

Meeting Report

New Approaches to Neurological Pain: Planning for the Future



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Tragically, soon after this conference concluded, one of the expert participants—a researcher renowned for giving both his head and heart to the quest for cures—died unexpectedly. Mitchell B. Max, M.D., an authority on the genetic basis of pain, was a senior investigator with the Center for Pain Research at the University of Pittsburgh Medical Center, and for more than 20 years a physician-researcher with the National Institutes of Health. Max’s scientific interests included the mechanisms and treatment of neuropathic pain and the genetics of chronic pain. His discoveries shaped the field and inspired countless scientists. With this conference report, Dr. Max’s colleagues would like to pay tribute to his brilliance, passion and generosity.

NEW APPROACHES TO NEUROLOGICAL PAIN: PLANNING FOR THE FUTURE

Meeting Report by Madeline Drexler

Introduction

Neuropathic pain is a blind spot in both medical care and research. Defined as the pain initiated or caused by a lesion or dysfunction of the sensory nervous system, the condition can be disabling and can drive patients to despair. To shed light on existing therapies for neuropathic pain and on the state of the science, and to map a future path in research and education, the nation's leading pain researchers gathered in Boston on October 20–21, 2008, for the conference “New Approaches to Neurological Pain: Planning for the Future.” This private scientific meeting, focused on the perspectives of neurologists, was sponsored by the Departments of Neurology at Harvard Medical School, Massachusetts General Hospital and the University of California, San Francisco.

Opening the conference, Joseph B. Martin, M.D., Ph.D., of Harvard Medical School, urged the participants to aim for three objectives. First was to educate general medical residents and frontline practitioners in the best methods for pain management. Second was to consider how the field of neurology could better inform clinicians and researchers about pain management—with neurology reclaiming the treatment role it had unwittingly ceded in the past. The final objective was to chart new research directions that could lead to therapies “not currently even imagined.”

These objectives reflect the fact that pain is poorly diagnosed and typically undertreated, and that pain research is underfunded. Nearly four million people in the United States experience neuropathic pain (including back pain). According to the National Institutes of Health, 45 percent of patients who are cared for in the U.S. seek treatment for persistent pain; 17 percent arthritic pain; and 15 percent frequent back pain. Lost productivity due to pain totals at least \$80 billion annually.

Pain patients are often thwarted in their efforts to seek relief—in part, because pain management typically falls between the cracks in the medical system, sending patients from one specialist to another without treatment coordination or cross-disciplinary consultation. “I’m still appalled by the way I, like many other pain patients, was treated initially by the medical establishment,” said health journalist Judy Foreman, whose *Boston Globe* column on her tortuous path to care for severe neck pain elicited an outpouring of similar stories from readers. Foreman asked the assembled experts not only for their scientific acumen, but also for their compassion. “Even if you come up with magic pills for pain,” she said, “please remember that we patients need your hearts as well as your brains. Empathy is real medicine.”

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*—Judy Foreman
Health Journalist*

Where We Are Now

Though pain research has dramatically advanced in the past 40 years, the discoveries have yet to be applied to the improvement of patient care. The reasons are many—from fragmented clinical care to turf battles across specialties to economic incentives that reward procedures rather than time-consuming diagnosis and treatment. Above all, the insights of neurologists have been vastly underutilized. “The argument for neurology is the scientific argument: What we know about the mechanisms of pain tells us that the training and interests of neurologists is highly appropriate to the diagnosis and treatment of these patients,” said Howard Fields, M.D., Ph.D., of the University of California, San Francisco.

Neurology has contributed fresh insights into the biology of pain. “This has been an amazing transformation: from knowing nothing—not even the cortical representation of pain—to understanding at a molecular level the transduction mechanisms, the transmission pathways, and the role of psychology top-down and bottom-up,” Fields explained. Functional imaging has enabled investigators to correlate symptoms in awake patients with blood flow in

specific areas of the brain—for the first time, an objective way to measure pain non-invasively in awake human subjects. It has also revealed, he said, that “as we divide up patients clinically into different groups, with reproducible symptomatology, histories and findings on exam, there are patterns of what appear to be differences in cortical shape and thickness that correlate with particular disease types.”

