

How to Move Pain and Symptom Research From the Margin to the Mainstream

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Abstract: Pain, dyspnea, nausea, and other physical symptoms receive rather little study despite their major public health impact and the similar neural circuitry that makes these symptoms tractable therapeutic targets. Pain accounts for more than 20% of medical visits and 10% of prescription drug sales but only 0.6% of National Institutes of Health research funds. Clinical pain research remains clustered in the few clinical specialties of the founders of the field—neurology, anesthesia, cancer, and dentistry. Remarkable recent advances in basic science have not been widely applied by cardiologists, gastroenterologists, urologists, and gynecologists. Research funding in dyspnea and nausea is an order of magnitude smaller than funding in pain, despite mechanisms that may be common to all three. Political pressure from an aging population may soon influence funding agencies to train additional researchers in these areas. Academic health centers that develop the cross-disciplinary infrastructure to conduct this research will win major shares of this influx of funding and improve the diagnosis and management of many diseases.

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Natural selection has robustly wired the neural pathways for pain, nausea, and dyspnea to trigger action. Each of these symptoms arises in pathways projecting to areas of the brainstem, hypothalamus, and cerebral cortex that generate aversive mood states and escape behaviors (Fig 1).^{10,17,35,41} Patients with advanced cardiopulmonary disease, cancer, infection, or renal failure report pain, nausea, or dyspnea on most days.¹⁴ Given this neural wiring, it is not surprising that these symptoms dominate the patient's experience, cause depression and anxiety, and degrade quality of life.

The puzzle that I explore in this article is that unlike individual organisms, the medical research system has responded very weakly to these symptoms. Although pain costs the United States an estimated \$79 billion a year in lost work productivity⁴⁵ and results in more than 20% of visits to physicians⁴³ and 10% of drug sales,²² only 0.6% of the current budget of the National Insti-

tutes of Health (NIH) is devoted to basic and clinical research on pain (NIH Budget Office, communication to American Pain Foundation, June 2002). This figure seems particularly low in view of breakthroughs in molecular understanding of pain processing.^{23,52} These breakthroughs have made possible advances in the management of pain caused by surgery, cancer, nerve injury, and migraine.⁴⁹ Research funding for dyspnea and nausea is approximately an order of magnitude smaller than funding for pain.^{13,18}

Foley and Gelband¹⁸ have discussed the "top-down" actions funding agencies might take to expand pain and symptom research. In this article, I focus on a bottom-up approach, suggesting the historical organization of medicine into specialties based on structural diseases has confined scientific discourse on pain and symptoms to a few specialties. Dissemination of basic scientific and clinical research insights across specialty lines, I argue, will result in

Editor's note: The commentary above by Mitchell Max, MD, entitled "How to Move Pain and Symptom Research From the Margin to the Mainstream," underscores the need for broader research in the field of pain. This is the first of several invited commentaries that will appear in *The Journal of Pain*, each addressing research needs in different disciplines of American Pain Society (APS) membership. These commentaries were invited from leading figures in the APS in observance of The Decade of Pain Control and Research, declared by Congress beginning Jan. 1, 2001. Authors were asked to critically evaluate the status of pain research and to identify areas that need more focus, as well as areas that offer significant promise.

Max notes that more than 20 percent of medical visits are attributed to pain, as are 10 percent of drugs sales, but that federal research funds are scant. Pain results in unnecessary suffering and costs the U.S. billions of dollars per year in lost work productivity. While strides have been made

in some areas of pain research, others remain unexplored. It is hoped that this and other commentaries to follow will promote research with a focus on improving care, enhancing professional awareness, and influencing federal policy.

