Special Article

The Ladder and the Clock: Cancer Pain and Public Policy at the End of the Twentieth Century

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Abstract

The origins of the WHO Cancer Pain Relief Program (the Analgesic Ladder) and its research basis in two very different research traditions, one at Memorial Sloan-Kettering Cancer Center in New York, the other at St. Christopher’s Hospice in London, are discussed. The Sloan-Kettering group emphasized precise relative differences in analgesic effects of various drugs, whereas Twycross at St. Christopher’s used patient well-being as the crucial benchmark. Despite these differences, both traditions presented evidence of the safe and effective use of strong opioids for cancer pain relief, in a setting of individualized attention and close physician monitoring. The success and limitations of the Ladder as a global health policy are briefly addressed. J Pain Symptom Manage 2005;29:41–54. © 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

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Introduction

The lovely sixteenth-century Villa d’Este on Lake Como is a poetic setting, but just outside of Milan, Italy’s major financial center, it is also a place for serious business meetings and policy conclaves. The 17 people who met there in October 1982 had serious business in mind. Jan Stjernswård, new head of the World Health Organization’s Cancer Unit, had invited their advice on the making of a new policy on cancer pain relief—a global public health program with major implications for national drug control policies, for cancer management protocols, and for the new field of palliative medicine—the care of the dying. A number of writers in the 1970s had described the pathetically “soul-stirring sights” of dying patients in pain, “in great need of relief that not infrequently does not come.” Their observations had been made in the U.S. and the UK, two of the most medically advanced countries in the world. In the rural villages of Africa, Asia, and Latin America, Stjernswård hypothesized that the situation was much worse; that there were “millions of sufferers... who have no hope of cure and little chance of adequate relief from pain.”

The moment seemed propitious for action. Although the expert cadre of six at the Milan meeting was small, they represented the growing conviction of a group of influential doctors that pain was not an inevitable subplot of the cancer patient’s short and tragic story. John Bonica, the charismatic anesthesiologist from...
Seattle, had campaigned for better pain management for more than 20 years before his efforts bore fruit in 1973 with the founding of the International Association for the Study of Pain (IASP). The other members of the group, like the growing membership of the IASP, represented several countries and disciplines: anesthesiologists Mark Swerdlow, Stjernswärd’s chief consultant, who had founded the first formal pain organization, the Intractable Pain Society, in Manchester in 1967, and Vittorio Ventafridda, the energetic pain specialist at Italy’s National Cancer Institute, whose efforts had brought the WHO group to Milan, his home city; palliative care physician Robert Twycross, who had conducted innovative drug research studies for Cicely Saunders at St. Christopher’s Hospice in London in the 1970s; neurologist Kathleen Foley, who had published the first taxonomy of cancer pain syndromes and who had been trained in pain research at Memorial Sloan-Kettering Cancer Center in New York; and pharmacologist Anders Rane of Stockholm.

The physicians’ concern was reflected and driven by the vocal anger of cancer patients and their families. Two journalists, Stewart Alsop in the U.S. and Colin McInnes in Britain, had written caustically about cancer pain before their deaths in the 1970s, and demanded the attention of the compassionate. The National Committee for the Treatment of Intractable Pain, an American volunteer group, was lobbying vigorously for more lenient drug legislation, including the legalization of heroin, to allow U.S. physicians “the freedom and responsibility” to control severe pain. The problem was how to privilege concern for suffering patients over the deep social concern over narcotic addiction—how to reframe the use of opioids as a therapeutic skill based on pharmacologic knowledge, rather than a risky practice inevitably leading to drug dependence.

For the new policy would be about drug use, and all the participants in Milan knew it. Although Bonica, Foley, Swerdlow, and Ventafridda were specialists in more complex pain management techniques, and these would be discussed in the guidelines, the core of WHO’s recommendations had to be a simple regimen that could be disseminated rapidly and cheaply to the rural villages of the developing world. What was needed were a few good drugs and a model for their use that was virtually transparent and translilingual, and yet rested on an implicit foundation of scientific authority.

But to introduce such a model and to include opioid analgesics would be to reinvent pain management and cancer care in the developed world as well. Although the Single Convention on Narcotic Drugs of 1961, the global treaty adapted by most WHO member states, supported the use of narcotics as “indispensable for the relief of pain and suffering,” it also required governments to control their production and use. Since 1949, the WHO’s own Expert Committee on Drugs Liable to Produce Addiction (later the Expert Committee on Drug Dependence) had labored to ensure that “drugs of a particular chemical type, analogues of which have proved to be habit-forming … [were] placed under control.” Specific restrictions varied from country to country; but reports indicated that physicians were frugal in prescribing opioids, even with the dying, and vigilant in observing patients for signs of tolerance or dependence. Customary practice in most major hospitals held that “morphine or other potent narcotics… should be used sparingly at first, so that tolerance will not raise the dose requirement” and that pain relief with larger dosages be weighed against “the inevitable addiction.”