Single nucleotide mutations in a voltage-gated sodium channel gene expressed in pain neurons can cause familial forms of either chronic pain or pain insensitivity. “For this discovery to be made, people who were interested in the problem needed to be examining patients,” Fields said. “We knew these channels were there. But until the families were described, we didn’t know that the channels had anything to do with pain.”

Yet it may take years or decades for such discoveries to yield treatments. Today, most pain sufferers treat themselves, with approaches ranging from over-the-counter medications to cervical collars to alternative modalities such as acupuncture. Patients who seek medical help often get shunted from one type of service to another. Anesthesiologists handle many cases in pain clinics and in in-patient pain services. Neurologists see some cases and physical therapists and rehabilitation specialists attend to others.

Under time and financial constraints, physicians often face triage decisions: Should I care for this patient? Should I send the patient home? Should I refer the patient? Should I do a diagnostic test? “I believe that the sooner you do a test and make the appropriate referral, the better off the patient is going to be,” Fields said. “But that just doesn’t happen. We don’t know why it doesn’t happen.” Meanwhile, certain pain syndromes, such as post-herpetic neuralgia, continue to represent the “last frontier” in medicine. “We don’t know what the mechanism is,” said Fields. “If we don’t know that, it’s very hard to adequately treat it. Then we’re back to symptom management.”

All these trends argue for a renewed emphasis on careful diagnosis, appropriate referral and treatment, and a commitment to basic research to illuminate disease mechanisms and effective therapeutics. As Fields summed up the situation, “If we don’t get the right patients to the right physicians with the appropriate interests, those diseases are not going to be fully understood. If they’re not fully understood, research is going to be stymied. This is one of the problems in our translational program: trying to get the great scientific achievements of the 20th century translated into the improved care of patients.”

Progress in Clinical Research

1. Emerging Therapies in Painful Neuropathy

Among the casualties of the nation’s obesity epidemic are the 20 million Americans who now suffer pre- or frank diabetes. More than 50 percent of them will develop neuropathy—and, of these, half will have neuropathic pain. “Despite expanding the clinical faculty in our neuropathy centers, we cannot meet our clinical demand for these patients,” said Eva Feldman, M.D., Ph.D., of the University of Michigan. Feldman, who has devoted her career to studying peripheral neuropathies, discussed emerging research on a disease that looms large in both quality of life and the national health care budget.

Older drugs such as tricyclic antidepressants are still considered the most effective and economical methods for treating neuropathic pain. In the last five years, nearly all clinical trials have focused on medications that affect pathways involved in the central integration of pain signals, such as SSNRIs (selective serotonin-norepinephrine reuptake inhibitors) and anticonvulsants. Feldman described new approaches, based instead on advances in nociceptor cell biology. One strategy springs from observations of the “inflammatory soup” bathing the nociceptor of the C fiber in peripheral nerves. Mouse experiments have shown that, in animals bred to be obese, nerve growth factor levels increase, which in turn spurs production of substance P—both linked to pain behaviors similar to those seen in humans. A second research path has tied fluxes in glucose levels to increased mitochondria in nerve cells—a possible clue to underlying pain processes.

“This is the decade of the C fiber,” Feldman declared. “For a peripheral nerve neurologist, it’s very exciting to understand nociceptor biology, C fiber biology, and the new pathophysiologic mechanisms that impact painful pre-diabetic and diabetic neuropathy.”

2. Complex Regional Pain Syndrome (CRPS) and Post-Traumatic Neuralgia

A “mystery disease” with unknown causes—first described by the renowned Civil War neurologist Weir Mitchell—is how Anne Louise Oaklander, M.D., Ph.D., of Harvard Medical School, characterized Complex Regional Pain Syndrome (CRPS). Like Mitchell, Oaklander was drawn to study the condition by the desperation of her afflicted patients. CRPS is a rare, chronic “pain plus” condition caused by trauma.

Oaklander hypothesizes that CRPS and post-traumatic neuralgias are analogous to diabetic and other polyneuropathies—triggered by focal lesions of the same small fibers. The condition has been linked epidemiologically to nerve injury pain, migraine and asthma. Oaklander and others have discovered axonal degeneration in painful areas. “The problem is not so much with the axons that are gone, but with the effects of the change on the remaining axons, on the regenerating axons and on the denervated tissues,” she said. “There are profound effects on the central nervous system. And secondary or tertiary processes that develop in these patients are independently painful.”

