Wound Healing Consequences of Psychological Stress

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Introduction

The well orchestrated and ordered process of wound healing involves biochemical and cellular responses that typically result in return to tissue continuity. Even so, post-surgical wound failure or infectionsin acute wounds, and chronic non-healing wounds occur and are a growing concern for health care providers. Associetal demographics evolve toward a proportionately older population with increased prevalence of chronic health problems such as diabetes, the balance is tipped toward a rise in healing problems and continued need to effectively prevent or reduce them. While much of wound healing research has addressed physiologic details of healing, there is increasing interest in and recognition of the interplay of biological, psychological and social (biopsychosocial) factors on healing. This has led to a developing body of research exploring the relationship of psychological stress to wound healing as a component ofsurgical recovery or other types of injuries where tissue repair is required (Glaser & Kiecolt-Glaser, 2005; Kiecolt-Glaser, Marucha, MacCallum, & Glaser, 1998).

Early responses to tissue injury include hemostasis, production and release of growth factors and enzymes and the migration of inflammatory cells to the site of tissue damage. The signaling and cellular processes are interdependent and establish local tissue conditions necessary for later responses that complete repair: synthesis of the provisional wound matrix and collagen, angiogenesis, epithelialization and finally wound contraction and remodeling. Studies of the effect of psychological stress have emphasized and explored effects on early post injury events. Research to date clarifiesmechanisms where psychological stress may be associated with system dysregulation and reductions in required transcriptional events, growth factor and peptide production, immune responses and clinical wound healing. In this paper we review evidence related to the association between psychological stress and healing and suggest a conceptual model to frame current and future investigations in this field.

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Stress and Wound Healing

As early as 1914, Walter B. Canon used the term stress with both a physiological and psychological reference (Canon, Bringer, & Fritz, 1914). He believed that emotional stimuli were capable of causing stress and were demonstrated by escalating physiological stress and strain. While Selye initially viewed stress as a biologic phenomenon, he subsequently demonstrated responses in rats that showed similarities in responses to both physiological and psychological stimuli (Selye, 1946).

The human responses to psychologic and physiologic stressors are multifold and varied. However, certain responses are common to this "fight or flight" system activation mediated through hormonal responses. Hormones secreted in responseto central nervous system simulation act to maintain hormonal and physiologic homeostasis. Those of interest relative to wound healing include the catecholamines epinephrine (E) and norepinephrine (NE), the glucocorticoid cortisol and the peptides interluekin-1 (IL-1) and interluekin-2 (IL-2).

The hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system (SNS) are implicated in the human stress response (Malarkey, Lipkus, & Cacioppo, 1995). Response of the HPA axis includes secretion of corticotropic releasing factor (CRF) from the hypothalamus (Chambers, Cohen,& Perlman, 1993). The secretion of CRF stimulates anterior pituitary release of adrenocorticotropin hormone (ACTH) which stimulates the release of cortisol, a glucocorticoid steroid, from the adrenal cortex. Activation of the SNS causes the release of catecholamines (E and NE) as well as dopamine (Chambers et al., 1993).

Circulating catecholamines primarily affect the cardiovascular system. Epinephrine increases cardiac output and blood flow to vital organs. It is complemented by norepinephrine which causes peripheral vascular constriction thus shifting blood to vessels dilated by epinephrine. This peripheral constriction alters perfusion to wound sites, lowering local tissue oxygen levels, and resulting indecreased availability of oxygen for healing (West, 1990; Whitney & Heitkemper, 1999).

