A Capsule History of Pain Management

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Pain is a complex clinical problem. Assessment depends on verbal report, and the patient's physical perceptions may be modified by cognitive and affective factors. The salience of pain as a problem in its own right has grown since 1945 and new therapeutic alternatives have developed from research and from new theoretical perspectives. This short historical review of the highlights of the history of pain management gives particular emphasis to the 20th century and to chronic and cancer pain.

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PAIN IS THE OLDEST MEDICAL problem and the universal physical affliction of mankind, yet it has been little understood in physiology until very recently. The philosophical, political, and religious meanings of pain defined the suffering of individuals for much of human history. Pain is the central metaphor of Judeo-Christian thought: the test of faith in the story of Job, the sacrificial redemption of the Crucifixion. In the utilitarian dialectic of the 18th and 19th centuries, pleasure was balanced against pain to determine the good of society.

But pain was also a medical problem. European physicians did their best to relieve their patients' pain, most often through the judicious use of opium or, after 1680, laudanum, the mixture of opium in sherry introduced by Thomas Sydenham. But they also inflicted it when necessary, to relieve evil humors or to amputate diseased limbs. The physician valued pain as a symptom, a sign of the patient's vitality, of the prescription's effectiveness. "[T]he greater the pain, the greater must be our confidence in the power and energy of life," one commented in 1826.[1] That men, women, and children endured physical suffering was inevitable; the meaning, rather than the fact of pain, was what mattered to the good life.

In the early 1800s, however, the utilitarian philosophy, with its emphasis on reducing the pain of the greatest number, combined with the new philosophy of individual rights and the Romantic poets' insistence on the importance of individual experience, gradually changed attitudes.[2] Was it not a positive good to relieve pain? The skilled surgeon took pride in his ability to operate rapidly, minimizing his patient's agony. But a few experimenters realized the possibilities of the sedative gases, particularly ether, often used as an analgesic for toothache. Following an unsuccessful attempt by his colleague Horace Wells, the American dentist William T. G. Morton gave his famous demonstration of anesthesia with ether on October 16, 1846. The British obstetrician James Young Simpson proposed the use of chloroform in childbirth and surgery soon after, in 1848.[1]

The introduction of surgical anesthesia was one of the great revolutions of modern medicine, but not all physicians were immediately enthusiastic. There was an extended debate over the ethics of operating on an unconscious patient in both Europe and the United States about the possibility that the relief from pain might actually retard the healing process. Religious writers called anesthesia a violation of God's law, whom they believed inflicted pain to strengthen faith and to teach the new mother the need for self-sacrifice for her children. But the surgeons could not long resist their new power to perform longer and more complex procedures, and most patients thought anesthesia a divine blessing. Still, for much of the mid-19th century, the practice was not universal. Physicians used a "calculus" to determine which patients were of the correct sensibility to need or benefit from the use of anesthesia.[1,3]

The anesthesia story illustrates the complexity of pain as a phenomenon and the way in which its cultural meanings have often complicated its treatment.[4] But the acceptance of surgical and obstetrical anesthesia promoted a general consensus that the relief of bodily pain was a positive good, if secondary to curative therapy. By the mid-1800s, pain had become the topic of 3 interrelated medical discourses that have continued to the present day: the symptomatic relief of acute pain, the palliation of severe pain in those suffering and dying from progressive diseases such as cancer, and the relief of intractable chronic pain from disorders such as tension and migraine head-

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ache; osteoarthritis; rheumatoid arthritis; diabetic neuropathy; postherpetic neuralgia; trigeminal neuralgia; recurrent lower back, abdominal, and pelvic pain; and the causalgiform disorders (reflex sympathetic dystrophies).

