Virtually all people and animals experience pain at some time in their lives. The pervasiveness of pain makes it important to pursue observations of potential immune dysfunction due to pain. These observations date back only 20 years, starting with reports from the laboratory of John Liebeskind that footshock suppresses natural killer (NK) cell activity and promotes tumor spread in the rat. Of relevance to the present survey (and discussed below) is that both studies also showed that opioids compromise immune function and promote tumor spread. Postoperative immune suppression had been documented years before the footshock studies, but the observed immune suppression was not attributed to perioperative pain. This issue of *Pain: Clinical Updates* reviews current knowledge regarding the impact of acute pain and opioids on immune function. It emphasizes the role of NK cells, a subpopulation of lymphocytes that plays key roles in cell mediated immunity, the first line of immune defense. Without prior sensitization, NK cells recognize and kill a variety of virally infected or neoplastic cells and initiate protection against some bacterial pathogens.

**Observations linking impaired postoperative immune function to pain date back only 20 years.**

**Acute Pain and Immunity**

Animal studies of the effects of experimental pain upon immune function have employed stimuli such as footshock, tail shock, and surgery. In addition to suppression of NK cell cytotoxic activity, pain from intermittent shock to the foot or tail impairs proliferative responses of mononuclear or spleen cells to mitogens and IgG antibody responses to novel antigen exposure. In humans, similar evidence for widespread suppression of immune function following surgery involves NK cell activity, lymphocyte responses to mitogen stimulation, and cytokine secretion by immune cells. The magnitude of immune suppression following surgery has been shown to be proportional to the magnitude of the invasiveness of procedures in both animals and humans.
Many aspects of immune function in preclinical and clinical studies are impaired by acute nociception.

Is It the Pain?

Pain is an exquisite stressor. Because pain (among other stressors) has both psychological and physiological components, to understand its effects it is necessary to clarify the relative contribution of each. One approach, used for over 30 years, is to evaluate the impact of nonpainful stress on immunity.\textsuperscript{13,14} The linked responses of the central nervous system (CNS) and the hypothalamic-pituitary-adrenal (HPA) axis to perceived stress involve a complex network of neurosensory signals including catecholamines, peptides such as endorphins, and corticosteroids such as cortisol. There is bidirectional communication between the immune and neuroendocrine systems, each affecting the other, as well as within-system interactions. Activation of the CNS and HPA axis affects immune function via multiple mechanisms, and immune changes also impact these two linked responses. Acute stressors such as public speaking, time-pressured arithmetic, and school examinations have consistently demonstrated suppression of NK activity and disruption of the balance of cell-mediated and humoral immune activity.\textsuperscript{15}

There is bidirectional communication between the immune and neuroendocrine systems, each affecting the other, as well as within-system interactions.

The impact of a given stressor on immune function is multidimensional and evolves over time. Single immune and neuroendocrine measurements are snapshots at the time of sampling, and do not capture the dynamic nature of immune and neuroendocrine responses to an event, nor their return to baseline. Techniques such as multiple blood samplings over time via an indwelling catheter can provide a better picture, but for the most part, blood and saliva samples have been reported at single or infrequent time points after a stressor. Given the dynamic nature of biological responses to stress, varying the sampling time can give distinct apparent results with different underlying explanations. For example, changes in aggregate NK activity may equally well reflect a change in the cytotoxic activity per NK cell or a change in the percentage of circulating NK cells. Thus, a decrease in NK cell activity can be explained by either a reduction in the activity per NK cell or a reduction in the number of circulating NK cells, or both. Among the first responses to a stressor is activation of the sympathetic nervous system, resulting in the release of catecholamines. During sympathetic activation, white blood cell (WBC) subpopulations mobilize from the marginating pool at stressor onset and then remarginate upon its resolution. Because $\beta_2$-adrenergic receptors on NK cells mediate suppression of their cytotoxic capacity,\textsuperscript{16} one might observe varying levels of immune competency at different sampling times attributable to demargination and/or elevated circulating levels of catecholamines. For example, sampling at the time of peak NK cell concentrations might reveal an increase in NK activity attributed to the greater number of circulating NK cells. Indeed, such may be the case in a recent human study that found electric shock to be NK-activity enhancing.\textsuperscript{17}

Further complicating this picture in postoperative models is the inevitable tissue damage and the associated release of inflammatory mediators such as prostaglandins.\textsuperscript{18} For example, prostaglandin $E_2$ ($\text{PGE}_2$) is a major contributor to both peripheral and central sensitization and hyperalgesia,\textsuperscript{19,20} but it also suppresses NK activity\textsuperscript{21} and enhances production of interleukin (IL)-6.\textsuperscript{22} Together with IL-1 and tumor necrosis factor (TNF)-$\alpha$, IL-6 promotes synthesis of acute phase proteins, induces fever, and mobilizes energy stores. IL-6 also helps initiate local antimicrobial defenses, wound healing, and behavioral guarding of the injury site via promotion of hyperalgesia.\textsuperscript{4} As the magnitude of injury becomes increasingly severe, so dooes the magnitude of these responses. The responses then may cease being homeostatic and can compromise survival following major trauma.\textsuperscript{23}

Surgery, Pain, and Immunity in Humans

If pain is indeed a factor in postoperative immune impairment, then it is logical to surmise that more effective analgesia could improve outcomes. Indeed, direct comparisons of inhalational versus epidural or spinal anesthesia for surgical procedures below the waist indicate that immune function is better preserved with spinal nociceptive blockade.\textsuperscript{10,24} Epidural anesthesia and analgesia are associated with fewer postoperative infectious complications\textsuperscript{25} than general anesthesia alone. In contrast, studies of perioperative systemic opioid administration have shown mixed results related to NK activity.