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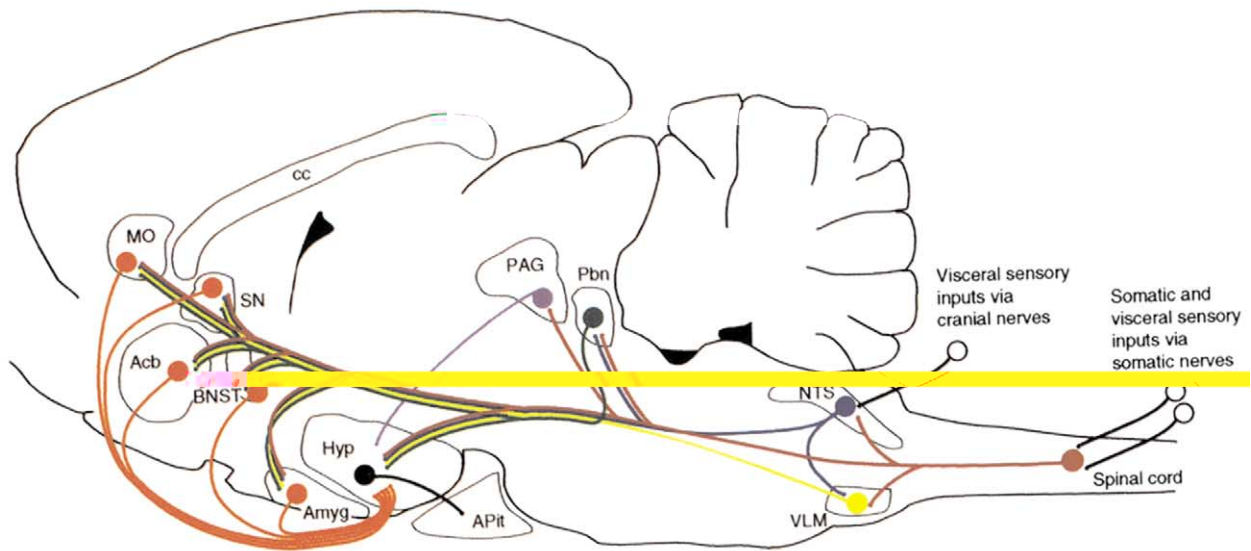


Figure 1. Schematic illustration shows neural pathways conveying somatosensory and visceral information to the hypothalamus and other limbic structures mediating mood, sleep, appetite, and endocrine and cardiovascular function. Line drawing represents sagittal view of the rat's brain. Sites of origin (*large circles*) and termination of neural pathways are indicated. Acute pain alters many of these functions in humans, but a better understanding of the mechanisms and consequences of chronic pain for these functions might decrease the morbidity of painful illnesses. Acb, nucleus accumbens; Amyg, amygdala; APit, anterior pituitary gland; BNST, bed nucleus stria terminalis; cc, corpus callosum; Hyp, hypothalamus; MO, medial orbital cortex; NTS, nucleus tractus solitarius; PAG, periaqueductal gray; Pbn, parabrachial nuclei; SN, septal nuclei; VLM, ventrolateral medulla. (Reprinted from Burstein R: Somatosensory and visceral input to the hypothalamus and limbic system. *Prog Brain Res* 107:257-267, copyright 1996, with permission from Elsevier.)

rapid expansion of the number of successful grant proposals from a broad range of subspecialties.

I focus on the triad of pain, nausea, and dyspnea not only because of their high prevalence among critically ill patients but also because a reasonable part of the neural circuitry of these symptoms is already understood. As a clinical neuroscientist, I can readily make analogies among them. However, other symptoms, such as fatigue^{1,5,50} and anxiety or depression triggered by disease,² may have great public health impact and deserve additional study.

Pain Research Remains Concentrated in a Few Disease Areas

In 1996, I conducted an unofficial count of the NIH extramural and intramural clinical pain grant database to prepare for a lecture. I was astounded by the mismatch between the organ distribution of the research and the pain complaints in the general population. There were 10 to 20 grants each for pain due to neuropathy, headache, cancer, surgery, spinal disease, and dental and oral disorders.³³ Only 1 grant each was related to cardiac, obstetric and gynecologic, and urologic pain, 2 to gastrointestinal pain, and none to neck pain, notwithstanding the fact that chest pain, abdominal pain, and neck pain are 3 of the most common reasons for visits to physicians.³ This relative dearth of research into visceral pain almost perfectly matched the specialties of the members of the International Association for the Study of Pain, whose clinical research members are predominantly anesthesiologists, neurologists, neurosurgeons, dentists, and nurses, with a sprinkling of oncologists. A look at the fiscal year 2003 Computer Retrieval of Information on Scientific Projects (CRISP) database¹³ suggests

that a few new investigators have augmented the list of clinical grants related to gastrointestinal pain and interstitial cystitis. However, cardiac, obstetric, gynecologic, and neck pain remain almost completely unaddressed.