Implications for healing relate to the local wound oxygen tension (PO_2) that is necessary for hydroxylation of proline and lysine residues on developing collagen chains. The resulting strength of scar is reduced when oxygen supply is limited. In addition, molecular oxygen is used by neutrophils and macrophages in the process of bacterial clearance (Babior, 1978). Understanding has recently expanded regarding reactive oxygen species (ROS) derived from molecular oxygen, suggesting they play an important role in directing molecular and cellular events related to tissue repair (Sen et al., 2002). ROS are produced in leukocytes through the catalytic action of NADPH oxidase and are used to kill bacteria (Babior, 1978). Oxidant production by neutrophils to control bacteria is reliant on oxygen as a substrate and requires local tissue PO_2 levels ranging from 45 to 80 mmHg (half maximal production) to greater than 300 mmHg (maximum production) (Allen et al., 1997). In addition to their role in phagocytosis, ROS are involved in healing, acting as mitogens for fibroblasts and other cells, inducing cellular adhesion in neutrophils and macrophages, and inducing expression of growth factors such as vascular endothelial growth factors (VEGF) (Lu, Youker, Ballantyne, Entman, & Smith, 2000; Sen, 2003). Consequently, biopsychosocial influences that change oxygen availability may be a factor in altering the normal course of healing and increasing individual vulnerability to healing

impairment.

Cortisol is needed for cellular metabolism and gluconeogenesis, but also inhibits the uptake and oxidation of glucose by many cells. Cortisol suppresses the pro-inflammatory cytokines: leukocyte production of IL-1, Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and decreases proliferation of fibroblasts in connective tissue leading to delayed wound healing (Padgett, Marucha, & Sheridan, 1998). Glucocorticoids have a direct effect on carbohydrate metabolism and appear to potentiate the effects of catecholamines. Chronic stress induces continued, increased cortisol levels that alone or in combination with acute stressors such as surgery may delay wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995; Peacock, Jr., 1984). Additionally, glucocorticoids antagonize the release of IL-1 and NK cells and inhibit their activity (Gatti et al., 1987). Caudell and Gallucci (1995), in their study of women's response to stress, found no early significant catecholamine or cortisol level changes but saw an unexpected increase over time of NK cells translating to a decreased immune efficiency. This would allow the presumption that under stress, with its resultant increases in catecholamine and cortisol production, there are decreases in wound perfusion and wound oxygen tension, down regulation of the pro-inflammatory cytokines necessary for adequate extra cellular matrix production and disruptions in immune system architecture. These responses to stressors then, appear to have both immediate and prolonged effects on tissue repair.

Influence of Acute versus Chronic Stress on Wound Healing

Existing data indicate that situations of both acute and chronic stress influence healing. Early research exploring acute psychological stress and healing by George and Scott (1982) suggested that meaning, acceptance and expectations of the surgery and both state and trait anxiety are all related to aspects of recovery, such as pain and limitation of activities. George, Scott, Turner and Gregg (1980) noted in 38 patients having dental surgery that those with expectations of significant post-surgical pain actually reported higher pain levels and had slower healing than those who had more positive expectations. As research in this area grew, effects of chronic stress on healing emerged. Healing implications were demonstrated in a model of naturally occurring chronic stress. In this model, caregivers of individuals with Alzheimer's disease (n=13) exhibited significantly higher levels of stress on a 10 item stress scale and significantly slower healing of forearm punch biopsies (48 days vs. 39 days) than their age and income matched controls (Kiecolt-Glaser et al., 1995). The caregivers were also found to have significantly less leukocyte production of IL-1 β mRNA, a potential explanation for the healing impairment.

SNS Mediated Responses

Activation of the sympathetic nervous system associated with perioperative stress prepares the individual for "flight" with the consequence of shunting of blood from skin to vital organs such as the heart and brain. While this response has adaptive value in some circumstances such as escaping

danger, if left unchecked it can result in peripheral tissue hypoxia, which in turn threatens optimal tissue repair. Perioperative stress responses result primarily from pain, fear, cold, surgical incision, and hypovolemia (West, 1990). Physiologically, the sympathetic nervous system is activated with the accompanying release of norepinephrine from postganglionic sympathetic nerve endings and epinephrine from the adrenal medulla. Elevated plasma catecholamines produce increased lipolysis, glycogenolysis, gluconeogenesis, heart rate, and blood pressure, as well as vasoconstriction in peripheral tissues (Cryer, 1980).

