers (Gouin et al, 2008). This highlights that not only everyday stressors, but also hostile behavioural patterns, social interactions, and anger control can alter immunity and tissue healing.

In a follow-up study, individuals who more fully engaged in the conflict discussion, as evidenced by a greater use of words indicative of cognitive processing, showed attenuated proinflammatory cytokine responses in the periphery (Graham et al, 2009), suggesting that relationship conflict may be less stressful if effective communication is utilised. Further, greater positive communication during the non-conflictive interaction related to higher oxytocin levels in blood, and individuals with oxytocin levels in the upper 25% healed blister wounds faster than the remainder of the participants (Gouin et al, 2010). Oxytocin is often released during stress, is considered to be an anti-stress peptide, and has been shown in animal models to reduce wound healing times (Detillion et al, 2004; Vitalo et al, 2009). Thus, while many studies demonstrate that stress often impedes healing, there is emerging evidence that positive social interactions may bolster it.

Emotional disclosure interventions, which involve participants writing about their thoughts and feelings, have been related to reductions in health visits, increased T-cell proliferation, and better antibody responses to hepatitis B and influenza (Weinman et al, 2008). Recently, emotional disclosure has been shown to speed the healing of a small dermal punch biopsy wound. On average, participants who wrote about traumatic personal events (three 20-minute periods) had wounds that were 11% smaller at 14 and 21 days after wounding, compared to control subjects who wrote about time management (Weinman et al, 2008). This illustrates the potential value of psychological interventions aimed at reducing the impact of long-term stressors.

Other interventions aimed at reducing stress have shown promise for improving healing. Patients who underwent cholecystectomy benefited from relaxation with guided imagery (RGI). These individuals demonstrated a reduced state of anxiety, lower cortisol levels, and less wound erythema compared to random control patients who did not undergo RGI (Holden-Lund, 1988). A meta-analysis of 191 studies found that psychoeducational care (i.e. patient education) can reduce distress and anxiety to patients, leading to better recovery with less

pain and reduced hospital stays (Devine, 1992). In addition, massage therapy has been shown to decrease levels of depression, anxiety, cortisol, and pain in burn patients undergoing debridement (Field et al, 1998). Thus, a variety of stress-reducing interventions appear to have some merit in buffering the negative effects of stress on post-surgical outcomes.

In summary, numerous stressors such as caregiving, university examinations, marital disagreements, and pre-surgical worry have been shown to impair wound healing. Many of these effects appear to occur through alterations in cytokine levels. Importantly, factors such as positive mood, optimism, and positive social communication can improve tissue repair as well as buffer the negative effects of stress. Behavioural interventions which attempt to improve post-surgical outcomes, such as stress reduction, should also focus on efforts to elevate positive elements such as happiness and optimism.

Stress and the skin barrier

The epithelial barrier is critical for providing pathogen resistance and limiting water loss from the body. Tape stripping is a relatively non-invasive method of assessing repair to this barrier. With this technique, the skin barrier is disrupted by repeatedly applying and removing cellophane tape from an area of dermis, often on the forearm. An evaporimeter is then used to assess transepidermal water loss (TEWL) over time. Interview stress (Trier Social Stress Test) has been shown to slow barrier recovery times (Altemus et al, 2001; Robles, 2007; Robles et al, 2009), and increase circulating levels of cortisol, norepinephrine, and proinflammatory cytokines (Altemus et al, 2001). Interestingly, during the stress condition, individuals with higher (self-reported) positive affect (i.e. mood) had faster barrier recovery times than those with lower positive effect (Robles et al, 2009). Thus, the negative effects of stress on skin barrier recovery are buffered by positive mood. Other studies have shown the stress associated with marital dissolution (Muizzuddin et al, 2003), university exams (Garg et al, 2001), and sleep deprivation (Altemus et al, 2001) relate to slower barrier recovery times. These effects were generally greatest in the individuals who reported the most stress. It is clear that skin barrier recovery, which is a critical factor in many skin diseases (e.g. atopic dermatitis, psoriasis) and in dermal healing, can also be impeded by psychological stress.