Opiates Throughout the 19th Century

Opiates, throughout the 19th century, were the standard treatment for acute pain from injuries and for recurrent pain, such as headache or toothache. Friedrich Wilhelm Sertürner had synthesized the "somniferous principle" in crude opium in 1804[5]; morphine was industrially produced in Germany in the 1820s and in the United States a decade later. Alexander Wood in 1855 devised a syringe with a hollow needle for subcutaneous injection, which was of immediate practical benefit. The syringe made frequent administration so convenient that it probably contributed to the overuse of morphine.[6] Opium and alcohol-based compounds, in the form of liquids, pills, and "headache powders," were unregulated and available over the counter in local pharmacies; many people used them to self-medicate. By the 1870s, physicians had begun to express concerns about "the morphine habit" or "narcomania" and its "repeated indulgence inducing bodily and mental prostration and mental perversion."[7] In 1898, the Bayer Company of Germany introduced diacetylated morphine under the trade name Heroin as a cough remedy. Early reports proclaimed that this new compound had less habit-forming potential than morphine. But by 1910, young working-class Americans had learned to crush the pills into powder and inhale it to achieve a concentrated high. The frightening spread in street use, coupled with rising alarm over iatrogenic addiction to morphine, encouraged the medical profession's support of the Harrison Narcotic Control Act, passed in 1914.[8(pp33-55)]

Bayer's chemists had also acetylated salicylic acid, a plant compound used in headache powders, which had often left the patient with severe gastric distress. The new compound, introduced as aspirin in 1899, proved to be remarkably safe and well tolerated by patients and highly effective as an analgesic and antipyretic. Bayer aspirin became an over-the-counter drug after the expiration of the American patent in 1917 and the appropriation of Bayer's subsidiaries abroad during World War I; it effectively supplanted the opiates for the treatment of mild to moderate pain.[9,10]

For the severe pain of cancer, opiates remained essential. Although the topic was not much discussed in 19th century medical literature, the available evidence is that a number of physicians advocated vigorous use of analgesics in seriously ill and dying patients; the critiques these writers directed at their colleagues suggest that this was not always the common practice. "Seldom does it afford more pride and pleasure to be a physician! . . . [O]ne of the chief blessings of Opium is to help us in granting the boon of a comparatively painless death," wrote the Bath physician John Kent Spender in 1874, adding, "[T]he medical man who (from ignorance or timidity) withholds hypodermic medicine from a patient afflicted with cancer, is . . . totally without excuse." Herbert Snow, while chief surgeon at the London Cancer Hospital (the Royal Marsden) in the 1890s, argued that the "morphia habit" would slow the progression of the cancer and condemned the approach of other physicians, which he described as "operate, or failing this, do nothing."[8(pp21-34)]

The conflict between the physician's desire to relieve the patient's pain and fear of inducing addiction persisted in medicine throughout the 20th century. Patients equated morphine use with a loss of autonomy that the strong should resist at all costs. A classic illustration is when the Finch children in *To Kill a Mockingbird*[11] spend weekends reading to their sick neighbor Mrs DuBose who is fighting to wean herself off morphine before she dies. Their father, Atticus, the book's noble hero, praises her courage. Physicians shared these attitudes. Although those few writers who discussed pain relief for patients with cancer recognized that "severe constant pain will destroy the morale of the sturdiest individual," they were "often loathe to give liberal amounts of narcotics because the drug addiction itself may become a hideous spectacle"[12(pp7-8)] and advised that "every effort should be made to put off [narcotic use] until all other measures have been exhausted" and the patient's life "can be measured in weeks."[12(pp13-33)]