From the perspective of wound healing, reductions in peripheral blood flow decrease the delivery of nutrients and molecular oxygen that are required for wound healing to proceed. It has been demonstrated that infusions of epinephrine, even below levels that occur in response to surgery, significantly decrease peripheral tissue oxygen levels (Jensen, Jönsson, Goodson, Hunt, & Roizen, 1985), and lower levels of tissue oxygen have been associated with increased risk of wound infection (Hopf et al., 1997). Catecholamines, through regulation of lymphocytic cyclic-AMP levels, alter lymphocyte proliferation, cellular migration and antibody secretion which, in turn, can decrease the body's ability to mount a successful immune response (Madden & Livnat, 1991). Similarly, postoperative pain could impair wound healing through significant vasoconstriction (Akca et al., 1999), though clinical wound outcomes have not been confirmed experimentally. Increases in catecholamines have been shown to reduce wound cell proliferation. Saito, Tazawa, Yokoyama and Saito (1997) analyzed the effects of postoperative patients' sera on the growth of mouse fibroblasts and also analyzed the patients' sera for concentrations of adrenalin, noradrenalin and cortisol. All of the mouse fibroblast cells cultured with the sera obtained from the patients on postoperative days 1, 3 and 7 demonstrated a significantly decreased proliferative ability compared tothat of cells combined with sera obtained from the patients preoperatively. Concurrently, the investigators found elevated levels of adrenaline, noradrenaline and cortisol in the patients with peak concentrations on postoperative days 1 or 3. These results suggest that the combined increases in adrenaline, noradrenaline and cortisol had a significant antiproliferative effect on fibroblasts within the context of a rodent model.

HPA Mediated Responses

Cortisol, the primary adrenal glucocorticoid released in response to HPA activation, acts to spare glucose, mobilize amino acids, stimulate lipolysis and alter inflammatory response after injury. Adrenocortical insufficiency impairs homeostatic responses to surgical stress through hemodynamic instability, though it may not impair wound healing (Udelsman et al., 1986). Elevated cortisol levels, however, have been associated with decreases in wound healing indices. Padgett et al. (1998) found wounds on control mice healed an average 3.10 days sooner than wounds on mice that were subjected to restraint stress (RST). Serum cortisol levels inthe RST group were significantly higher than in the controls. Furthermore, when the RST-stressed animals were treated with the glucocorticoid receptor antagonist RU40555, their healing rates were comparable to those of control animals.

Glucocorticoids disrupt the kinetics of wound healing early in the process by targeting selected macrophage functions such as production of TNF-α,

IL-1 and IL-6 (Bendrups, Hilton, Meager, & Hamilton, 1993), reducing phagocytic activity (Shurin, Kusnecov, Hamill, Kaplan, & Rabin, 1994), and limiting macrophage's ability to clear wound debris (Padgett et al., 1998). The proinflammatory cytokines IL-1α and IL-1β and TNF-α stimulate expression of numerous growth factors in vitro, including keratinocyte growth factor (KGF), transforming growth factor alpha, platelet-derived growth factor AA and VEGF (Hubner et al., 1996). Production of these growth factors is decreased by cortisol's interference with macrophage functions such that early wound repair kinetics are disrupted. However, not all growth factors are similarly reduced under conditions of stress. In RST mice with full thickness open surgical wounds, TGF-β1, -β2, and -β3 were not reduced by stress (Horan et al., 2005). There was, however, significant delay of wound contraction and closure ($p < .01$) through the 5th postoperative day in RST mice compared to controls indicating altered wound healing responses through other channels.

The wound healing effects of cortisol at levels occurring within normal or near normal physiologic variation are less well understood. In adrenalectomized monkeys undergoing cholecystectomy, there were no differences in wound chamber hydroxyproline accumulation for those receiving subphysiologic, physiologic or supraphysiologic levels of replacement hydrocortisone (Udelsman et al., 1986). In 1992, Matsusue and Walser studied bursting pressure of intestinal anastomoses in adrenalectomized rats that, at the time of surgery and post surgery, had plasma corticosterone levels maintained with corticosterone pellets at, above or below normal physiologic levels. Their data showed intestinal bursting pressures that were decreased (compared to sham controls) in all groups except for the group that had plasma levels similar to normal pre-surgery levels. These data suggest that average, unstressed concentrations of corticosterone are advantageous for the support of wound healing. Higher levels that would occur in response to surgical stress or trauma may decrease healing and wound strength.