This was not the first time the six experts had met: they had argued the same issues at the IASP World Congress in Florence in 1975, at the First International Symposium on Advanced Pain in Cancer in Venice in 1978, at the Swedish Academy of Sciences’ conference on Narcotic Analgesics in the Treatment of Cancer and Postoperative Pain in Stockholm in 1981. Raymond Houde, one of Foley’s mentors, had said in Venice, “Ironically, the capacity to induce a sense of well-being, or euphoria, is a property of the narcotics which we have been making a great effort to eliminate from the so-called ‘ideal analgesic’ of our aspirations.” As he suggested, it was not only pain relief that had been neglected in cancer care, but the patient’s “sense of well-being,” in favor of an elusive concept of “ideal” therapy. The Milan meeting was intended to force a resolution of this paradox. The group called their model a ladder.
Planning a New Cancer Pain Policy

Jan Stjernswärd began planning his new Cancer Pain Relief initiative in early 1981. He envisioned pain relief as one of three arms of the WHO Cancer Unit’s program, along with prevention and early detection and treatment. On March 30, he wrote to Mark Swerdlow, outlining his plan to gather “original WHO data [from] target clinics in various countries” on the incidence of cancer pain and the availability of treatment, then to bring together a small group of experts to devise a “simple but effective scheme.” The two men agreed to meet in Geneva on May 22.

It was a fruitful meeting. Swerdlow was able to provide much helpful information on the activities of the IASP and the organizational and fundraising skills of John Bonica and Vittorio Ventafridda. He agreed to become a WHO consultant and to try to recruit cancer specialists from developing countries at IASP’s upcoming World Congress in Edinburgh. Stjernswärd hoped to identify ten physicians who would carry out a questionnaire study of the pain experience of 50 patients at their home institutions and provide data about local facilities and practices. Once the data were gathered, the expert group would meet to work on a “simple scheme of... recommended therapeutic methods;” the recommendations would be evaluated in one or two test countries and then released worldwide. The two men formulated their goal in a few words: “to achieve world freedom from cancer pain by the year 2000.”

A major priority was fundraising, as WHO depended heavily on outside support. Funds would be needed for the planned meeting of experts and the data collection. Stjernswärd wrote to Bonica, and approached pharmaceutical firms without success. In early July, Swerdlow had another idea: the Floriani Foundation of Milan, which had sponsored the first International Symposium on Pain in Advanced Cancer in 1978. Ventafridda, who sat on the Foundation’s Board, “had a passion” for the problem of pain management; with his assistance, Floriani was persuaded to provide the funding for the meeting of experts. It must have been at their request, or Ventafridda’s, that the venue was moved from Geneva to Milan. They agreed to pay Bonica’s way from Seattle; he visited Stjernswärd in Geneva in October 1981 and wrote Ventafridda that he was “delighted to help in any way.” Swerdlow was pleased: “It is good to have him on our side!” By March 1982, the “group of experts” had been chosen, and it is likely that Bonica and Ventafridda, who had together organized the Florence and Venice meetings on cancer pain, helped to choose the remaining conference.

A crucial task was to identify physicians in developing nations to report on local conditions and to gather the evidentiary data from surveys of target clinics. During a trip to Brazil in July 1981, Stjernswärd recruited Dr. Miriam Martelete of Porto Alegre, who became an enthusiastic and hardworking participant. In June of the following year, Swerdlow’s timely visit to Stjernswärd’s old friend, Dr. Sivayoham, in Sri Lanka, brought the Department of Health there on board. Stjernswärd wrote him on receiving their set of 40 questionnaires, “Guess we know we can always rely on Sri Lanka.” But there were many difficulties in collecting data from busy physicians, particularly after it was decided, in consultation with the WHO Collaborating Center for Biostatistics at Harvard University, to compile 250 questionnaires from each of 10 countries. Although sets of questionnaires were sent to contacts in Nigeria, Egypt, Turkey, Ireland, the Philippines and the Sudan, very few of these were returned. Even Anders Rane found he had to do all the work on the Swedish questionnaires himself, and was nevertheless unable to complete the survey in time to meet the September deadline.

Some of the doctors approached may have felt that WHO was condescending or misinformed. A hint of such an attitude appears in the response of a Bangkok university physician to the questionnaire on facilities in his country: “We have doctors to take care of cancer patients. They have good knowledge to deal with pain.” But in many countries, pain therapies were only available at urban medical centers, where the doctors often emphasized expensive procedures such as anesthetic or neurolytic blocks. In Panama, “If they can’t go [to health centers], they get no treatment.” Martelete wrote. In India, as L. J. De Souza reported, there were many traditional treatment methods in use, some of them possibly effective, but these
“are lost amidst the plethora of quacks and spurious drugs and methods.”