Having reproduced the major symptoms of CRPS in animal models, Oaklander is now investigating its pathogenesis. In published work, she has reported that small nerve injuries are enough to produce large effects on glial cells and interneurons within the spinal cord. “Some people are able to regenerate and heal from this, whereas in other people these problems persist. The blood vessels within the spinal cord are denervated and vasodilate, permitting leakage of fluid into the nerve itself. This causes the neighboring axons to misbehave, entrains the central nervous system and leads to the CRPS phenotype.”

Oaklander surmises that CRPS is “a complex disease that has both genetic and environmental—possibly even dietary—origins.” Nearly a century-and-a-half after Weir Mitchell first described the syndrome in Civil War soldiers, CRPS remains rare, elusive and devastating.

3. Headache

The most common problem that sends outpatients to a neurologist is headache. “I’ve seen patients’ lives regularly and routinely ruined by their headaches. And I’ve seen many physicians not understand that terribly well,” said Peter J. Goadsby, M.D., of the University of California, San Francisco. “Headache is the commonest symptom found in neurologic outpatients—and, paradoxically, the least taught to neurology residents. It’s like training electricians, but not telling them about light bulbs.”

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—Peter J. Goadsby

Simple pain explanations are inadequate for disorders such as migraine, Goadsby said. “It’s a systems disorder of the brain.” Luckily, brain imaging has begun to suggest therapeutic targets for this highly prevalent condition. Goadsby emphasized that many patients are eager to participate in such studies. “It’s high time that the neurology community—and the funders—understand that patients are willing to get in a scanner, put this silly thing on their head and have a migraine triggered,” he said. Indeed, “Patients find it very reassuring to know that there is a way to get to these problems.”

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—Peter J. Goadsby

Imaging has revealed distinctive patterns of brain activation. With careful history-taking and precise phenotyping, imaging could help distinguish subtly different conditions such as cluster headache and paroxysmal hemicrania.

Goadsby has also explored neuropeptide changes, in both humans and cats, after stimulation of the trigeminal system. This research led to the development of an oral calcitonin gene-related peptide (CGRP) receptor antagonist for acute migraine—a bench-to-bedside success story. “How many areas in neurology have staged randomized placebo-controlled trials of totally new chemical entities that work—with no other indications?” he asked. “This is an exciting place to be.”

Looking ahead, Goadsby envisions genetic studies of migraine, which is a clearly heritable problem. “The benefits of the human genome initiative need to be turned to migraine. We have the lab options in experimental animals—mouse models, rat models and cat models. We’ll be able to analyze the information that we get and use imaging to

bridge the two. A consortium-based approach, and spending just a dollar on every migraineur in this country, would really change the world.”

4. Toward a Molecular Epidemiology of Pain

“Pain is a vast problem—yet it’s a rather small research field,” said Mitchell Max, of the University of Pittsburgh. The rich potential of molecular epidemiology to solve the riddles of pain may someday come to fruition in large genome-wide association studies (GWAS). Today, however, there is no ongoing, well-powered GWAS for pain. Among the first 400 published GWAS investigations, none focused on pain.

Such studies could have far-reaching benefits. “In humans, one could identify novel mediators of pain, beyond the few hundred commonly discussed in neurobiology literature,” Max noted. “GWAS studies could be one way to have human knock-outs and human hyper-expressers. Before you even went into the chemistry and the toxicology, you could prioritize among the many existing pain targets for drug development or physiological studies with human data.” In order to be funded for GWAS, pain researchers would need large groups of patients with the same pain phenotype, epidemiological expertise and close coordination with pain researchers doing animal studies.

Max and his colleagues have demonstrated the feasibility of this approach by studying one of the most common pain disorders: sciatica caused by a herniated intervertebral disc. Working with the Maine Lumbar Spine Study cohort, and using data from Clifford Woolf’s work on rat models of neuropathic pain (see below), he identified a candidate gene whose normal genetic variability appears to increase or decrease the risk of being left with persistent sciatica after low-back surgery.