Relationship of Psychological Stress to Human Wound Repair

One difficulty in interpreting the clinical meaning of existing data is that results are largely generated from animal or cell culture models. Several investigators have noted differences in wound cell responses to glucocorticoids depending on species (Claman, 1972; Durant, Duval, & Home-Delarche, 1986; Matsusue & Walser, 1992). A growing number of studies in healthy individuals document psychological and physiological stress responses and their association with wound healing. Glaser et al. (1999) examined the relationships between psychological stress and the secretion of pro-inflammatory cytokines at the wound site. The investigators induced suction wound blisters on the forearms of 36 women and assessed stress using the Perceived Stress Scale (Cohen & Williamson, 1988) and Inventory of Life Event Scales (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978). Outcome measures included plasma cortisol, growth hormone and salivary cortisol. Women who reported more stress produced lower plasma levels of IL1-α and IL-8 and demonstrated increased levels of salivary cortisol. Though the immunological changes in peripheral blood were not reflected at the wound site, it was hypothesized that increased stress slows the appearance of the cytokines in the early

stages of wound healing and stress induced glucocorticoid levels can change the biomechanics of the inflammatory response by suppressing IL1-α production. Further data in support of this premise was reported recently by Kiecolt-Glaser et al. (2005) using a cross-over design that included 42 couples, the forearm wound blister model and conditions of stress associated with marital conflict compared to a situation of structured social support. Marital conflict was associated with slower blister healing and lower wound blister levels of pro-inflammatory cytokines IL-6, TNF-α and IL-β1. Additional data from a small sample of 24young to middle aged men with punch biopsy wounds confirms the negative stress-healing correlation and enhances our understanding of its relative importance as a factor in healing (Ebrecht et al., 2004). Higher levels of perceived stress correlated negatively withspeed of biopsy healing at 21 days post injury, while no significant relationships were identified between healing and several health related behaviors including alcohol consumption, nightly hours of sleep, hours of weekly exercise and diet composition.

Changes in growth factor production are potentially linked to delays in tissue repair through other steps involved in the healing process. Selected growth factors are associated with the transcription of enzymes involved in healing including matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). MMPs and TIMPs are involved in balancing the degradation of collagen that occurs during healing as the extracellular matrix is both synthesized and remodeled. Depression, plasma norepinephrine and cortisol levels in healthy young to older adults were studied in relation to MMP-2 protein present in blister wound fluid (Yang et al., 2002). There was no correlation between depression scores on the Beck Depression Inventory and changes in MMP-2, though none of the participants were categorized as clinically depressed. There was on the other hand, a significant positive correlation between norepinephrine and MMP-2 levels and a significant negative correlation between cortisol and MMP-2 levels, indicating modification of MMP expression with SNS and HPA activation. Changes in MMP were not associated with changes in rate of blister healing. Still, stress related modification of MMP levels may have important consequences in the context of chronic wounds, which typically show altered MMP and TIMP profiles (Mirastschijski et al., 2002; Weckroth, Vaheri, Lauharanta, Sorsa, & Konttinen, 1996). Chronic wounds often lack healing progression or are non-responsive to therapies and are characterized by excessive degradation of tissue rather than tissue synthesis (Diegelmann & Evan, 2004).