Five physicians came through with data for the meeting in October: Martelete; Sivayoham; Swerdlow’s old friend Jesmond Birkhan from Haifa; Dr. De Souza’s colleague, P. B. Desai, from Bombay; and Fumikazu Takeda, from Saitama, Japan. They submitted a total of 919 patient questionnaires on patients with every type and in every stage of cancer, offering support for Stjernswärd’s hypothesis: Only 10% of the patients in pain reported complete relief. Worse, 29% of those who experienced severe pain were receiving little or no relief. Although clearly inadequate as a statistical sample of cancer pain sufferers, the questionnaires provided compelling emotional evidence.

The testimony from Asia and South America was supported and given added meaning by the data that had been gathered earlier in the U.S. and the UK, and summarized by Bonica in many of his presentations. Colin Murray Parkes’s 1978 study of cancer in Britain had found that 22% of hospital patients and 50% of home care patients died in severe and almost constant pain. Pain was the major symptom of 58% of 300 cancer patients surveyed in Sheffield, Dr. Eric Wilkes had reported. Houde and Foley in New York estimated that 38% of adult patients suffered from pain, but that the figure rose to 60% as death approached. At St. Christopher’s, Robert Twycross had found that 80% of the terminal patients required regular medication for pain. Setting all these numbers side by side, the Milan group had no difficulty in drawing the intuitive conclusion. In much of the world, a cancer diagnosis meant a prolonged and painful death, because pain was not properly managed.

**Ignorance and Inevitability**

The WHO conferees had reached a prior consensus on the reasons for this distressing state of affairs: ignorance and wrong ideas about pain and pain treatment shared by physicians, nurses, and other health care workers. Bonica had quantified the knowledge gap by having his students laboriously count the number of pages in nine standard cancer texts used in medical and nursing schools; only 17 out of 9,300 pages included any discussion of pain. Many physicians, Kathleen Foley had asserted, lacked knowledge of the specific nature and causes of cancer pain, attributing patient distress to the unpreventable progression of a debilitating disease. But the major documented area of misinformation and prejudice was the inappropriate utilization of opioid analgesics, following years of legal restrictions and anti-drug campaigns.

“Our international treaties have imposed a variety of constraints which have impaired the proper use of narcotics for cancer pain,” Ray Houde said. Twycross observed more bluntly that “anxiety and confusion surround” the use of morphine, heroin, and related drugs. Marks and Sachar had found that house staff at two major New York hospitals overestimated the addiction liability of opioids, while showing relative unconcern about barbiturates: “for many physicians these drugs [opioids] may have a special emotional significance that interferes with their rational use.”

The effects of doctors’ misconceptions and biases on their practice were compounded by the fact that patients, nurses, and families shared their assumptions. At the London Hospital, Jennifer Hunt had found that patients in pain postponed asking for medication because they “did not want to get used to pain killers.” The nurses praised such patients for their stoicism. Marks and Sachar observed that a behavioral norm for patients was to “tolerate [pain] without creating a disturbance.” Ada Rogers, Houde’s research nurse, summarized her observations: “Most patients are extremely concerned about taking too much medication [and] will suffer needlessly... because of misunderstandings about the nature of addiction. This may be reinforced by the nurses, and this produces more anxiety and guilt.” As these researchers suggested, both cancer patients and nurses often appeared to consider some degree of pain “an inevitable component of illness or necessary if the patient is to adapt a sick role.”

Stjernswärd’s group of experts had thus formulated their problem before they arrived in Milan. First, it was urgent: dying patients were suffering both in the developed and developing world. Although pain relief was the only available treatment for many Third World patients with “no hope of cure,” the information from the U.S. and the UK described a problem that cut across ethnic and economic strata. Second, the patients’ distress was not simply the result of their disease or because there was no known
treatment. The primary cause was the medical profession’s lack of knowledge, which was reflected in the attitudes of other professionals and of laypeople; therefore, a program of public health education, utilizing WHO’s prestige and expertise, was an obvious strategy to correct the problem.

But the knowledge gap was not solely based on the lack of information. The prescription of opioid analgesics was linked to “emotional” and irrational attitudes that were expressed as anxiety, disapproval, and guilt. Third, therefore, the goal of the educational effort, rather than the presentation of new evidence, would have to be the reframing of pain treatment, and particularly the use of opioids, within a clearly structured regimen. Such a framework would guarantee safety and confidence, not only by reference to scientific knowledge, but also by locating each physician and patient at a specific secure place among many others in the world cancer community. Clearly delineated practice guidelines would also reassure national governments that they could safely ease legal restrictions.

The Milan consultants had two well-respected research traditions to draw on, both of which had produced clinical and pharmacological evidence about the use of opioid analgesics in cancer. Kathleen Foley represented the first, begun at Memorial Sloan-Kettering Cancer Center in New York in 1951 by Raymond Houde. Robert Twycross embodied the second, which was based on Cicely Saunders’s concepts of pain management in hospice care, but had only developed as systematic research after he came to St. Christopher’s Hospice in London in 1971. Because these two traditions were the basis of what was to become the new WHO policy, they will be discussed in some detail.