With these targets, scientists may uncover the mechanisms behind pain syndromes. “We shouldn’t think of pain just as a symptom to be treated,” he reminded the audience. “There are specific pathways by which pain can cause even more morbidity,” including depression and anxiety, sleep disturbance, limited movement, impaired cognition, and maladaptive coping.

“Can we use molecular epidemiology studies, including GWAS, to reveal some of these mechanisms?” Max asked. “What are the transmitters that connect pain inputs to the symptoms of depression, anxiety, sleep outputs? If we knew what those were, we could design drugs that specifically relieve the mood change or the insomnia caused by the pain.”

Progress in Basic Science

The basic science of neurological pain is moving forward on several fronts: animal models, genetics and anatomy/physiology. All are critical to gleaning the mechanisms of pain and developing new treatments.

Animal models are essential because of their central role in the iterative research process that integrates clinical input and laboratory experiments, leading to advanced therapies.

Genetic research is crucial because molecular changes have been tied to both excessive pain and insensitivity. “It’s likely that the finding of a rare cause of a phenotype in a very isolated family or population is going to impact, in a major way, our understanding of the more common forms of the disease,” said Stephen L. Hauser, M.D., of the University of California, San Francisco. “Genetics is important, even if it isn’t genetic in all of the people who are afflicted with the phenotype.”

Studies of anatomy will reveal physiology and function, and enable researchers to quantitate and measure syndromes that can’t be discerned clinically. “For pain, this is such an important issue,” said Hauser. “The ability to quantitate pain is validating for patients and critical for us as we try to stratify our patients into different groups, based upon their underlying disorders.”

1. Animal Models of Pain

“Human genetics and imaging are great for coming up with new ideas,” said Jeffrey S. Mogil, Ph.D., of McGill University. “But ultimately, if we’re going to have new mechanistic understanding at the cellular and molecular levels, all roads lead to animal models.”

Mogil suggested that much of the failure to translate basic research into clinical treatments can be blamed on inadequate animal models. The main stumbling block, he said, is pain measurement in animal subjects. “Regardless of how clever our injury is, ultimately what we have so far been measuring in our animal experiments are nociceptive reflexes—and there’s a camp of people who believe that it would be a much better idea to minimize the importance of the reflex measurements and move to operant measures. The second objection is that there is an important disconnect between the symptoms of chronic clinical pain and the dependent measures in our pain experiments.”

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Mogil has refined an “ethological” approach to developing and validating new measures in mice for chronic pain. His “Mouse Grimace Scale” has proved reliable and accurate in preclinical pain assays. When he focused on a mouse model of migraine, Mogil found that telling behaviors, such as blinking and head grooming, increased in migraine-prone mutant mice and that standard human migraine treatments quelled those behaviors. “Indeed, for every single behavior that is significantly higher in a mutant mouse versus the wild type, we see dose-dependent and complete reduction.” Mogil’s findings suggest that measuring facial expression in rodents may indicate an animal’s current pain level, and thus provide a way to test new drugs for pain-relieving potential.

“New measures of pain can and are being developed in animals,” Mogil said. “And these new measures are much more labor-intensive than the current assays—which is why they haven’t been widely adopted. But if we really think that we’re in a hole at the moment, these new, more labor-intensive methods are necessary.”

2. How Genotype Leads to Phenotype in Pain Syndromes

“How do changes in the genome influence the pain experienced by patients? When we look at the pain phenotype, what actually *is* it?” asked Clifford Woolf, M.D., Ph.D., of Harvard Medical School. “Why are some individuals at risk?” asked Woolf. “And what is happening in those individuals who do not develop chronic pain after a nerve injury?”

Woolf has tackled the question through a discovery-based strategy that he characterizes as “screening in an unbiased way and finding something which you may not have anticipated.” By looking for changes in messenger RNA levels in the dorsal root ganglion (DRG) of rodents after peripheral nerve injury, he discovered a synthetic pathway for the molecule BH4, a critical cofactor for neuronal signaling. “Now we have a new form of modulation of neural activity, one that is driven by changes in the level of a cofactor, rather than changes in the level of the enzyme or of its substrate. That’s quite exciting: a new way in which nervous system activity may be modulated.” A collaboration between Woolf and Mitchell Max verified that a genetic variation in GCH1, a gene involved in the regulation of BH4, is associated with reduced pain after nerve injury in both humans and experimental animals.