These data suggest a historical explanation.^{4,32} Until the late 1700s, pain was a major focus of medical thinking.¹⁶ After the autopsy began to shape medical thinking in the early nineteenth century, medical specialties, practice routines, and research agendas developed around the organ-based structural disease model.^{20,31,32,40} Pain was demoted to a mere clue to structural diagnosis; it was not a high-priority subject for study. To correct this neglect, anesthesiologist John Bonica and neurophysiologist Patrick Wall in 1973 organized the International Society for the Study of Pain. Despite the great progress made by the members of this society in the past 3 decades, meeting attendance has remained largely limited to the few specialties represented at the organizing meeting. Members of other specialties remain largely unaware of opportunities offered by new basic and clinical methods of research into pain. Pain researchers' appeals to leaders of medical schools or organ-based funding institutes to proactively expand pain and symptom research have repeatedly failed. This is not because these leaders lack compassion—we have treated patients with many of them—but because without a countervailing institutional accountability for symptom research, symptom initiatives cannot overcome the natural pull to favor the institution's established investigators and programs.¹⁸

The dearth of clinical research into visceral pain is a missed opportunity. Many lines of evidence suggest that the mechanisms, and hence the management, of various

types of visceral pain may differ from bone, joint, or nerve pain. A larger proportion of visceral than somatic afferent pain fibers have peptidergic neurotransmitters.²⁶ Once pain signals have reached the spinal cord, pelvic visceral pain may be transmitted by a different mix of spinal pathways than is somatic pain.⁵¹ The optimum therapy for visceral pain may differ from treatments developed with the standard industry studies of postoperative and arthritic pain.

Consider the recently discovered peripheral nerve terminal receptor hypothesized to signal angina pectoris, acid-sensitive ion channel 3 (ASIC3).⁴⁷ In the 4 years since basic scientists published the finding that amiloride, a widely available diuretic, blocks this channel,¹² no clinical cardiology researcher has studied amiloride in angina. (A small controlled study before the discovery of ASIC3 had shown an increase in angina patients' exercise tolerance with amiloride, and this effect was ascribed to an unknown effect of a diuretic.³⁸) This neglect of a discovery that might benefit approximately 6 million Americans illustrates the strong influence of the silo-like traditional medical research structure.

Can New Discoveries in Pain Physiology Refine Our Diagnostic Methods?

Some of the maxims relating temporal and spatial patterns of pain to diagnosis are centuries old, and all predate the modern explosion of sensory neuroscience. The clinician rarely has trouble locating a lesion causing complaints of the distal limbs, the nerve fibers of which densely map onto many segments of the cervical and lumbar enlargements of the spinal cord. Diagnostic dilemmas abound, however, in pain of the proximal portions of limbs, of the trunk, and of viscera, the nerves of which converge on relatively few spinal neurons.¹⁹ In the emergency department, we may be hard pressed to differentiate pain from an ischemic heart, acid-irritated esophagus, ascending aortic aneurysm, or inflamed costochondral joint. After months of diagnostic testing, the wisest surgeon may not know whether hip pain will be relieved by a hip or by a spinal operation. However, application of a new generation of physiologic principles underlying visceral and musculoskeletal pain referral patterns^{6,21,42} might enhance the diagnosis of structural disease as well as the physician's ability to provide comfort.

Basic Neuroscience Research: Lag of Dyspnea and Nausea Research behind Pain

Nausea and dyspnea are far less studied than pain (with the exception of the established industry niche of oncologic antiemetics). Moreover, nausea and dyspnea researchers have not applied the novel ideas developed in the past 20 years of pain neurobiology to these other 2 symptoms. For example, pain researchers have defined distinct markers and receptors on unmyelinated peripheral pain afferents that specify function²³ and offer targets for selective drug treatment, but my literature search showed no use of these markers by nausea or

dyspnea researchers to examine the similar types of unmyelinated afferents involved in those symptoms. To take another example, the dominating concept in recent pain research has been plasticity: painful input to the nervous system changes the structure of the sensory cells in such a manner that the same stimulus causes more action potentials when repeated. A PubMed search³⁹ conducted as I wrote this essay yielded 433 hits for the search terms "pain and plasticity" but only 2 for "nausea and plasticity" and none for "dyspnea and plasticity."