Effects of pain on wound healing

Pain can be conceptualised as both a physical and psychological stressor and, as such, may affect wound healing directly and indirectly (Kiecolt-Glaser et al, 1998; Soon and Acton, 2006). Although a range of symptoms from discomfort to intense pain typically accompany both acute and chronic wounds, few studies have examined the impact of pain on wound healing specifically. One study, conducted in 17 young to middle-aged women, examined the association between pain following an elective gastric bypass surgery and the healing of a dermal punch biopsy wound that was placed on the upper arm the same day as the surgery. Participants who reported greater acute or persistent post-surgical pain took longer to heal the experimental wound than others (McGuire et al, 2006). This study controlled for depression, pre-existing persistent pain, and health status, although the possible impact of other factors, such as pain medication and anxiety, were not examined. To the authors' knowledge, there are no published reports of the impact of acute experimentally manipulated pain on healing in humans, and certainly none involving manipulation of chronic pain, which would be unethical. It is thus difficult to know the extent to which pain specifically affects healing independent of pain-linked factors such as wound severity, psychological stress, and mood. As reviewed below, empirical evidence linking pain, mood, and stress responses suggests it is likely that pain impairs wound healing. In support of this, the immune dysregulating effects of surgery (which include inflammation) are lessened by the use of analgesics to control pain (Beilin et al, 2003).

Pain and healing connections can be partly explained by linkages between pain and mood, as illustrated in *Figure 6.1*. Pain is strongly and most likely bi-directionally associated with negative mood states, such as depressed mood, anxiety, and anger. One key reason why pain leads to depressed mood is because it interferes with important pursuits, including relationships and work (Cannella et al, 2007). This is particularly the case for chronic pain conditions, which are often linked with feelings of futility, failure, and intense psychological distress (Rudy et al, 1988). Indeed, the treatment of negative mood is seen as a pivotal element in the treatment of chronic pain. Pain and anticipation of pain are also associated with anxiety and maladaptive cognitive patterns and appraisals (Gaskin et al, 1992; Turk et al, 1995). As reviewed above, anxiety, hostility, and depressed mood have been associated with slower healing. Pain may lead to poorer

Figure 6.1: Key biobehavioral mediators of stress, pain, and healing connections. Psychological stress can be defined as the perception that one's resources are taxed in a manner that one is unable to effectively cope with negative events. Perceived stress is linked with pain and healing via a number of routes involving mood (e.g. depressed mood, anxiety, anger), health behaviour (e.g. alcohol use, sleep), and alterations in immune function and inflammation (e.g. proinflammatory cytokines). For example, perceived stress can lead to increases in negative mood, decreased sleep, and increased proinflammatory cytokine activity, all of which can serve to increase pain and impair healing. Similarly, pain can increase both proinflammatory cytokines and stress hormones, altering and potentially delaying the healing process. In turn, proinflammatory cytokines (i.e. inflammation) can increase negative mood and pain, which feed back to increase perceptions of stress. It becomes clear that pain, stress and inflammation can each activate similar pathways through a different part of this loop, and thereby promote the other two conditions. This has important therapeutic implications, as not only inflammation but potentially also pain, mood, and stress responses can be targeted for intervention to improve tissue repair and regeneration.

healing via negative mood and associated stress. In turn, healing difficulties may exacerbate negative mood, creating a self-perpetuating cycle. As reviewed later in this chapter, pain can lead to maladaptive health behaviours that are linked with healing, such as loss of sleep, inactivity, and alcohol use (Graham and Streitel, 2010).

In addition to connections via mood, pain leads to physiological changes that are relevant to healing, such as alterations in cortisol levels, inflammatory cytokines, and prostaglandins. Prostaglandins are proteins that activate pain signalling in response to nerve damage; they do so in part by activating inflammatory cytokines, and are themselves activated by cytokines (Watkins et al, 2007). There is growing evidence that inflammation not only causes pain (via tissue swelling and damage, and cytokine activation of pain signalling), but also that pain causes circulating levels of proinflammatory cytokines to increase. One example in humans is that injection of capsaicin (a pain-stimulating component of chili peppers) into the arm increases circulating IL-6 levels (Lutgendorf et al, 2004). Elegant work examining central nervous system activation of proinflammatory cytokines has demonstrated that cytokines may aggravate pain and that treatment with anti-inflammatory agents may improve pain (Watkins et al, 2007). Moreover, pharmacologically increasing IL-10 (which has anti-inflammatory actions) in the central nervous system reduces neuropathic pain in animal studies and is currently being investigated as an adjunct/alternative to morphine in humans (Watkins et al, 2007; Loram et al, 2009).