When we look at the pain phenotype, what actually is it?

—Clifford Woolf

If an estimated 50 percent of pain phenotypes can be attributed to genes, “it alerts us to the possibility of personalized medicine in the pain field,” said Woolf. “By genotyping individuals, we can generate biomarkers to show whether people carry this particular haplotype and whether this affects their risk of developing pain . . . Human genetics has shown us that there is a polymorphism in some individuals that reduces their pain sensitivity and appears to reduce their risk of developing pain. The challenge to the pharmaceutical industry is: can you mimic this experiment generated by human genetics?”

3. Descending Modulation in Neuropathic Pain

Addressing what he called the “puzzling discordance between the tremendous explosion of knowledge in the neurobiology of pain and our failure to translate that information into novel therapies,” Frank Porreca, Ph.D., of the University of Arizona, discussed the descending modulation of pain, which originates in the brainstem. “We know very well that, in humans, pain is a sensory experience,” he said. “And pain is influenced dramatically by the emotional state of the individual, by the degree of attention or distraction, by changes in expectation, by changes in stress. All of these are critical because they tell us that pain in humans is more than the sum of nociceptor activation.”

Porreca emphasized the importance of “top-down modulation,” partly because descending pain modulatory circuits have been clinically validated by actions of analgesic drugs, such as opioids. One hypothesis is that abnormal brain processing of pain can be maintained by low levels of pathological signaling from peripheral pain neurons. “So changes within the central nervous system may be essential in modulating the abnormal persistent input. This has led to the idea of long-range loops—spinal cord to brainstem to spinal cord loops, in which there is a process of central disinhibition or enhanced facilitation.”

Pain is influenced dramatically by the emotional state of the individual, by the degree of attention or distraction, by changes in expectation, by changes in stress.

—Frank Porreca

Conceivably, chronic pain could be reduced by breaking such long-range circuits, particularly by augmenting the descending paths that inhibit incoming pain signals. “There is a distinction in the mechanisms that initiate the pain process and the mechanisms that sustain the process over time,” Porreca said. The latter mechanisms are of most interest, he added, because chronic neuropathic pain is a condition caused by a cascade of physiological events—a cascade that should be the target of clinical trials.

4. Imaging CNS Degeneration and Chronic Pain

A. Vania Apkarian, Ph.D., of Northwestern University, has shown that chronic pain has a more profound effect on the brain than previously recognized. “The cortex is more important for pain perception than has been appreciated until now,” he said. “It is fundamental. Looking at the properties of the cortex, we can learn more about specific clinical conditions.”

In his research, Apkarian uses various imaging technologies: MR spectroscopy, functional MRI, MR morphometry, and diffusion tensor MRI. He has found that the representation of chronic pain is unique for distinct clinical conditions and that pain-related brain anatomy is plastic, changing in different clinical conditions. This brain reorganization can directly affect cognitive abilities and our ability to accomplish simple everyday tasks. Because these mechanisms can be reproduced in animal models of chronic pain, they suggest new clues to brain circuitry and novel therapies that target the cortex rather than the periphery or descending pathways.

Apkarian’s studies of patients with chronic back pain and complex regional pain syndrome showed that these individuals are differentially impaired in standard gambling and face-recognition tasks. He also found that chronic back pain patients have a more acute sense of taste than normal volunteers. “The joke is that you should not go to Las Vegas with chronic pain patients, but you should go wine tasting with them.”

Apkarian also finds correlations between brain activation patterns and clinical measures of chronic back pain, as

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—A. Vania Apkarian

well as between brain activation patterns and the number of years a subject has had chronic pain. These brain activation patterns vary according to disorder. “Each has its own signature,” he said. “Different chronic pain populations seem to show unique patterns of brain regional atrophy.”

Chronic pain, Apkarian concluded, leaves specific signatures on the brain. “The long-term implication is that, in the future, each type of chronic pain condition has to be treated independently—based on its own circuitry and anatomy and activity.”