The Ordeal of Chronic Intractable Pain

If patients with cancer and their physicians faced a terrible dilemma, patients with chronic "pain without lesion" confronted a different, but equally agonizing, ordeal. Nineteenth-century physicians neither ignored nor trivialized these pains, which persisted in the absence of evident pathology and often failed to respond to treatment with opiates. They proposed a number of creative etiologies of nerve malfunction, including François J. V. Broussais' concept of functional lesion (1826), Benjamin Brodie's hypothesis of spinal irritation (1830s), and the idea of a disorder of *Gemeingefühl*, or cenesthesis, an individual's ability to correctly perceive his internal sensations.[13] S. Weir Mitchell, the US neurologist who wrote classic descriptions of pain syndromes such as phantom limb pain and causalgia based on his Civil War observations, strongly asserted the reality of his patients' physical illness, despite their unexplained pain and odd behavior. Of causalgia, the burning pain in an extremity that persisted after an injury had healed, he wrote that it was "the most terrible of all the tortures which a nerve wound may inflict. . . . Under such torments[,] . . . the most amiable grow irritable, the soldier becomes a coward, and the strongest man is scarcely less nervous than the most hysterical girl."[14] The patients reported pain at the slightest touch; when they allowed him to treat them, Mitchell tried ammonia blisters, electricity, and morphine, with some success. Many of the men still suffered pain 30 years later.[15]

As neurologists more tightly defined their field through the develop-

ment of specific diagnostic tests and identification of meaningful signs in the later 1800s, they began to eliminate unexplained chronic pains from their professional purview, while alienists and psychoanalysts found these disorders useful clues to mental or emotional disease.[13] This disciplinary shift was further supported by the development of neurophysiological evidence that supported the idea of "true" pain as a direct, proportional response to a specific noxious stimulus. *Specificity theory* became the standard model taught in US medical schools.[16,17] By the 1920s, therefore, those who suffered from unexplained chronic pain syndromes were often regarded as deluded or were condemned as malingerers or drug abusers. As morphine and other narcotics were heavily regulated and prolonged administration was sanctioned only in the dying, the only options available for most patients suffering from chronic intractable pain were psychotherapy or neurosurgery—ligature, resectioning, or crushing of the nerve fibers—to prevent the transmission of sensation to the spinal cord and brain. Surgeons progressively refined these operations, developed between the 1870s and the First World War, to vitiate only the nerves involved in the specific pain disorder; but the procedures were disabling and drastic remedies.[18-20]

Harvard pharmacologist Reid Hunt realized the need in clinical practice for a strong nonaddicting analgesic, a drug that would fill the empty niche between aspirin and the narcotics; he hypothesized that "a thorough study of the morphine molecule might show a possibility of separating the analgesic from the habit-forming property."[21,22] His idea sparked the development of the Committee on Drug Addiction, formed under the aegis of the National Research Council in 1929, with the financial support of the Rockefeller-backed Bureau of Social Hygiene, to supervise a research project initially based at the Universities of Virginia and Michigan. The analgesic development program moved to the new National Institute of Health in 1938 and is today part of the Laboratory of Medicinal Chemistry at National Institute of Diabetes and Digestive and Kidney Diseases.[8(pp57-83)] Under the leadership of Lyndon Small, Nathan Eddy, and Everette May, the program has tested many new analgesics, including oxycodone, meperidine, methadone, and pentazocine. But the strong nonaddicting morphine derivative has continued to elude the researchers.[8(pp57-83)]

There were a few clinicians between the first and second world wars who found specificity theory too limiting and the available therapeutic options inadequate. The French surgeon Rene Leriche, who treated many patients with nerve-injury—his "pariahs of pain"—during World War I, proposed careful resection of the arteries near the injury, followed by a large injection of procaine (the precursor of cocaine, synthesized in 1905) to block all sensation. Only if the procaine failed to provide substantial relief did he advocate ligation of the periarterial sympathetic nerve fibers or of the sympathetic ganglia supplying the limb. A number of neurosurgeons had adapted his method as a diagnostic procedure by the late 1930s, moving immediately to sympathectomy if the procaine injection provided relief.[23] Oregon surgeon William Livingston refused to rush into the operating room but treated his unhappy patients with multiple procaine injections, sometimes as many as 8 over a period of 2 years or more. He found that this serial blockade often resulted in permanent remission. Livingston fiercely refused to "deny such cases an organic basis and to ascribe the symptoms to psychic causes for which the patient may be responsible."[17]