Among those with chronic pain conditions, limited research explores how pain and physiological stress responses play out or how they are related to wound healing. A recent study suggests that among those with acute back pain, emotional distress is associated with alterations in the HPA axis, such as greater cortisol responses (Sudhaus et al, 2009). Conversely, among individuals with chronic low back pain, levels of depressed mood and certain pain coping responses were associated with blunted cortisol awakening responses (Sudhaus et al, 2009), which have been linked to depression. Together, these results suggest that pain and HPA axis linkages are complex and may vary with chronicity of pain and cognitive responses to pain. Similarly, a study with fibromyalgia patients found that perceived overall pain and depression were associated with greater cortisol output over the course of a day, whereas experimentally induced pain was not associated with cortisol release (Wingenfeld et al, 2010). This again suggests that mood may be a pivotal modulator of the effects of pain on the HPA axis (Wingenfeld et al, 2010).

In a six-year longitudinal study among older adults, overall bodily pain was associated with higher levels of C-reactive protein (CRP), a well-established marker of inflammation (Graham et al, 2006). This association was significant only among the participants who were experiencing, or had recently experienced, the substantial stressor of being a caregiver for a spouse with dementia (n=113), as opposed to age-matched non-caregivers (n=101). Depressed mood, health behaviours, and demographic risk factors for elevated inflammation were controlled in this study. Thus, there is evidence to suggest that pain and inflammatory connections are strongest during times of stress (Graham et al, 2006). Although none of these studies have examined healing specifically, they show connections between pain and specific physiological pathways related to healing.

Research on surgical recovery implies an important role for pain and suggests that adequate pain management is critical to the healing process. For example, worry about pain has been linked with longer surgical recovery times and lowered postoperative immune functioning (Kiecolt-Glaser et al, 1998). Importantly, adequate pain management appears to reduce immune suppression that is common following surgery. When adequate levels of opioid analgesics are used, they attenuate the immune dysregulation otherwise observed subsequent to surgery (Beilin et al, 2003), even though opioid pain medications themselves can be immune suppressive (Page et al, 2001; Page, 2005). Other efforts to control pain may also lead to improved healing.

For example, patients use less pain medication when they are given more control over its administration (Vadivelu et al, 2010). Greater attention to clinical dressings is also beneficial; patients report less pain and anxiety when appropriate clinical dressings are utilised and when they are guided in techniques to distract them from pain (Solowiej et al, 2010).

Tissue differences: dermis versus mucosa

The site of injury is an important consideration in both wound research and its treatment. Although the majority of wound research involves dermal wounds, mucosal healing is necessary in most surgical outcomes and the vast majority (90–95%) of all infections start at mucosal surfaces (Bosch et al, 2003). These two tissues are intrinsically different. The mucosa has a higher epithelial turnover rate than the dermis and, due to its high vascularity, it takes less time for inflammatory cells to

infiltrate mucosal tissue following injury. In addition, the mucosa is coated in fluids which contain a supply of cytokines, growth factors, and other immune components beneficial to healing. As a result, mucosal tissues heal faster, with less inflammation and, for reasons not entirely understood, with little to no scarring compared to dermal tissues (Lee and Eun, 1999; Szpaderska et al, 2003).

Importantly, factors which modulate wound healing often do so in a tissue-specific manner. For instance, women heal skin wounds faster than men (Ashcroft et al, 1997; Jorgensen et al, 2002; Ashcroft and Ashworth, 2003), but are slower than men to heal oral mucosal wounds (Engeland et al, 2006). This surprising inconsistency may exist because women mount higher inflammatory responses than men (Giglio et al, 1994; Miller and Hunt, 1996), and a high inflammatory response in mucosal tissues can be maladaptive. A similar example involves stress. As discussed previously, in dermal wounds long-term stress inhibits early inflammation and delays wound closure. In mucosal wounds, the stress of university examinations similarly delays wound closure but causes hyper-inflammation in the tissue (Engeland et al, 2008). Although stress alters inflammation and negatively affects healing in both types of wounds, it does this through the inhibition of inflammation in dermal tissues and the promotion of inflammation in mucosal tissues. Thus, both gender and the negative effects of stress can modulate wound closure rates but the mechanisms involved, and even the healing outcome, may depend on tissue type. These differences should be kept in mind both in research and when reviewing the literature, where there is a tendency to generalise across tissues. Direct comparisons between dermal and mucosal tissues are generally inappropriate.