5. C fibers and Neuropathic Pain

John W. Griffin, M.D., of the Johns Hopkins Brain Science Institute, studies the role of C fiber nociceptors in generating neuropathic pain, and the roles of growth factors such as nerve growth factor in amplifying neuropathic pain. He and his colleagues have developed techniques for assessing nerve fibers within the skin that are used both to investigate peripheral pain in the laboratory and to diagnose nerve diseases that affect peripheral pain fibers.

“The skin is a complex multicellular neurobiological unit that is both affecting and being affected by its afferents,” Griffin said. As a result, the skin can change its nociceptive arbor day-to-day, “tuning” its responsiveness to potentially painful stimuli.

Burning foot pain is a common problem among patients with diabetic neuropathy and similar nerve diseases. “The virtually universal finding is a partial loss of C fibers within the epidermis in the affected distal regions. There’s an element of dying back of these small sensory nerve fibers,” said Griffin. At question is whether this spontaneous activity arises entirely in injured fibers or also in uninjured neighboring fibers.

In experiments on mice, Griffin looked at changes in innervation after nerve injury. He found that after one of the major nerves that innervate the paw—the sciatic nerve—was cut, fibers from the remaining uninjured nerve, the saphenous, grew into skin previously innervated by the sciatic nerve. By 90 days after injury, the entire paw was innervated by the saphenous nerve. All of the fibers that had sprouted were nociceptive C fibers.

The trigger for this dramatic sprouting appeared to be exposure of nociceptive fibers in the saphenous nerve to a marked increase in growth factor made by the skin formerly innervated by the sciatic. This changed the saphenous nerve fibers. “They enlarge, so that the original saphenous fibers become much bigger than they used to be. They are responsive to mechanical stimulus. They’re also quite responsive to both heat and cold stimuli,” Griffin explained. “Some factor in the denervated epidermis is sufficient to change the behavior of the peripheral fibers of the afferents.”

Such changes in the properties of nociceptive neurons contribute to the altered processing that underlies chronic neuropathic pain. “Looking to the future, it’s important to attend to the surround of C fiber terminals in the skin,” Griffin said. But to continue this line of research, he cautioned, “We need better ways of measuring ongoing pain in animals and a better understanding of the process of centralization—as well as the efferent effects of these altered afferents on the skin, and the contribution of the cells and molecules of the immune system.”

Progress in Education

Who are today’s pain doctors? In the United States, anesthesiologists provide most pain treatment—although their training typically focuses more on palliative care and less on the detailed history-taking and diagnostic tools required to ferret out the causes of chronic pain.

Economic incentives are partly responsible for this trend. Anesthesiology is procedure-oriented, and a physician who spends ten minutes administering an injection of local anesthetic is reimbursed far more than a neurologist who takes a detailed medical history and performs the type of examination required to develop a long-term treatment strategy. “You get paid much less for 40 minutes of cognitive work than you get for the ten minutes that you spent sticking a needle in someone’s neck,” said Howard Fields. “Whether it works or not, the payment differential is still there.”

Tracing the root of the problem, medical students receive only 12 hours of training to meet medical licensing requirements for pain medicine training. “Pain is fighting with everything else: cardiology, vascular physiology, immunology, genetics,” said Fields. “There’s a turf battle across specialties.”

To help address these issues, James Rathmell, M.D., of Harvard Medical School, has worked to make pain-fellowship training more rigorous and consistent. Rathmell authored the 2007 Program Requirements for the Multidisciplinary Pain Medicine Training Programs, which were adopted by the Accreditation Council for Graduate Medical Education.

We want to bring together neurologists and physical medicine and rehabilitation specialists and psychiatrists to answer the question: How can we create the best training across disciplines?

—James Rathmell

The goal in revising pain-fellowship training is to improve the quality and consistency of training; to ensure access to training programs across specialties, particularly for non-anesthesiologists; and to reduce fragmentation that would arise if each specialty created its own pain medicine training programs. “We want to bring together neurologists and physical medicine and rehabilitation specialists and psychiatrists to answer the question: How can we create the best training across disciplines?” Rathmell explained. Among the most important alterations to the new program

requirements: a multidisciplinary core teaching faculty.