The Quest for the Ideal Analgesic: New York, 1951–1971

In 1947, following a wartime hiatus, the U.S. National Research Council reorganized its Committee on Drug Addiction and Narcotics, originally created in 1929 with the specific goal of finding an “ideal” analgesic that would be as powerful as morphine and heroin (diacetylated morphine), but non-addictive. The research program continued into the 1960s under the leadership of Committee Secretary Nathan B. Eddy. Promising new opiate derivatives developed and tested on animals were sent to the Public Health Service’s Addiction Research Center, a combination prison/hospital/research facility in Lexington, Kentucky, and evaluated for withdrawal liability on the ex-addict prisoners.40,41 By 1950, this process had identified a number of potential “new analgesics” which were hypothesized to be less dangerous than morphine. The American occupation of Germany had opened up a number of laboratories in that country where an even greater number of morphine alternatives, as many as 500 by the Committee’s estimate, awaited testing.40

The final phase of the process was to evaluate the new analgesics on patients in pain. Memorial Sloan-Kettering’s James Ewing Hospital, with a large population of poor and working-class New Yorkers suffering from advanced cancer, was a logical site for such tests; Cornelius Rhoads, the hospital’s director, drafted a young internist, Raymond Houde, to direct this project. He was sent to the University of Michigan to learn pharmacology and to Lexington to observe the withdrawal experiments. In 1951, he began work with the assistance of a research nurse, Ada Rogers, and a psychologist, Stanley Wallenstein.42 Although much of their work was never published, Houde’s meticulous and patient-sensitive methods were recognized by the late 1950s as the standard for analgesic trials.43

The patients came to James Ewing when they were too sick to care for themselves and often stayed until they died. There was nowhere else for them to go and limited treatment that could be given. Their doctors were the house staff, who prescribed a standard analgesic, aspirin, codeine, or morphine, prn; if there were patients who didn’t want to “get used to pain killers,” or hesitated to “create a disturbance,” they may have suffered in silence. When Houde and Rogers asked them to participate in a pain study, however, there was a chance of relief and a new interest in the monotonous days. Once she had given a test drug from a coded vial, Rogers visited her study patients every hour to collect data and was quick to act if they reported problems such as nausea or difficulty in breathing. She was at the hospital 10 hours a day, every day. Few patients in any hospital received such a level of personalized attention.44
Houde believed that the patient would give him an accurate, objective report if he defined the choices clearly and removed any possibility of bias. He understood the value of double-blinding, but scoffed at the idea that it was some kind of “magic” key in itself. From Henry Beecher at Harvard, and from his own experiments with student volunteers at Michigan, he had learned that the perception of pain was modified by multiple variables—emotional state, expectations or fears for the future, previous medications or treatments, and the course of the disease itself. “I have no way of knowing actually what these people are feeling,” he reasoned. “So the only thing I can do is to have them serve as their own control.”

Houde made each patient his “own control” with a double-blinded crossover study design, in which the patient received a series of graded doses of a test drug, randomized against graded doses of a known standard, usually morphine or aspirin. The test or “challenge” doses were given once a day; at other times, patients received their normal medications. Rogers asked each patient to report his or her level of pain and pain relief on a four- or five-point scale. She asked about any other unusual symptoms; and she made her own observations. If a patient reported continuing pain, even moderate pain, she would give rescue medication with a known drug. “I’d give them a little bit more and then tell Dr. Houde, and then of course he would change the orders.” The data from the multiple test series conducted on multiple patients was presented in terms of relative degrees of analgesia. Houde explained, “We sought out a balance between a drug’s good effects and its bad effects... the only way we could determine that, of course, was in relative terms.”

The extended analgesic testing program had ended by 1970. With the introduction of radiation treatments and chemotherapy drugs, cancer patients spent less time in the hospital and were usually there to receive experimental treatments. Houde was limited to conducting short-term studies in postoperative patients. He and Rogers were by then devoting much of their time to pain consultation. They developed a patient-centered philosophy, balancing each patient’s individual needs against their extensive knowledge of the particular effects of each drug: “Each particular patient presents a problem which should be approached in an individual way.” “The patient expects to be treated as a whole human being... Our aim... is an understanding of his suffering and, through understanding, relief.” Memorial Sloan-Kettering approved the creation of an official Pain Consult Service and a Training Fellowship in 1971; Kathleen Foley became one of the first Pain Fellows.

“New Hope and Incentive:” The British Hospice Movement, 1951–1978

Cicely Saunders developed her innovative program for the care of the dying as a medical student volunteer at St. Joseph’s Hospice in East London in the early 1950s. Hospice patients with terminal disease received strong opioids—often in the form of a euphoriant elixir such as the Brompton Cocktail—on a “by-the-clock” or “regular giving” regimen, receiving follow-up doses before the effects of the previous one had dissipated. The patient never had to endure pain while waiting until the “right time,” nor did he have to complain or supplicate in order to receive relief. The opioid could be either morphine or heroin (diamorphine), which British hospice physicians believed to be the superior drug, faster-acting and less likely to produce side effects.