Chronic wounds

The studies reviewed above have centred on experimentally-induced wounds in controlled laboratory settings, which are of course critical to understanding causal associations between factors such as stress and healing. Studies employing more naturally occurring wounds (e.g. diabetic foot ulcers, surgical wounds, accidents) are limited by greater difficulties in controlling for morbidity and medication use, the exact size and nature of the wounds, and by clinical dressings that may complicate the assessment of wound healing. However, compared to experimental studies, clinical wound studies provide valuable

information about how stress may affect larger and more chronic wounds where maladaptive outcomes can have serious implications.

Chronic wounds, such as those that can occur with diabetes, are particularly problematic for both patients and physicians. Chronic ulcers, for example, can be disabling and distressing, particularly as time goes on, as well as expensive, complicated, and time-consuming to treat (Ruckley, 1998; Alvarez et al, 2007). The majority of individuals dealing with a leg ulcer will experience either a long-term ulcer or a recurrence (Ruckley, 1998), indicating that healing such wounds is particularly difficult. Among 53 adult patients with chronic leg ulcers due to venous disease with or without ischaemic disease, higher depression and anxiety scores were associated with delayed healing (Cole-King and Harding, 2001). Furthermore, patients who scored in the top 50% on these measures were four times more likely to be categorised as a slow healer than patients who scored in the bottom 50%. In summary, psychological stress can delay the healing of both acute and chronic wounds.

Wound healing and ageing

The treatment of impaired healing costs United States health services over $9 billion per year, much of which has been attributed to age-associated delays in wound closure (Ashcroft and Mills, 2002). In the UK, the financial burden of wounds is estimated to be between £1.8bn and £4bn, which is 2–4% of the annual NHS expenditure with total chronic wound care costs being substantially more (White, 2010). The elderly have the highest occurrence of wounds of any age group in the United States (Pittman, 2007) and comprise the fastest growing population in Western countries. Clearly, the impact of ageing on wound healing is an important issue in health care, both in the United States and worldwide.

It is well established that ageing alters skin morphology (Ashcroft et al, 2002; Gosain and DiPietro, 2004). The skin of older adults has reductions in vascularisation, granulation tissue, collagen production and density, elastin, mast cells and fibroblast numbers. As one ages from 20 to 70 years, epidermal turnover reduces by about 50%. This is likely due to lowered responsiveness of keratinocytes to growth factors, resulting in a reduced proliferative capacity of these cells. Overall, with age, the dermis becomes less dense, less cellular and less vascular (Thomas, 2001). This reduction in vascularity limits oxygen

and nutrient availability and reduces immune cell infiltration to tissues (Tsuchida, 1993). Numerous age-related changes in wound healing have been reported in humans. These include enhanced platelet aggregation, increased rates of infection, decreased wound strength and macrophage function, and delayed re-epithelialisation, angiogenesis, macrophage infiltration, collagen deposition and remodeling (Lober and Fenske, 1991; Ashcroft et al, 2002; Gosain and DiPietro, 2004). These changes do not appear to pertain to cellular defects, but are more qualitative and relate to differences in the timing and degree of cellular infiltrate into tissues (Freedland et al, 1995).

Despite the above findings and statistics, it is unclear if being elderly is truly a risk factor for delayed wound healing. The reason for this uncertainty is that most studies in this area which report poorer healing with age (Goodson and Hunt 1979; Fenske and Lober, 1986; Gerstein et al, 1993) have not controlled for potentially confounding factors that are particularly common in older individuals, such as medication use and co-existing illness/disease. Other studies have reported no differences in healing rates between younger and older adults (Thomas, 2001; Ashcroft et al, 2002). Animal studies have generally found age-associated healing impairments (Ashcroft et al, 1995; Swift et al, 2001; Gosain and DiPietro, 2004), but appear to be poor predictors of clinical wound healing (Thomas, 2001). Thus, it remains unclear if ageing *per se* impairs wound healing (Engeland and Gajendrareddy, in press).