Stress, Surgery and Wound Healing

There are relatively few studies that delineate the stress-healing relationship in patients experiencing surgery. In her study of 24 patients undergoing cholecystectomy, Holden-Lund (1988) reported decreases in state anxiety, cortisol levels (postoperative day 1), and wound erythema (a subscale item on a visual wound assessment done on postoperative day 3) for those who participated in a relaxation intervention using guided imagery pre and postoperatively. This early study did not include measures of specific cellular responses or collagen synthesis, making interpretation of the wound healing implications difficult. A similar clinical outcome was observed in patients undergoing saphenous vein harvest (Wipke-Tevis & Stotts, 1998). In their sample, wound cosmetic score based on visual analogue

scale assessments was moderately and significantly correlated with pain and distress. A recent study of general surgery patients explored whether psychological stress reduces the production of growth factors and enzymes involved in wound healing. Broadbent, Petrie, Alley, and Booth (2003) assessed psychological stress and worry prior to surgery and then followed wound fluid levels of IL-1, IL-6 and MMP-9 in 47 patients having inguinal hernia repair. Higher stress scores and greater worry about surgery significantly predicted lower IL-1 levels (p=.03) and lower MMP-9 levels (p=.03). These changesmay influence surgical incision healing but the study was not designed to evaluate healing outcome of the surgical site.

In summary, a number of studies have evaluated stress and its relationship to physiologic responses involved in wound healing. Existing data emphasize the capacity of psychological stress to negatively influence events that occur early in the healing trajectory through both SNS and HPA activation. Immune related responses appear to be particularly vulnerable and may be implicated in slower wound healing, as evident by documented changes in pro-inflammatory growth factors (Glaser & Kiecolt-Glaser, 2005). Other immune changes were recently reported by Khanna et al. (2005). In a initial, very small sample (N=4) stress-sensitive transcripts in neutrophils at wound blister sites that suppress transcription of selected proteins were identified, providing further evidence of immune cell alterations. Psychological stress likely contributes to less than optimal conditions at the time of injury and in turn may yield wound complications and a poor final healing outcome. The timing of perioperative interventions close to the time of injury to reduce risk, (e.g., systemic warming and provision of oxygen designed to prevent postoperative wound infections (Greif, Acka, Horn, Kurz, & Sessler, 2000; Kurz, Sessler, & Lenhardt, 1996)) illustrate this principle. Therefore, interventions to reduce stress and concomitant SNS and HPA responses are likely to be most effective if targeted before or at the time of injury, or as soon as possible after injury.

Framework for Studying Stress Responses and Healing

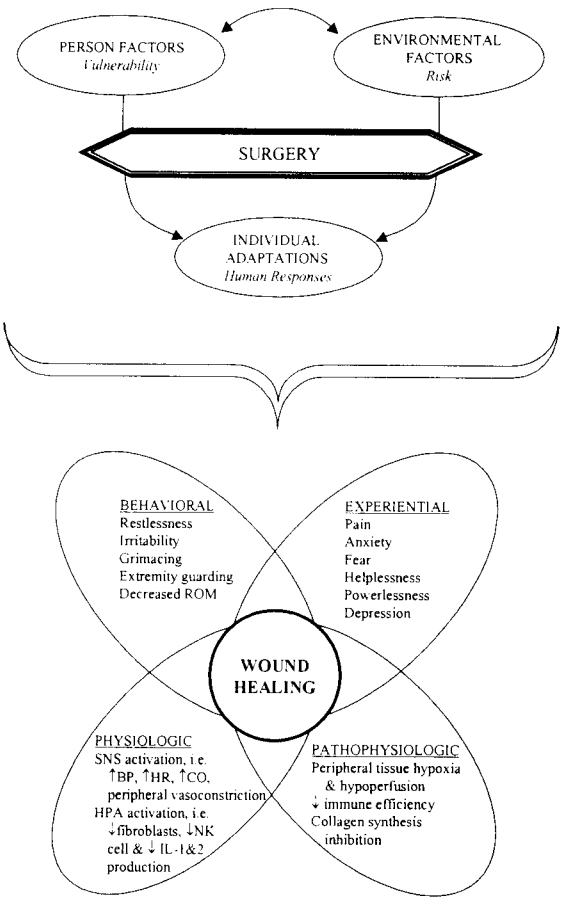

Figure 1. Framework for HUMAN RESPONSES to

SURGICAL STRESSORS

Human responses to stressors are multiple and varied. The Human Response Model (Mitchell, Gallucci, & Fought, 1991) provides a framework that identifies biopsychosocial domains and relevant individual responses to a stressful event such as surgery or trauma and the potential impact of responses on wound healing (Figure 1).