These practices were almost unknown in the rest of Europe and in the U.S., which had led the way in teaching physicians and nurses to be wary of opioid use. Nathan Eddy, who directed the American search for an ideal nonaddicting analgesic, was also a dominant figure of the WHO Expert Committee on Drug Dependence. Although Eddy and the WHO Expert Committee recognized that the opioids were essential to medical care, they saw the benefits of their use as diminished by “the degree of risk to public health.” Morphine, and especially heroin, they stated in 1952, “will always produce compulsive craving, dependence, and addiction in any individual... Such drugs cause individual and sociological damage and must be rigidly controlled.” Britain was one of only two countries that had not banned the use of heroin by 1960.
Cicely Saunders’s work developed from the maverick British hospice traditions, including their liberal attitude toward medicating with narcotic analgesics. But her vision of hospice care was much larger, one of ministry to the patient’s psychological, social, and spiritual, as well as physical well-being, one incorporating teaching and research. After earning her medical degree in 1957, she embarked on a ten-year fundraising and organizational effort to build her model hospice. She traveled and wrote extensively during this period to raise awareness of the need for better care for the dying; in 1963, she visited and shared ideas with Houde and Rogers at Sloan-Kettering.42,45 Saunders’s work reached fruition in 1967 with the opening of St. Christopher’s Hospice in South London. One of her goals for the new facility was to demonstrate with research evidence the most effective ways of maintaining patient well-being in terminal illness.45 To this end, she invited the young doctor Robert Twycross to carry out a comparison of the effectiveness of heroin and morphine, to test their relative effectiveness and risk of dependence. He arrived at St. Christopher’s in the spring of 1971.47

Twycross’s work opened up the discussions on narcotics and analgesia like a bracing dash of cold water. He established, in a double-blinded crossover study, that oral morphine and oral heroin were basically similar in effect and participated in the pharmacological studies which demonstrated that they produced equal concentration levels in the blood.38,48 (This research was corroborated by pharmacokinetic analyses which showed that heroin breaks down rapidly in the body into morphine and 6-acetylmorphine.49) British hospices soon changed their practice to rely more heavily on morphine, although retaining use of the more soluble heroin for injections.47 His demonstration that the cocaine and alcohol in the Brompton Cocktail added little to the analgesia and prompted repugnance in many patients discouraged the use of this lively drink in favor of a single strong drug.50

But he went further. Twycross took the concept of regular giving of strong opioids and made it the golden rule for the optimum care of patients with cancer pain. He challenged the idea that tolerance was unavoidable in patients receiving opioids by prospectively charting the medications of 115 patients over a period of seven years. Although those patients who died soon after the study began often required higher dosages in their last days, those who survived for longer periods were often able to reach a stable plateau level in which dosage did not vary for months. Some were able to reduce their dose or even stop taking the drug altogether.51 Reported at the Florence meeting in 1975, these findings were greeted by his British colleagues with enthusiasm, but by the Americans with incredulity. Twycross recalled this as the moment when “battle lines [were] drawn up.”47

**Point–Counterpoint in Venice**

His presentation on the closing day of the Venice meeting in 1978 was a tour-de-force. He rejected the suggestion that he thought of opioids as a panacea; they had to be part of a full program of care. Good pain management included the use of aspirin-like drugs; reassurance; modification of movement; diversion; and adjuvant drugs to treat anxiety, nausea, or other symptoms. “Pain unrelieved by other measures, not short life expectancy,” was the indication that strong opioid prescriptions should begin. The dose must be titrated to relieve the patient’s pain, first to allow for untroubled sleep, then to keep the patient pain-free while at rest during the day. Both objectives were possible with “time, patience and determination.” Medication by the clock, at regular intervals sufficient to prevent the analgesic from “wearing off,” relieved not only suffering, but anxiety and depression. To keep the patient pain-free when standing or walking was desirable, but not always possible.52

Twycross presented a chart that defined three progressive stages of analgesia: aspirin, codeine, and morphine. As the patient reached the limits of each stage of relief, the physician should move her on to the next. At the third stage, dosage should be adjusted higher if the patient experienced new or increased pain: “The top of the analgesic ladder is not reached simply by prescribing morphine or diamorphine.” Freed from the fear of death as extended torture, the terminal cancer patient, Twycross assured his audience, would have “new hope and incentive... [and] begin to live again.”52
Ray Houde challenged him on several points. He responded positively to Twycross’s contention that “by administering narcotics by-the-clock in amounts sufficient to prevent the patient from having pain, the daily amount of narcotic is less than if the patient were requesting it on-demand. We have little reason to doubt this from our observations... the on-demand prescription forces the patient to re-experience pain before taking or requesting medication, which can be very damaging to the morale of many.” But he could not agree that regular dosing was desirable for every patient, unless he or she was closely monitored. If the pain lessened or was intermittent, the patient might be overmedicated; if the patient experienced some new complication that would normally produce pain, the sensation might be masked by the continuous analgesia. Twycross did not dispute the need for monitoring and reassessing the patient; as he put it at the end of one talk, “REVIEW. REVIEW. REVIEW. REVIEW. REVIEW.” But he insisted that “continuous pain requires regular preventative therapy.”