The healing of mucosal tissues is involved in most surgical recoveries. In addition, mucosal tissues do not undergo cumulative ultraviolet (UV) exposure and thus may provide a better indication of intrinsic ageing than skin. Engeland et al (2006) controlled for the potentially confounding factors of comorbidity and medication use, and showed that older individuals (50–88 years) healed oral mucosal wounds more slowly than younger individuals (18–35 years), regardless of gender. Five days after wounding, wounds were 56% larger in older subjects and 3.7 times less likely to be considered healed compared to younger adults. Older women healed the slowest and their wounds were 95% larger than young men (the quickest healing group) at this time point. These findings indicate that older women are at the highest risk for delayed healing in mucosal tissues. Interestingly in women, the deleterious effects of age on wound healing were only seen after the start of menopause (Engeland et al, 2009).

Overall, it seems that wound closure is delayed to some degree in the elderly, but importantly healing is essentially normal. New events

in healing do not occur, expected events are not absent, and the same end point of healing is often reached as in younger adults. Moreover, wounds often heal with a better aesthetic outcome (i.e. less scarring) in older adults (Cook and Dzubow, 1997). As a result, surgical procedures are routinely performed in the elderly with normal, although slightly slower, recovery outcomes. To date, ageing *per se* has not been shown to clinically impair wound healing.

The major increased risk to older individuals undergoing surgery pertains not to age but to other factors which impair immunity and affect healing. Importantly, the effects of age are interactive with such risk factors, including: comorbidity (e.g. diabetes), medication use, obesity, immobility, nutrition, and importantly for this chapter stress, pain, and depression (Engeland and Gajendrareddy, in press). These risk factors all occur more commonly in the elderly and are more likely to exacerbate healing in the aged, increasing the risk for chronic infection and post-surgical complications (van de Kerkhof et al, 1994). The presence of any of these risk factors in the elderly should serve as a red flag for the clinician, and such individuals should be given more aggressive post-surgical attention.

Health behaviours

In addition to the neuroendocrine and immune-related pathways connecting stress and healing reviewed above, behavioural responses to stress may also affect healing (*Figure 6.1*). Psychological distress is often associated with changes in behaviour, such as decreased sleep, poor nutrition, reduced exercise, greater smoking and alcohol use, and general self-neglect (Steptoe et al, 1996; Vitaliano et al, 2002). These 'health behaviours' do not appear to account fully for the effects of stress and mood on wound healing (Ebrecht et al, 2004), as direct linkages via HPA and SNS activation clearly exist (as reviewed above). However, health behaviours help explain individual responses to stress, as they can exacerbate the effects of stress on healing. Moreover, specific patterns of behaviour are potentially modifiable and are, thus, appropriate targets for intervention to improve healing.

Sleep is an important example. Inadequate sleep commonly occurs during times of psychological stress and even mild sleep disruption is known to impair immunity, such as by disrupting macrophage and lymphocyte functions and altering proinflammatory cytokine profiles and growth hormone secretion (Leproult et al, 1997; Vgontzas et

al, 1999; Irwin, 2002). Such physical changes may in turn promote feelings of sickness, depression, and anxiety, which may further affect immune parameters relevant to healing, creating a vicious cycle involving insufficient sleep, stress, and poor health. Severe sleep disruption has been shown to impair healing specifically. One night of sleep deprivation resulted in dysregulated cytokine levels, altered natural killer (NK) cell activity, and slower recovery of skin barrier repair after tape stripping among a sample of 11 healthy women (Altemus et al, 2001).

Smoking is another key behaviour which relates to stress, pain and healing. Smokers are slower to heal both naturally occurring and surgical wounds as compared to non-smokers (Silverstein, 1992). Compared to those receiving standard care, individuals who have participated in smoking cessation programmes for 6–8 weeks before surgery have reduced wound-related and other post-surgical complications (Møller et al, 2002). The negative effects of smoking have been attributed to nicotine and other toxins in cigarette smoke, which have been shown to reduce macrophage function and oxygen levels in the blood (Silverstein, 1992). Specific to wound healing, smoking has been shown to reduce collagen deposition and alter exctracellular matrix turnover (Jorgensen et al, 1998; Knuutinen et al, 2002). Interestingly, however, although smoking is a risk factor for chronic pain, experimental studies suggest that nicotine itself has analgesic properties (Shi et al, 2010).