Mitchell et al. characterize human responses within four major domains: behavioral, experiential, physiologic, and pathophysiologic. Behavioral responses are directly observable and are measurable motor and verbal behaviors. Experiential responses include concepts of introspection and personal experience and may be captured by self-report. Physiologic responses include normal biologic responses and include phenomena measured by biologic instruments and methods. Pathophysiologic or altered responses result from disordered biologic functioning and are also observable by instruments of the biologic science methods. These four domains are not only interrelated with one another, but also interact with personal and environmental factors in determining an individual's responses to illness (Heitkemper & Shaver, 1989). An individual's responses to a stressor such as a surgical event and the wound healing consequences can be located and explored within this framework.

Behavioral responses that follow surgical procedures may include restlessness, irritability, grimacing, guarding of the extremity, and decreased range of motion (ROM) or mobility. *Experiential responsesto* surgery may include pain, anxiety, fear, helplessness, and depression, all of which can lead to augmented SNS and HPA activation. The *physiologic responses* to surgery and wound healing are described in detailin several other papers. Activation of the SNS and HPA as a result of surgical stress is well documented (Chernow et al., 1987; Pflug, Halter, & Tolas, 1982; Udelsman & Holbrook, 1994) and has been linked directly to the severing of afferent nerves (Chernow et al., 1987; Halter, Pflug, & Porte, Jr., 1977; Nikki, Takki, Tammisto, & Jaattela, 1972; Vlachakis, Pratilas, & Pratila, 1981). The magnitude of the response is generally proportional to the severity of the surgical stress involved. The *pathophysiologic responses* of increased HPA and SNS activation include peripheral tissue hypoxia and hypoperfusion, decreased immune efficiency and inhibition of collagen synthesis. Clinical studies addressing surgical or chronic wound populations and the effect of increased SNS and HPA activation on wound repair are limited. Studies conducted over several years have identified perioperative plasma catecholamine and cortisol levels in different surgical populations but few have included direct clinical or tissue measures of wound healing to assess the effect of these increased physiologic hormone levels on measures of actual wound repair or final healing outcome of the wound (Chernow et al., 1987; Holden-Lund, 1988; Jakobsen & Blom, 1989; Keicolt-Glaser et al., 1995; Ortega et al., 1996; Sgoutas-Emch et al., 1994). Studies that include clinically important wound healing outcomes are needed to confirm and translate results obtained in healthier populations. In addition to improving understanding of stress and its relationship to acute injury and healing, there is much to be learned about psychological stress as a factor in non-healing or slow to heal chronic wounds. Understanding the complexities of stress within the biopsychosocial context and the acute and chronic wound healing consequences is necessary to intervene effectively and prevent or reduce wound related complications and improve patient outcomes. Studies of patients most vulnerable to chronic or acute wound prob-

lems are needed and will help to validate findings obtained from dermal wound models and younger, generally healthy people. An important question that remains unanswered is whether stress related cellular and healing changes that are documented in dermal wound models also exist in individuals with surgical wounds or chronic ulcers. Finally, if these changes exist we need to have a better understanding of their relationship to clinical healing endpoints.

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Abstract

Wound Healing Consequences of Psychological Stress

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The relationship of psychological stress to human health is of interest to health care providers and researchers in the field of psychoneuroimmunology. The effect of stress on wound healing is a sub-component of study within the larger context, with relevance to both wounds that are acute and chronic in nature. Data from several studies that explore the influence of stress on events early in the trajectory of wound healing suggest that activation of both the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis are involved. There is consistent evidence that psychological stress is associated with dysregulation of immune and other responses to tissue injury that are required for healing and also to the final wound healing result. Current data pertinent to psychological stress and its wound healing consequences is reviewed and a biopsychosocial framework for future studies in this area is suggested and described.

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