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Psychoneuroimmunology and the pediatric surgeon

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ABSTRACT

The mind–body connection is receiving increasing scrutiny in a large number of clinical settings, although research has lagged in the pediatric specialties. Psychoneuroimmunology (PNI) is a novel interdisciplinary scientific field that examines the relationship of the mind to the patient's neurologic, endocrine, and immune systems by examining critical parameters such as the effects of mental stress on wound healing and infection rates. Techniques that modify a patient's emotional and mental responses to illness and surgery have positive effects on their physiology resulting in improved recoveries and higher patient satisfaction rates. In the appropriate clinical settings, an awareness of PNI can enhance outcomes for pediatric surgical patients.

Thousands of years ago, the ancient Greeks made a direct connection between our emotions and our health. This concept began to change during the Renaissance, when cadaver dissection yielded abnormal pathology. Thus "disease" became associated with abnormal "anatomy" and for centuries the role of the healer was focused upon the physical rather than the emotional aspect. In the 1800s, Freud and others recognized that a patient's mental state could cause physical symptoms. Their work led to an increasing recognition of the impact of the mind on health.[1] Sir William Osler (1849–1919), the first Professor of Medicine at Johns Hopkins Hospital, was an important proponent of the mind–body connection. He is attributed to have made the following empathic statement in 1932: "It is as important to know what kind of man has the disease, as it is to know what kind of disease has the man."[2] Despite this awareness, during most of the 20th century the advancement of the basic sciences surpassed our understanding of the importance of the individual's mental and emotional status on their disease processes. There is now a growing recognition of the impact of psychological factors upon surgical diseases and the recovery from surgical procedures. It has become clear that our emotional state, thoughts, and feelings have considerable influence on specific physical phenomenon including pain, healing, and ability to fight infection.

The last few decades have witnessed the development of sophisticated tools to visualize physical changes in the brain as it responds to physical and emotional stimuli. Functional magnetic resonance imaging (fMRI) is a non-invasive radiologic procedure that measures brain activity by detecting associated changes in blood flow.[3] fMRI monitors the flow of blood to different regions of the brain in response to a specific stimulus such as a sound, a memory, or even a touch, thus producing movies starring the brain. High-definition electroencephalogram (HD-EEG) is a 256-lead EEG that offers the combination of sub-millisecond temporal resolution and superior spatial resolution to traditional EEG. These techniques, along with others, have begun to elucidate the complex biology of how the mind interacts with the body.[4] Results from these advanced imaging techniques are leading us back to the ancient idea that "emotions are inextricably linked to our physical health."[5]

Psychoneuroimmunology (PNI) is the scientific study of interactions between behavior, the brain, and the immune and endocrine systems,[6] and thus seeks to understand the exquisite and dynamic interplay between the mind and the body.[7] It fits under the umbrella of "Mind–Body" medicine, or the more recent name of "Integrative Medicine." George Solomon coined the term psychoimmunology[8] and Ader and Cohen changed the term to psychoneuroimmunology in 1975.[9] In 1991, Bovbjerg[10] postulated that psychosocial influences on immune function could potentially provide an explanation for the association between psychosocial factors and cancer prognosis. In 1995, PNI received significant exposure with a Lancet review article,[11] followed by a rapid increase in subsequent research of the effects of psychosocial factors on disease states.[12–20]

The brain and immune systems form a bidirectional communication network. The immune system operates as a diffuse sense organ, with activation of immune cells producing physiological and behavioral changes that are collectively called sickness.[21] The

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immune system informs the brain about events in the body as it functions to promote recuperation. The "fight-or-flight response" is one manifestation of this immune–brain circuitry whereby the body's need to respond to a perception of physical danger in an anticipatory fashion is coordinated via this interaction.[21] Two of the most important and well-described pathways in the "fight-or-flight response" are the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal axis (HPA). In response to acute stress, the SNS stimulates the adrenal glands to release the catecholamines adrenaline and noradrenaline. Likewise, the HPA axis releases cortisol into the bloodstream under the control of adrenocorticotrophic hormone (ACTH). In addition, cytokines are also modulators of the HPA axis and do so in a bidirectional way.[22] Inflammatory cytokines such as interleukin-1 (IL-1), IL-2, IL-6 and tumor necrosis factor-alpha (TNF-alpha) stimulate ACTH and thus cortisol,[23,24] while ACTH and glucocorticoids can modulate proinflammatory cytokine production.[25,26]

There is a complex biochemical link between stress, the immune system, and illness. When stressed, the brain activates the adrenal glands resulting in the release of adrenaline and cortisol. These hormones have numerous effects that are essential for survival. However, a byproduct of that stress response is suppression of the immune system, making the patient vulnerable to infection, concomitant diseases, and poor wound healing. This has particular importance for surgical patients whose recovery is dependent upon timely healing of incisions, anastomoses, and wounds.