There was also disagreement between the Sloan-Kettering and the British hospice groups on the question of tolerance. Houde and Rogers contended strongly, on the basis of more than 25 years of observations, that “The continuous use of narcotics will inevitably produce tolerance” of both analgesia and many of the negative effects (e.g., nausea and constipation), as well as a degree of physical dependence, but that these patient responses were not the same as addiction and were reversible. Their recommendation was to start with low doses of the strong opioids and escalate gradually, adjusting in accordance to the patient’s needs. Twycross responded that “tolerance is not a practical problem” if the dose was properly titrated and if the physician was attentive to all aspects of the patient’s care. “Please get away,” he implored the audience, “from all that you have learned from the addiction center at Lexington.” Any dependence the patient developed could be reversed by tapering off the dose if the pain lessened.

A final issue concerned the use of oral morphine, preferred in the hospices for reasons of patient comfort. Houde and Rogers had found parenteral morphine more effective, dose for dose, whereas Twycross’s patients reported very good relief with regular oral dosage.

To an impartial observer, it must have been clear that the two researchers were closer in philosophy and practice than their combative stances might have suggested. Twycross’s crossover methodology was directly based on that developed in the 1950s by Houde. Both approaches relied on patient report, used analgesics within a patient-centered context of care, and stressed the importance of continuing reassessment. Houde and Twycross could not agree on the inevitability of tolerance, but they concurred that it was manageable. The Sloan-Kettering studies had been based on prn prescriptions, rather than a “by-the-clock” regimen, but Rogers’s regular visits had ensured that patients were not forced to wait for relief. She and Houde had instructed the patient to ask for drugs: “I didn’t want to force the patient to say they had severe pain [to] get medication. I said, ‘Well... for anything other than slight pain, we’ll medicate you.’”

But there were crucial differences in perspective between the two research traditions that were traceable to their historical origins. Houde’s program was part of the decades-long quest for the ideal analgesic for all pain patients. Until this grail was found, his job was to determine “the balance between a drug’s good effects and its bad effects.” He defined his results in terms of very fine relative comparisons between drugs and between each new drug and morphine—which was by definition not the hypothetical ideal. Therefore, it was essential to him and his team to make precise observations of tolerance potential. It was appropriate to make meticulous calculations of oral to parenteral potency ratios, the latter uncontaminated by the carryover effect from earlier medications. Each report of relief had to be tied to a prior report of pain level, to allow for the determination of the comparative analgesic effects of two drugs; thus prn medication, rather than by-the-clock dosing, was the appropriate protocol for the Sloan-Kettering studies.

The patients too were participants in the quest. Houde and Rogers knew their patients as individuals, following many until they died: “[T]hey really became not patients but friends.” But, more importantly, the patients were research colleagues; their active participation and rational ability to discriminate
levels of pain intensity were essential to the accuracy of the study results. “This group of heroic patients can help teach us” better management of all pain problems, Houde’s students Kathleen Foley and Richard Payne would write in 1984.54

At St. Christopher’s, the goals of research were not so much patient-centered as patient-driven. Cicely Saunders has described it this way: “They [the patients] are challenged to meet adversity and the achievement must be theirs, not ours. We are there as facilitators for what they can do... your ultimate aim is not just to see the pain gone, but to see a patient free of pain doing something.”45 In this context, by-the-clock medication was not merely humane, but entirely consistent. The physician or nurse assessed the patient’s pain not as a medical datum, but to facilitate relief, so she could get on with “doing something”. If tolerance did develop, it was a problem only in so far as it might interfere with her comfort or ability to function. Oral medication was preferable because the patient had more freedom; the potency of morphine was only significant within the mandated regimen of long-term regular dosage.47 Although each patient was to be evaluated and treated individually, there was little preoccupation with the distinctive characteristics of the various “new analgesics,” which Twycross described as “all morphine lookalikes.”47

Hospice therapeutics was not an unsophisticated program. As Twycross described, analgesia in the hospice context required a systematic and careful assessment, not only titrating the dose to the pain, but also determining the particular site and mechanism and evaluating the patient’s level of anxiety, anger, fear, or depression. These practices were parts of the Sloan-Kettering methodology as well. But the end toward which Houde and his team, including the patients, worked was a universally applicable differential taxonomy of the various available analgesic drugs and a calculus of their benefits and problems as applied to cancer pain. The end sought by Saunders and Twycross at St. Christopher’s was individually defined by the transient achievement of “new hope and incentive” for each patient, with the successful relief of pain.