Clinical epidemiological studies suggest that undertreated postoperative pain compromises immune function.

A key function of NK cells is anti-tumor immunity.\textsuperscript{7} There is substantial corroborating evidence in humans that NK function is important for cancer resistance. Decreases in NK activity during the perioperative period are associated with greater rates of cancer recurrence and mortality. Specific cancers for which such relationships have been found include those of the breast, head and neck, colon and rectum, and lung.\textsuperscript{26}

Surgery, Immunity, and Cancer Metastasis in Animals

As opposed to observations in humans, which must rely on epidemiology and correlations, animal studies provide convincing evidence for a causal link between low NK activity and
increased susceptibility to metastatic outcomes. Although no animal model is a perfect reflection of the clinical metastatic process, there are obvious, major ethical and methodological obstacles to experimentally studying this phenomenon in humans. Studies in animals using tumor lines whose growth is modulated by NK cells have implications for understanding the in vivo biological significance of this interaction. In well-established mouse and rat tumor models, animals given antibodies or drugs to reduce NK activity have more extensive and aggressive metastases, while those given drugs to augment NK activity appear relatively protected.

**In well-established mouse and rat tumor models, antibodies or drugs that reduce NK activity promote more extensive and aggressive metastases, while drugs to augment NK activity are relatively protective.**

Not surprisingly, for a variety of tumor models in mice and rats, the metastatic process is exacerbated by surgery and postoperative recovery. The earliest findings were documented in 1958. The first preclinical study to test the hypothesis that perioperative analgesia influences postsurgical enhancement of tumor growth was published 33 years later by Yeager and Colacchio. They provided pre- and postoperative morphine to rats undergoing and recovering from major abdominal surgery and found that this regimen significantly reduced tumor burden compared to saline-injected control animals. Since then, multiple reports have demonstrated a surgery-induced worsening of metastatic outcomes, and its amelioration by systemic administration of the opioids morphine, fentanyl, and tramadol, and the nonsteroidal anti-inflammatory drug (NSAID) indomethacin. Additionally, spinal injection of a local anesthetic combined with a very low dose of morphine also inhibited surgery-induced increases in metastatic susceptibility.

Most of these studies employed experimental designs to rule out some drug effect other than pain relief, such as a direct impact on the tumor or on NK cells. A simple 2 x 2 design as was used in the majority of studies (surgery versus no surgery, by treatment versus no treatment) would exclude that possibility. Virtually all studies that used this design observed that drug treatment improved tumor resistance only in the operated animals, i.e., in the presence of postoperative nociception. The spinal blockade findings also bolster the argument that antinociception is essential for protection from the tumor-enhancing effects of surgery.

In contrast, and paradoxically, another well-established literature indicates that opioid administration suppresses immune function and metastatic resistance. To reconcile that literature with the strong experimental evidence for beneficial effects of opioids on perioperative in vivo NK function and tumor resistance, several points must be made. First and foremost is that opioids most clearly improve in vivo cancer resistance only in the context of postoperative nociception. Studies that found deleterious immune and metastatic effects of opioid administration tested normal animals under basal conditions. Indeed, some non-operated control groups in studies of animals undergoing surgery studies confirm that morphine administration in the absence of nociception results in a minor (generally statistically insignificant) stimulation of tumor growth. Second, the surgical studies used opioid doses in the analgesic range, but most studies that found opioids to be immunosuppressive used much higher doses than those necessary to produce analgesia. Finally, several studies report behavioral observations consistent with postoperative pain relief from systemic opioids, NSAIDs, or spinal anesthetics. Specifically, untreated animals were inactive and inattentive to their environment soon after abdominal surgery, while animals given systemic analgesics exhibited activity levels that were not different from those of unoperated animals.

**The beneficial effects of perioperative opioid analgesia upon immune function contrast with the immune impairment seen when high doses of opioids are given to unoperated animals under baseline, resting conditions.**

**Conclusions and Implications**

Strong evidence indicates that acute pain is an acute stressor that impairs immune function, notably NK activity. Given the key role played by NK cells in defending the organism against viral and bacterial invasion, and inhibition of tumor metastases, it would seem particularly important to preserve immune capacity in those undergoing surgery. Encouragingly, there is direct evidence in animals and indirect evidence in humans that effective perioperative pain control preserves perioperative NK function. Animal studies show that optimal analgesic techniques provide significant protection against the tumor-promoting effects of surgery, documenting an important biological consequence of NK suppression. Although animal findings cannot be directly applied to humans, existing clinical evidence is consistent with these preclinical studies. In aggregate, the evidence that poor pain control promotes tumor growth after operations (especially in the case of individuals with potentially metastasizing tumors) further strengthens current humanitarian, ethical, economic, and physiological arguments that perioperative pain relief is not simply a high priority, but a fundamental human right.
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Erratum
In Volume XII, No. 7 of Pain: Clinical Updates, entitled “Anxiety and Pain,” the word “pain” should be changed to “analgesic pharmacotherapy” and the word “anxiety” should be changed to “psychopharmacology” in Figure 1. The legend should read: “Overlapping circles emphasize the concordance between analgesic pharmacotherapy and psychopharmacology.”