The impact of stress on wound healing has been well studied. Kiecolt-Glaser et al.[27] reported in 1995 on the impact of chronic stress on wound healing. A cohort of subjects who were caring for a relative with Alzheimer's disease underwent punch biopsies and their wounds were compared to a control, non-stressed group. Wound healing took significantly longer in the stressed caregivers than in controls (48.7 vs. 39.3 days, $p < 0.05$). In addition, peripheral-blood leukocytes from stressed caregivers produced significantly less IL-1 beta mRNA in response to lipopolysaccharide stimulation than did controls' cells. In a related project, hostile marital behaviors were evaluated.[28] Couples' blister wounds healed more slowly and local cytokine production (IL-6, TNF-alpha, and IL-1beta) was lower at wound sites following marital conflicts than after social support interactions.

Additional studies have looked at aspects of wound healing that are more analogous to stressors seen in an acute surgical situation. Marucha et al.[29] placed two 3.5-mm punch biopsy wounds sequentially on the hard palate of 11 dental students, the first timed during summer vacation, whereas the second was placed 3 days before the first major examination of the term. Students took an average of 40% longer to completely heal the wound during examinations, and production of IL-1beta mRNA declined by 68% during examinations. McGuire et al.[30] examined the role of postsurgical pain and mood in a group of patients undergoing elective gastric bypass surgery. Greater acute postsurgical pain and greater persistent postsurgical pain were significantly associated with delayed healing of a 2.0-mm punch biopsy wound, providing the first evidence that pain plays an important role in postsurgical wound healing.

It has been observed that occasionally after extirpation of a primary tumor, distant metastases appear in short order, thereby giving the appearance that definitive surgery somehow "spread" the tumor. Although this observation is mostly anecdotal and not well studied, Judah Folkman hypothesized that, in some cases, the primary tumor secretes something that keeps microscopic metastases at bay. Indeed, using this hypothesis, he isolated the antiangiogenic peptides angiostatin and endostatin.[31,32]

Psychoneuroimmunology (PNI) offers an alternative explanation. Control of tumor metastasis is performed by cell-mediated immunity (CMI) as well as other non-immunological factors. Stress impacts the immune system,[11,33] and the immunosuppression that occurs after surgery may be deleterious to metastasis control.[34] This immunosuppression may be directly related to the physiologic stress response from the surgery, or the psychological component related to the patient's response to this disease.

Mavros et al.[35] performed a systematic search to identify studies examining the association of preoperative psychological variables or interventions with objectively measured, early surgical outcomes. In the 16 published studies, anxiety, anger, active coping, and subclinical depression appeared to complicate recovery, while optimism, religiousness, anger control, and low pain expectations seemed to promote healing. Psychological interventions (guided relaxation, couple support visit, and psychiatric interview) also appeared to favor recovery.

Looking at objective parameters, Blomberg et al.[36] examined associations between psychological adaptation indicators (mood and quality of life—QOL) and cytokine production in women who had recently undergone surgery for early-stage breast cancer. Lower anxiety related to greater production of the interleukin-2 (IL-2). Greater positive mood (affection) related to greater production of IL-12 and interferon-gamma (IFN-gamma) and better QOL related to greater production of tumor necrosis factor-alpha (TNF-alpha).

While there is minimal data on the effect of stress on pediatric wounds, there is a plethora of data on the effect of stress on other aspects of a child's health including the growing evidence that maternal prenatal stress may produce lasting effects on the infant's health status, immune system, and neurocognitive development.[37] A landmark evaluation of the long-term effects of infant and pediatric stress is the Adverse Childhood Experience (ACE) study.[38,39] The ACE study included 17,337 adult HMO members and retrospectively assessed eight adverse childhood experiences including abuse, witnessing domestic violence, and serious household dysfunction. The number of ACEs (ACE score) was used as a measure of cumulative childhood stress. More than half of respondents reported at least one and one-fourth reported two or more categories of childhood exposures. The results showed that there was a graded, "dose–response" relationship between the number of categories of childhood exposure and each of the adult health risk behaviors and diseases that were studied ($p < 0.001$). Persons who had experienced four or more categories of childhood exposure, compared to those who had experienced none, had 4- to 12-fold increased health risks for alcoholism, drug abuse, depression, and suicide attempt; a 2- to 4-fold increase in smoking, poor self-rated health, greater than 50 sexual intercourse partners, and sexually transmitted disease; and 1.4- to 1.6-fold increase in physical inactivity and severe obesity. The number of categories of adverse childhood exposures also showed a graded relationship to the presence of adult diseases including ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease. Multiple subsequent studies have demonstrated the broad and profound long-term impact of childhood experiences on adult mental health,[40] disease,[41,42] obesity,[43] risk behaviors,[44,45] and addiction.[45] The authors conclude that the prevalence of adverse childhood experiences is clearly a major determinant of the health and social well-being of the people of the nation.[46]

An additional concern is that these children may not be receiving optimum intervention to obviate the subsequent physical and mental sequelae from these ACEs. Ameratunga et al.[47] noted "while typically the child's physical injuries are assessed and dealt within the hospital setting, it is acknowledged that their emotional needs and concerns typically are not." Children who are hospitalized in the absence of a supportive system are of great concern as it relates to physical and mental health outcomes and long-term well-being. In addition, the non-accidental trauma