Regional nerve blocks had been used during surgical procedures before 1900. Rudolf Schlosser had experimented with alcohol blocks for trigeminal neuralgia in the early years of the century and others tried the same method for cardiac pain in the 1920s. The therapeutic use of an anesthetic rather than a neurolytic block appears to date from the work of Leriche and Livingston. Although Livingston gave credit to Leriche, his original use of procaine may have been suggested by a football coach, who had often given blocks to injured players.[16,17,24] The first anesthesiologist to open a nerve block clinic for pain relief was Emery Rovenstine, at Bellevue in 1936.[25]

New Ideas Generated at Wartime

World War II, which provided an unprecedented opportunity for organized teams of clinicians to observe and work with complicated injuries, was a watershed in the management of pain. Livingston, who treated 1279 nerve injury cases at a California naval hospital, called the war years "the most exciting and productive of my life."[17(ppviii-x)] In 1947, he established a research-based pain clinic at the University of Oregon; among the fellows he trained was the young psychologist Ronald Melzack.[17(ppviii-x)]

It was at Anzio and other World War II battlefields that Henry K. Beecher, the Harvard anesthesiologist, observed that seriously wounded soldiers reported much lower levels of pain than had his civilian patients in his Massachusetts General Hospital recovery room. Based on his inference that clinical pain was a compound of the physical sensation and a cognitive and emotional "reaction component," he challenged laboratory studies in healthy volunteers and argued that pain could only be legitimately studied in the clinical situation. These observations formed the basis for a new analgesic testing method, using double-blinded crossover trials and simple numerical scales to quantify patient report, developed by Beecher and refined by Raymond Houde and Ada Rogers at Memorial Sloan-Kettering .[26-29]

The young anesthesiologist John Bonica found himself handling pain problems that baffled him at Madigan Army Hospital in Washington, during the war. Consulting with other colleagues, he found that they knew little more than he did, but that each benefitted from discussion with the others. This experience was the genesis of Bonica's 20-year campaign for multidisciplinary pain clinics and an inter-

disciplinary pain field, which would promote the sharing of clinical and laboratory evidence. His opening 1953 salvo was the monumental work *The Management of Pain*,[16] which gathered together all available information about the etiology, diagnosis, and treatment of human pain.[30] As a practitioner, Bonica refined and promoted the use of therapeutic nerve blocks. A small number of other anesthesiologists, including Duncan Alexander in Texas and Mark Swerdlow in Manchester, England, were also working with these methods, starting pain or nerve block clinics in the 1950s and early 1960s. The use of serial anesthetic blocks enabled the physician to manage many difficult pain problems without having to resort to surgery.[16,30,31]

The United Kingdom in this period saw the beginnings of another medical initiative that presented pain as a complex multidisciplinary problem. The physician Cicely Saunders,[32,33] who had dedicated her life to the care of the dying, was planning a model hospice that would provide exemplary palliative care and would incorporate teaching and research programs. She frankly avowed the regular giving of strong narcotics, including heroin and the Brompton cocktail mixture of morphine and gin, as the proper regimen to ensure that a pain-free patient could maintain quality of life in the last days[8(pp85-98)] Saunders' concept of "total pain," a clinical phenomenon that compounded physical and mental distress with social, spiritual, and emotional concerns, echoed and transcended Beecher's formulation of a "reaction component," demanding a holistic concept of management focused on the individual patient.[34]

Formation of the Pain Field

In 1965, the Canadian psychologist Ronald Melzack and the British physiologist Patrick Wall,[35] building on the ideas of the Dutch surgeon Willem Noordenbos,[36] published their classic "gate control" article, proposing a spinal cord mechanism that regulated the transmission of pain sensations between the periphery and the brain. The neurophysiological specifics of their model were less important than the challenge to the specificity theory and the implication that clinical reports of pain unrelated, or out of proportion, to any external stimulus could be explained in terms of neural mechanisms. In the words of Isabelle Baszanger,[37] Melzack and Wall's model opened gates in disciplinary barriers and offered a plan for "the construction of a world of pain." The observations and methods of clinical medicine and psychology would form "two new axes" around which a conceptual "complexity almost beyond comprehension" could be mapped.