The Ladder Takes Shape in Milan

The “simple but effective scheme” of cancer pain guidelines developed at the Milan meeting incorporated the findings of both the Sloan-Kettering and hospice traditions; but the defining phrases, “by the ladder” and “by the clock,” are clear reflections of the Twycross protocol. Mark Swerdlow’s summary of the meeting explained that “the proper use of narcotics” was to titrate against the pain until the patient reported complete or good relief, and then to give regular (“by-the-clock”) doses. “There is a step-by-step approach. Non-narcotic → weak narcotic → strong narcotic ± adjuvants.” Morphine was the first choice of strong narcotic, but alternatives, such as methadone, were suggested if the patient could not tolerate the drug or reported insufficient relief.33

The draft guidelines published by WHO cite the same points and include a diagram of rising steps which mirrors the three-stage analgesic profession Twycross had described in Venice.1,52 The idea of three steps seems already to have been known in the group; a similar schematic had appeared in an earlier article by Rane.50 Stjernswärd recalls a “ladder” sketch done by Ventafridda on “a serviette,” when he was asked for “a simple method that an idiot like me can know.”19

The person who played the key role in reconciling the two research perspectives may have been Kathleen Foley. She came to represent Sloan-Kettering, and although relatively young, was an important participant at Milan; the discussion of etiologies, sites, and types of cancer pain syndromes in the guidelines is based on her work.1,56 Stjernswärd “found Kathy very operational;” she “could always bridge over arguments and... [make] a constructive solution.”19 It appears likely that, although she believed in the research perspective in which she had been trained, she recognized that the goal of the meeting was to produce clearly understandable guidelines with the WHO imprimatur: to ease the suffering of patients who had no opportunity to be “heroic” research subjects, to replace physicians’ fears of narcotics with confidence, and to encourage more research.

Her own thinking is well-documented in her published papers at the time. Although she did not specifically mention the ladder metaphor, she certainly accepted the basic principles. “For patients with advanced disease, pain control should be sufficient to allow the patients to function at a level that they choose and to die
relatively free of pain.”57 As did Houde, she insisted that cancer patients became more tolerant of opioids with long-term use, but sharply differentiated tolerance from abuse: “Analysis of the patterns of drug intake in our series of cancer patients suggests that drug abuse and drug addiction should not be the primary concern of the prescribing physician.”36 The escalation of drug dosage by cancer sufferers was associated in her experience with the progression of disease and greater severity of pain. But unlike Twycross, she maintained that “tolerance is a practical clinical issue” requiring physician management.58 Above all, Foley saw a need for further rigorous research: “Carefully controlled clinical studies are lacking, and there is a need for a strong impetus to develop guidelines of care based on facts, not anecdotes.”36 She later said of the hospice studies, “they were wonderful survey studies that told you [the analgesic practices] worked. But they didn’t give patients placebos, they didn’t give them varying doses, and they didn’t drop things out of the cocktail to see if one versus the other worked.”59

But in Milan, she listened to Stjernswärd and Twycross “who, when I was trying to make it complicated, they kept telling me to keep it simple… And that concept came out of the WHO expert committees… that if you were to introduce a simple program that advocated for freedom from cancer pain and if you provided a simple, inexpensive method for people to do it, it was more likely to happen.”59 The challenge for the Milan meeting was to translate the experience of two very specific local cultures, in which the cancer patient had played a defined role in an ongoing dialogue with physicians and nurses, into a global script that could be followed in any setting, whatever the language, religion, or health care system. The patients of the developing world were not protected, should they become drug-dependent, by the respectability of research or the secular spirituality of the hospice. Their well-being had to be reimagined within a prescriptive, almost ritualistic, structure that measured the course of their lives and illness, represented by the twin structural metaphors of the ladder and the clock.

The interim guidelines, and the official handbook, Cancer Pain Relief, that followed it in 1986 “kept it simple,” but they were not intended to be simplistic.1,60 The clock and ladder principles were the highlights; but the experts included material on six alternative strong opioids if the patient could not tolerate morphine or reported inadequate relief; five different categories of adjuvants to treat attendant symptoms and enhance analgesia; and the management of undesirable side effects. As Twycross has commented, the WHO program is “the basis of… many sort of wheels within wheels of [a] very complex system of using combination[s] of drugs to intercept pain messages at a variety of points.” But, he added with some asperity, “if people use it as the magic three-step analgesic ladder and fail to use it with imagination… ‘Here’s my three-step analgesic ladder, that’s what I’m going to do, that’s what I’m going to do, that’s what I’m going to do,’ then it is horribly mechanistic.”61

**Geneva and Afterward: The Ladder as Global Health Policy**

Stjernswärd and Swerdlow’s plan called for the two years after the Milan meeting to be devoted to field-testing of the interim guidelines in the five countries, followed by a re-evaluation session in Geneva. An ambitious multinational trial was to be jointly coordinated by Ventafridda’s National Cancer Institute in Milan and the WHO Collaborating Center for Biostatistics at Harvard.62 In the event, only Takeda was ready to report on his successful experience in Saitama by the time of the Geneva meeting in December 1984: 87% of his 156 patients in Saitama had reported complete freedom from pain, and only 4% had said they had less than “acceptable” relief.60 (Ventafridda was also using the Ladder in Milan and would later report on the successful treatment of 70.9% of 1,229 patients with the methodology.63)