As this training regimen evolves, the question becomes: Is pain medicine a primary discipline or a sub-specialty? The American Board of Pain Medicine has twice petitioned the American Board of Medical Specialties to create a primary discipline called pain medicine, which would mandate a four-year residency after medical school encompassing both

general and sub-specialty training. To date, the parent boards have denied this request, instead working toward improving subspecialty fellowship training programs through the efforts of Rathmell and his colleagues.

Rathmell thinks that will change. “I believe that we’ll get there. But we’re going through this transition of a sub-specialty, so that we can create a homogeneous group of practitioners. Once we have a homogeneous group of pain medicine specialists, then we’ll be able to train others in the discipline.”

Mapping the Future: Research, Funding and Visibility

Despite scientific and institutional constraints, the pain field is replete with research possibilities, said Kathleen Foley, M.D., of Memorial Sloan-Kettering Cancer Center. One potentially fruitful study could follow injured military personnel from current wars in Iraq and Afghanistan. Among the more than 30,000 soldiers injured in the conflicts, 50–90 percent suffer disability due to pain. “Is this the prospective study that we need to be engaged in—looking at their genetics, at their pain symptoms, and at what happens to them over time?” she asked.

The poor efficacy of therapies for neuropathic pain lends urgency to such a study. “Clinically meaningful pain relief occurs in less than half of the patients half of the time with the available anti-depressants and anticonvulsants,” Foley said. Meanwhile, physicians are often unwilling to prescribe long-term opioid therapy for chronic, non-malignant pain. “It’s not that the patients don’t exist. It’s not that the treatments are not out there. But we don’t have at present a network or a mechanism for capturing these patients to study,” she explained. “We desperately need careful studies of the long-term efficacy of these drugs. We need to be following these patients over a long time, with large cohorts.”

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—Kathleen Foley

Dying patients are another urgent research priority. According to a 1995 study, half of patients dying in hospitals experience significant untreated pain. Untreated pain is even more prevalent in children dying of cancer. “In the best of treatment approaches,” Foley said, “30–40 percent of cancer patients are still inadequately treated.”

Though 2001–2011 was designated by Congress as the Decade of Pain Control and Research, “It’s been a decade that’s been underfunded, disorganized and has had a lack of vision,” Foley lamented. In 2003, pain research made up only 1 percent of the NIH budget. Even in 2009, there is no NIH institute on pain.

Yet recent developments offer glimmers of hope. The Pain Care Coalition (made up of the American Academy of Pain Medicine, the American Pain Society, the American Headache Society, and the American Society of Anesthesiologists) has since 1998 worked to shape federal healthcare policy via legislation, regulation and research. The Department of Defense’s 2008 Military Pain Care Policy Act requires comprehensive pain care for active and retired military personnel. The 2008 Veterans Mental Health and Other Care Improvement Acts establish a pain care program within all inpatient Veterans Affairs facilities—another potential research base. According to Foley, “They offer a unique opportunity for us to look at the acute-to-chronic process, at the nature of pain, at the genetics, and at treatment approaches.”

Meanwhile, foundations and society at large are beginning to address the problem. The American Cancer Society launched the National Palliative Care Research Center, supporting pilot projects and young investigators. Other foundations—including the Mayday Fund, the Rita Allen Foundation, the Robert Wood Johnson Foundation, and the Soros Foundation—have also supported pain research. The National Pain Care Policy Act, now being considered by Congress, establishes a National Center for Pain and Palliative Care Research within the NIH. Some groups have even argued that pain relief is a “universal human right.” “If nothing else,” Foley said, “it serves as symbolic language for us who wish to argue for better treatment of patients.”

“The patients are just ordinary people who every day have to live with terrible pain,” said Foley. “We can do better.”



“Pain is, regardless of the constraints on funding, a very important part of the NIH portfolio,” said Patricia A. Grady, Ph.D., of the National Institute of Nursing Research and the NIH Pain Consortium. “There’s really good science that is going to inform what we do. More to the point of the National Institutes of Health: Pain is extremely costly to individuals and to our society—in terms of everyday activity, productivity, quality of life.” The NIH’s pain research budget, flat for the past six years, will be \$221 million in FY 2009.

Twenty NIH institutes and centers, collectively known since 1996 as The Pain Consortium, are involved in interdisciplinary approaches to pain research. “Our job was to create a research agenda across the board that was not Institute-specific,” Grady explained, “but which was much more pain-specific, i.e., substantively specific.”