Interest in the gate model, both supportive and antagonistic, drew attention to pain as a problem. The psychologist Richard Sternbach[38] argued that physiological and affective perceptions of pain should be understood as learned responses of the nervous system, interactive with the individual's learned behaviors in coping with pain experiences. A learning theory of pain suggested a therapeutic approach based on relearning or conditioning. One such method, the childbirth education techniques of Grantly Dick-Read and Ferdinand Lamaze, was already well established in obstetrics by the 1960s. In the early 1970s, Wilbert Fordyce and his colleagues[39] introduced operant conditioning into the treatment of chronic pain, using physician attention as a reward to help patients learn to self-manage their pain and to resume normal functioning through graded activity.

Also in this period, David Mayer, Huda Akil, and John Liebeskind[40,41] at the University of California-Los Angeles reported that stimulation of certain areas of the brain produced analgesia in animals, an effect reversible with the narcotic antagonist naloxone. This observation supported the assumption that there were endogenous neurochemical reactions to pain that might be useful therapeutically, a premise soon realized when Candace Pert and Solomon Snyder[42] identified the opiate receptor in neural tissue and Hans Kosterlitz and John Hughes[43] isolated enkephalin.

By 1972, John Bonica, who had been trying to build an interdisciplinary pain "world" for 20 years "was about to give up. . . . [D]octors said, 'Pain is a symptom of disease, and that's it.'" But the surge of interest that followed the gate control article motivated him to act.[30] He invited 300 researchers and clinicians—everyone he could find who was working on or had written about pain—to a 3-day meeting in May 1973 at an isolated convent near Seattle, Wash. He drew on the energy and interest of the assembled participants and won their endorsement of an interdisciplinary organization, the International Association for the Study of Pain, and a dedicated research journal, *Pain*. Bonica had himself nominated as the first president-elect and led the new group through its formative years.[30] The organization today has more than 6700 members representing more than 100 countries and 60 disciplinary fields (L. Jones, written communication, August 28, 2003).

The formation of the International Association for the Study of Pain facilitated a confrontation between 2 groups focused on the treatment of cancer pain: the Houde and Rogers team at Memorial-Sloan-Kettering,[44(pp263-273,302)] which had conducted extensive and rigorous research on the differential effects of various analgesics (many originating from the decades-long search for a strong nonaddicting drug), and Cicely Saunders and her colleagues at the new St Christopher's Hospice, who were promoting the regular use of heroin and morphine in doses strong enough to alleviate all pain. In the mid-1970s, Kathleen Foley[44(pp59-78)] at Memorial Sloan-Kettering created the first taxonomy of cancer pain. Her analysis refuted the casual assumption that "advanced cancer is painful," showing that different patients suffered from different kinds of pain, some related to the progression of the disease and some to other causes. At the same time, the studies of Robert Twycross[44(pp291-300,617-633),45] at St Christopher's demonstrated the supe-

rior reliability and efficiency of oral morphine over heroin and reported the absence of tolerance or addiction in cancer patients, even with long-term use.

In 1982, the new head of the World Health Organization Cancer Unit, Jan Stjernswärd, brought together a small group of cancer pain consultants, including Bonica, Foley, Swerdlow, and Twycross, to develop a practice regimen for global education and dissemination. The result was the World Health Organization ladder: a set of guidelines for the physician, recommending that she or he prescribe analgesics on a regular schedule and titrate dosage to the patient's pain at each of the 3 steps: from a nonsteroidal anti-inflammatory drug, like aspirin, to a weak opiate, like codeine, to a strong opiate, like morphine.[46] Although many adjunct drugs are recommended for patients who fail to respond to opiates or who find the adverse effects intolerable, oral morphine—cheap, reliable, readily available, and with extensive documentation of efficacy——remains the mainstay of cancer pain treatment today. A number of physicians advocate its carefully managed use for patients with chronic noncancer pain as well, a recommendation endorsed by major pain organizations.[45] Regulatory barriers to morphine use and clinician and patient concerns about addiction nevertheless persist in many parts of the United States and in many countries abroad.[8(pp163-191),47]