Nevertheless, Stjernswärd felt that his consultants were ready to issue “a state-of-the-art report on the comprehensive management of cancer pain” and to begin the active dissemination phase; the Geneva meeting, which included interested physicians, pharmacologists, and public health officials from 15 countries, endorsed his plan.64 The final guidelines were written by Twycross, whom Stjernswärd appointed Rapporteur: “It’s his language, he has a very sharp pen, and he could simplify it.” The
two men stayed on in Geneva for a week until Stjernswärd “got it as I wanted it.” The chief of WHO publications, however, was opposed to the document’s release, calling it an attempt to “spread morphine all over the world.” It took two years of negotiation before the guidelines finally appeared as *Cancer Pain Relief (CPR)*. With the assistance of national departments of health and pharmaceutical companies, the small handbook was translated into 15 languages and distributed around the globe within two years, quickly becoming a “bestseller.” In addition to explaining the mechanics of the ladder methodology, closely following the Milan draft, *CPR* presented the tables of recommended drugs within the context of a program of continuing care, helping “patients to live as actively as possible in the face of impending death.” On the question of drug dependence, *CPR* was reassuring, noting that the regimen was designed for the cancer patient “for whom the likelihood of recovery is limited” and including references to nine studies which offered evidence that continued opioid use did not invariably lead to abuse.

It is not the purpose of this article to detail the many studies, projects, and volunteer activities that Stjernswärd and his colleagues mobilized to spread their message about cancer pain relief as public health policy. The efforts of advocates such as Swerdlow, Mitchell Max, David Joranson, and June Dahl are well known to many readers. By 1989, WHO had gained the cooperation of the United Nations International Narcotics Control Board, which recommended that Member States develop plans to facilitate supply and to ensure the education of health care workers. The heaviest increases in morphine use, 450% from 1984–1993, occurred initially in the developed countries of Europe, North America, and Australia/New Zealand; opioid usage in the rest of the world rose by only 150%. But there has been a recent trend toward revision of legal barriers and promotion of appropriate medical use of opioids. Among the countries working toward these goals in the 1990s were Chile, China, Colombia, India, Indonesia, Italy, Mexico, and Malaysia. At the same time, pharmaceutical companies have introduced effective, but expensive, new products, such as the slow-release formulations; these enhance application of the ladder and clock principles, but may reduce the availability of cheap morphine for poorer patients.

Evaluation of the WHO guidelines also took place on a global level. Ventafridda’s multicenter field test compiled data on 664 cases from 15 different countries. Many of the patients had been suffering from unrelieved pain for five to six months. Although a large number of cases were lost to follow-up, pain control where documented was higher than 75% with the Ladder; “strong opioids proved to be important in obtaining optimal results.” There were independent trials in ten other countries, and a large number of published articles have since documented the use and assessment of the WHO Analgesic Ladder in Europe, Asia, and the Americas.

Jadad and Browman published a critical review of the ladder literature in *JAMA* in 1996, in which they pointed out that a number of the better-known studies were retrospective, while others had poor follow-up or high withdrawal rates. Although some authors had shown a good knowledge of the guidelines and their complexity, others had been preoccupied with the “mechanistic” matching of patients and drugs to the steps of the ladder. By 1997, moreover, a number of palliative care specialists were arguing that the WHO program, although updated in 1990, had not kept pace with the rapidly changing developments in oncology and pain research. They reminded colleagues that the ladder method consistently failed to provide sufficient relief to 10–20% of advanced cancer patients with pain.

“Keep it simple,” Twycross had advised Foley. The WHO cancer pain relief guidelines were designed as a public health manual with the primary goal of teaching health professionals in many settings and countries how to relieve suffering with easily obtainable tools. The Analgesic Ladder and the catchphrases, “by-the-clock” and “by-the-ladder,” met the criteria of a “simple, effective scheme,” and became readily familiar in the literature; by the 1990s, hardly any article discussing cancer pain did not make reference to the WHO method. But its very clarity, and the assumption that it had been conceived as a barebones program, “the least that could be done” in medically underdeveloped countries, have left the Ladder open to criticism as too simple or “mechanistic.” Evaluation studies often supported this interpretation.
by emphasizing the stepwise approach above the other aspects of care discussed in Cancer Pain Relief. Unless applied with “imagination,” Twycross has said, the Ladder is a “cookbook” approach to medication, “which is what’s happening in many backwards areas of the United States and many other countries.”61

In this writer’s view, Twycross’s frustration points to a basic flaw in the Ladder as a global script for public health policy. The brilliance of its prescriptive structure and the authority of the two research traditions which supported it obscured an essential truth about why opioid analgesia worked so well at Sloan-Kettering and St. Christopher’s. Patients played the central role in both settings; they received individual attention and close monitoring, as both Houde and Twycross stressed in their public presentations. It is this factor which is most difficult to export to other medical settings, where doctors may be too few or too overburdened; but it is also the key to solving the paradox of the well-being of the patient with cancer pain, within the framework of the ladder and the clock.

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