Medical and Psychiatric Implications of Spinal Projections to Hypothalamus and Limbic System

Every medical and dental student learns that detailed information about pain location, quality, and intensity is projected to the brain by way of the spinothalamic tract. However, another large projection system that courses from spinal dorsal horn to hypothalamic and limbic nuclei was independently described in the 1980s by several laboratories.^{10,41} This largely neglected system may be more important than the spinothalamic system in generating the misery and medical consequences of pain and other visceral symptoms. Rami Burstein, one of the discoverers of this system, and his colleagues described the specific pathway by which hypothalamic projections of trigeminal nociceptors may account for the anorexia often accompanying migraine.²⁹ One can also speculate that fear and avoidance of normal activities, so important among patients with chronic pain and often resistant to verbal reassurance, may result from spinal projections to the amygdala. Because the neurotransmitters at synapses linking pain projections to limbic structures may differ from those originating from the cerebral cortex, understanding these pathways might lead to antidepressants and anti-anxiety drugs specific for altered mood caused by pain. The changes of sleep, endocrine, cardiovascular, and immune function that accompany acute pain have had little rigorous study in chronic pain. All might be better understood and managed through study of these forebrain projections.

Barriers to Innovation in Pain Research by Private Industry

One might argue that the mismatch between the proportions of drug sales and NIH research devoted to pain suggests that we can leave this research to industry, with the market's "invisible hand" guiding companies to neglected clinical areas. Such an argument is plausible but wrong. In each major market segment of new pharmaceuticals for pain and symptom control—including sustained-release opioids, cyclooxygenase 2 antagonists, drugs for migraine and neuropathic pain, and oncologic antiemetics—industry did not invest until academic research had demonstrated proof of concept in animal models and developed replicable clinical trial methods. During dozens of consultations with pharmaceutical companies, I have watched clinical research executives reject their academic consultants' advice to test drugs in diseases and pain types other than the usual handful of commonly studied conditions: postop-

erative pain, dysmenorrhea, headache, osteoarthritis, and diabetic neuropathy. The researchers were dissuaded from these attempts because of the possibility that the first few studies of a new condition might fail while the methods were being refined. Perhaps the short tenure of industry clinical scientists, who seem to be promoted or to leave a company after a year or two in one job, may account for such risk-averse behavior. This caution may be wise for a cash-strapped startup company with one bullet in its gun but is irrational for a large company that could reap billions of dollars by taking the lead in a new market niche.

The development and marketing of inventions can have an impact that goes beyond the increments in effectiveness produced by the invention. Most major innovations change participants' views of an area of concern by moving what was formerly a marginal practice to the center.⁴⁴ For example, when patient-controlled analgesic (PCA) devices were conceived, hospital patients controlled little more than their meal choices. Medical procedures, especially drug administration, were firmly under the control of physicians and nurses. The conception and implementation of PCA machines disclosed a large class of activities—recognition and management of symptoms—that would be better controlled by patients. New technologies allowing patients to report high-intensity symptoms may have as broad an effect (CS Cleeland et al, unpublished data). Academic pain and symptom researchers rarely use the full force of private entrepreneurship in our efforts to alter patterns of care and research. We might improve treatment faster if we were to use our scientific society meetings to bring together academic researchers with representatives of government small business funding programs, venture capitalists and small company executives, or business professors.

Advantages of Studying Pain and Symptoms Together

I argue earlier that the similarities in neural processing of pain, nausea, and dyspnea might offer immediate advances at the bench if basic scientists were to study them together. Moreover, the similarities of clinical research challenges among pain and other symptoms, including measurement of symptom intensity, the placebo effect, and the effects of mood, have been recognized since Henry Beecher's pioneering work.⁷ Clinical researchers in palliative medicine,³⁴ alternative medicine,²⁸ somatization,²⁴ dentistry,^{25,46} and nursing¹⁵ have begun to adopt this cross-cutting approach.

Cross-Fertilizing the Approaches of Pain and Symptom Researchers and Mainstream Specialists

Scholars of innovation have noted the large and rapid returns that can result when diverse disciplines first explore a common concern and combine their well-honed practices.⁴⁴ The following developments in pain research exemplify this principle: (1) *Pain as an indicator of malignant spinal cord compression*. Twenty years ago, National Cancer Institute-funded centers integrating neurologist pain specialists with oncologists promulgated

new diagnostic algorithms to prevent epidural cord compression,¹¹ improving both function and systemic treatment opportunities for cancer patients. (2) *Refractory angina pectoris*. European cardiologists and pain clinicians are reporting that approaches developed in back pain clinics can be used to reorganize standard algorithms for the management of angina (<http://www.angina.org/index.htm>), markedly reducing the numbers of coronary procedures and heart transplants.³⁰ (3) *Rheumatological pain as a window into the physiologic mechanisms of chronic pain*. Although most patients visit rheumatologists because of pain, this field's research has focused on immunology with rather little emphasis on pain. Research leaders should note the gains made by several cross-cutting efforts. Jon Levine, the only pain neuroscientist trained in clinical rheumatology, has shown that a combined examination of peripheral immune and inflammatory processes and pain initiation by peripheral nerve yields a steady stream of surprising discoveries.²⁷ Arthritis clinical trials groups, larger and more experienced than pain research groups, are becoming innovators in pain clinical trial methods.⁸