There are a number of other health behaviours which are both sensitive to stress and relevant to healing outcomes, including diet, alcohol use, and exercise. Nutritional deficits (e.g. vitamin deficiencies, low protein, low glucose intake), as well as heavy alcohol use, are associated with slower healing (Benveniste and Thut, 1981; Wild et al, 2010). The mechanisms involved are numerous and span the breadth of the healing process. For example, rodent studies have shown that alcohol consumption, either before or after wounding, can impair inflammatory responses needed in the initial stages of healing, perhaps via impaired neutrophil activity (Fitzgerald et al, 2007). It is unlikely that nutritional supplementation will improve healing except among those with nutritional deficits. However, regular exercise may improve healing rates. Although a three-day exercise regimen among 10 women did not affect healing (Altemus et al, 2001), a four-week exercise regimen led to 25% faster healing of punch biopsy wounds (nine days faster) in a study of 28 older adults (Emery et al, 2005), independent of (perceived) stress levels.

It is important to note that pain itself (as opposed to general stress) is known to lead to maladaptive health behaviours that are linked with healing, particularly loss of sleep, reduced exercise, alcohol use, and self-neglect (Boyapati and Wang, 2007). In university students pain was a strong and independent predictor of poor sleep quality (controlling for depression, overall perceived health, and demographic factors) among those who self-identified as having ongoing pain (Graham and Streitel, 2010). Among patients coping with leg ulcers, for whom healing is critical, pain was associated with sleep loss and less physical activity (Herber et al, 2007). Although few studies have explicitly linked pain *per se* to healing (as noted above), connections between pain and healing via health behaviours are likely to exist. Although a full discussion of these behavioural effects is beyond the scope of this chapter, it is important to appreciate their contribution to stress-impaired healing.

Summary and perspectives for the clinician

Only recently has it become accepted that chronic stress can negatively affect immunity and alter tissue repair. This has significant clinical implications, as patients undergoing chronic stress are at a higher risk of delayed healing following surgery. This occurs through activation of both the SNS and HPA axis, and is mediated primarily by the release of cortisol and norepinephrine into the periphery. Through these pathways, stress dysregulates immune functions and alters early wound repair, impairing bacterial clearance and prolonging the inflammatory phase of healing. This ultimately delays wound closure, which increases the risk for infection, post-surgical complications, and poorer surgical outcomes (e.g. decreased wound strength, greater scarring, impaired functionality).

Pain frequently accompanies the healing process, either from the wound itself or secondary to disease processes or injuries. Pain can be viewed as a unique stressor, with both physical and psychological components. It can alter immune functioning through both direct (e.g. via cytokine activation) and indirect (e.g. via stress pathways and behaviour) mechanisms, and exacerbate the negative effects of stress. Importantly, pain and stress are typically not additive, but instead synergistic in their effects. Not only does each negatively affect healing, but each promotes the other via a constellation of physiological and immune responses, and by alterations in mood and health behaviours.

The negative effects of stress and pain on healing are also potentiated by other risk factors for slowed healing, such as diabetes, obesity, comorbidity, and medication use. This is particularly relevant in the elderly, who experience stress and pain more regularly than young adults. Because all these factors increase the risks for impaired healing, infection, and post-surgical complications, elderly individuals (and others at high risk) should be given more aggressive post-surgical attention to optimise healing outcomes (Engeland and Gajendrareddy, in press).

Effort should be made to reduce psychological stress before and after surgery. Interventions aimed at reducing pre-surgical stress have had some success in improving post-surgical outcomes. Although not always possible, elective surgery ideally should be scheduled during a relatively stress-free period to promote better recovery. Post-surgical stress and pain can also impair immunity, thereby delaying healing, and should be similarly minimised as much as possible. Not only pain, but also its anticipation, can be a substantial source of anxiety for post-surgical patients, as can concerns about the healing process. Current therapeutic efforts to reduce physical pain do not typically address such concerns and should be altered to do so. An emphasis should be placed on both psychological and behavioural therapy where appropriate, particularly in chronically stressed individuals and in the aged.

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