Recent Therapeutic Innovations

Research in the last 30 years has developed a variety of alternatives or adjuncts to opiates for chronic pain, including neuroactive medications, counterstimulation methods, and cognitive-behavioral therapies. Behavioral conditioning or modification programs following the work of Fordyce, have proved helpful to many patients. These modalities are expensive and time intensive, however, and have been replaced or augmented in many multidisciplinary pain programs by cognitive-behavioral methods, which emphasize the teaching of coping skills. Although cognitive-behavioral theory shares with learning theory the assumption of reciprocal relationships between sensation, cognition, emotion, and behavior, it makes the additional assumption that "individuals are active information processors able to change the way they think, feel, and believe."[48] Such programs have been markedly effective in improving mood and function and decreasing pain and disability levels in such refractory problems as lower back pain. But the subjectivity of pain and cognition and the difficulty of devising a placebo control make the rigorous evaluation of these methods difficult.[49] Some observers, moreover, have criticized cognitive-behavioral programs for shifting the burden of therapeutic responsibility to the patient, who must alter his or her cognition and behavior to get pain relief.[37,50]

The gate control model had suggested a neural mechanism to explain how counterstimulation methods used by practitioners for many years, such as skin blistering, electricity, and simple touch, might work. The most successful modern application has been the transcutaneous electrical nerve stimulation device to stimulate the large sensory fibers and close the gate. Counterstimulation, like acupuncture and placebo mechanisms, may produce analgesia by activating an endorphin-mediated analgesia system, which is part of a cascade of endogenous synaptic and cellular responses to stress or injury.[51-54]

Clinical observations in depressed patients suggested that tricyclic antidepressants such as amitriptyline and imipramine, which increase available levels of norepinephrine in the nervous system, could be effective in relieving chronic pain. These drugs were already being used to treat headache when laboratory findings suggested the involvement of norepinephrine in endorphin-mediated analgesia. The tricyclics are now widely used in the treatment of postherpetic neuralgia, among other syndromes.[55-58]

More recently, drug developers are using pharmacological and physiological evidence to synthesize targeted medications that will block the formation or activity of a specific compound in the nervous system implicated in the development of persistent pain. Some of these new targets include inflammatory mediators, sodium and N calcium channels involved in afferent fiber transmission, and specific neuropeptide agonists or receptors.[59] A well-known example is the selective cyclooxygenase-2 inhibitor, which inhibits cyclooxygenase 2 that is localized in inflammatory tissues, but the inhibitor does not interfere with the more ubiquitous cyclooxygenase 1. Use of these compounds may prevent the gastric and renal problems associated with use of the nonsteroidal anti-inflammatory drugs.[60] The work of Clifford Woolf[61] and Gary Bennett[62] has pointed to the role of *N*-methyl-D-aspartate [NMDA] in creating a state of central sensitization, producing chronic pain, and suggested the development of an *N*-methyl-D-aspartate–receptor antagonist for analgesia.[63]

The productivity of pain research and analgesic development since 1973 has not altered the truth of one clinical fact: no one treatment works for every patient, even for pain of the same type and etiology. As Beecher, Bonica, Saunders, Sternbach, and many others have argued, the meanings of pain—cognitive, affective, behavioral—are different for each individual and shape the pain experience and response to therapy. Perhaps these individual variances explain why Portenoy and Foley[64] found, in a study of opioid analgesics in chronic noncancer pain, that the most important treatment factor contributing to outcome was "the intensive involvement of a single physician," and why, with many new resources available, pain management remains a challenge for the clinician.

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