Model for Increasing Clinical Research Funding at a University

An academic health center leader or philanthropist interested in expanding the school's research funding might consider the successful track record of psychologists trained in pain research. Unlike physician pain researchers, who have had difficulty accessing patient groups, psychologists have consistently reached out to a broad range of clinical specialties to win grants in such understudied areas as the pain of cardiac, gastrointestinal, and genitourinary pain, dyspnea, and nausea.^{9,36,37,48} In several academic health centers, the combined expertise of a psychologist and physician specialists in diseases with little previous symptom research was so successful in winning NIH grants that the psychologist had to stop writing new grants. The success of these investigators suggests that a university official or philanthropist might expand this model into a continuing core "pain and symptom grant-writing team" that includes expertise in psychology, basic neuroscience, clinical pharmacology, epidemiology, oral medicine, nursing, and other relevant disciplines. Such a strategy might almost double the funding of many disease-oriented clinical specialists by adding a pain or symptom grant in the same population the specialist is already recruiting for a disease treatment grant. At some institutions, such cross-disciplinary research cores already exist in dental or nursing schools, and costs could be shared. Although a cross-specialty bench-to-bedside pain and symptom proposal does not to my knowledge fit into any NIH funding category, I predict that philanthropically funded efforts would generate enough innovative research projects to demonstrate the value of this model to NIH and industry funders.

Conclusion

The slow rate of increase of clinical visceral pain, dyspnea, and nausea research shown in the CRISP database from 1996 to 2003 suggests that a laissez-faire approach

may leave another generation of patients to suffer unnecessarily. Now that we can elucidate and potentially manage pain, nausea, and dyspnea in terms of structure-based hypotheses, it is time to reincorporate our traditional concern with relief of suffering into the mainstream of medical research.

Recommendations

Scientific societies are critical for cross-fertilizing research approaches and facilitating contacts between the academic and business sectors. Societies interested in pain and symptom research might support joint symposia at meetings of groups studying organs the symptoms of which are under-researched. Officials of granting agencies could be invited to these meetings to encourage potential applicants and consider novel mechanisms for nurturing collaboration and training, including small business grant initiatives.

Pharmaceutical companies, business scholars, and drug regulatory agencies might examine the distribution of research and development across various diseases and test my claim that innovation is retarded by the short-term incentive structure of clinical researchers in industry.

Medical, dental, and nursing school leaders and their philanthropic colleagues might consider building pain and symptom research initiatives around strong disease-related programs, improving the diagnosis and management of the disease as well as patients' quality of life, and augmenting the grant support of any disease-oriented clinical investigator.

Political advocates for increased pain and symptom research might bear in mind that merely earmarking this area may only deliver additional funds to existing pain and symptom researchers, who will tend to focus on their traditional disease of interest. An alternative approach

might join forces with advocates of research into major diseases that have been the subjects of little pain and symptom research. The new alliance could argue that continued increases in NIH funding are needed to correct the relative underfunding of pain and symptom research pertinent to these disorders, even after the current doubling is complete in 2003.

Priorities for fostering innovation might include the following:

- Encouraging basic scientists to apply recent breakthroughs in the molecular physiology of pain to dyspnea, nausea, and analogous symptoms.
- Providing training in pain and symptom research to clinicians from specialties underrepresented in these concerns.
- Increasing the supply of new medical psychology researchers, who have been the leaders in seeding pain research into new medical specialties. Because many psychology students make career choices before receiving their doctorates, programs that bring biomedically based psychology researchers into psychology graduate programs might enhance these efforts.
- Tapping the experience of the small cadre of extramural program officials dedicated to pain and symptom research to devise new structures for nurturing interdisciplinary research, including training mechanisms, center grants, regional or national "glue" grants, and clinical trial networks.

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