Among the Consortium’s key research themes: basic mechanisms of pain response; pain management and treatment; individual differences in pain response; environmental influences on pain; and emotional and bio-behavioral aspects of pain. These research directions have led to discoveries related to improved treatments for neuropathic pain, genes that increase rheumatoid arthritis risk, microRNAs in inflammatory muscle pain, and other findings. Funding opportunities in neurological pain research range in subject from cancer and immune disorders to migraine to chronic fatigue syndrome. The NIH Transformative R01 Program has invited applications on the Acute to Chronic Pain Transition.



“Pain is an elephant. There’s the tail and the ears and the feet and the trunk and the belly. And to try to wrap all that up into a single thing or a set of things that people can understand is very difficult,” said Story Landis, Ph.D., Director of the National Institute of Neurological Disorders and Stroke (NINDS)—the largest funder of pain research at NIH. To convince a Congressperson on an appropriations committee of the need for more pain research funding, Landis spun out several three-minute “elevator talks.”

One pitch, she said, would underscore the fact that current treatment strategies are “woefully inadequate,” and would tie basic science advances, such as the 1997 cloning of the capsaicin receptor, to the promise of therapeutics.

A second pitch would emphasize the bench-to-bedside track record of recent breakthroughs. “We worked very hard as a scientific community to understand the changes that occur in sensory neurons when acute pain transitions to chronic pain,” she said. “As a consequence of that, we have a list of proteins whose expression increases”—a list that pharmaceutical companies could exploit to search for new treatment strategies.

“Obviously, we should also be thinking about going from bedside to bench,” Landis reminded the group. A third pitch might explain that the transition from acute to chronic pain is an example of maladaptive plasticity—not unlike that which occurs in the development of epilepsy. “What this means, scientifically, is that we have the opportunity to harness all the advances that have come out of our understanding of learning and memory—plasticity at the molecular level, the synaptic level, the circuit level—and apply it to this very present problem of acute pain.”

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—Story Landis

Summing up, Landis conceded that, “The issue of pain is incredibly complicated.” She offered a bracing public relations challenge to the assembled experts: “What you need to do as a field is to come up with relatively simple messages that we can use to get more money, which then can be used to fund you.”

By the end of the conference, the participants agreed that the field of neurological pain research was poised to make giant strides. What it needed to transform this promise into reality was institutional commitment, financial investment, public visibility, and energetic advocacy. “No one would stand up and say, ‘I’m against pain research,’” said Kathleen Foley. “They’re just not *for* it enough.”

Workshop Recommendations

Research Goals:

- Describe the circuitry of the general factors underlying pain: nociceptor, dorsal root ganglion, spinal cord, brainstem, thalamus, and cortex.
- Identify pain biomarkers for use in screening compounds.
- Describe the shared biology among pain syndromes, to better understand the conditions and to predict their response to therapy.
- Investigate whether genetic studies can offer clues to the mechanisms of pain, by examining differences and commonalities among patients with the same and different pain diagnoses.
- Explore the potential of fMRI in pain research—correlating imaging with phenotyping; looking for common changes in the brain among patients with chronic pain, regardless of etiology; and developing signatures of various pain syndromes and their responses to therapies.
- Identify the pain generator in acute, sub-acute and chronic back pain.
- Develop better rodent models, testing standards, and phenotypic criteria for pain research.
- Develop mechanism-based treatments for pain based on insights into disease pathogenesis.

Treatment Goals:

- Develop tools to identify which individual patients will respond to which specific therapies.
- Develop protocols to define which pain patients need to see a neurologist.
- Leverage genetically-identified risk factors to drive drug development.
- Create new tools that would make pain diagnosis and therapy more of a science and less of an art.
- Encourage a pharmacogenomics approach to evaluating analgesic agents in patients.

Education Goals:

- Find ways to expose more neurology residents to pain patients, to spark their interest in the field.
- Identify academic champions of pain research that students and residents can seek out.
- Recruit the most gifted teachers and employ the best teaching methods in pain education.
- Conduct a survey of all neurology residencies, to find out what they offer in pain training and what proportion of their residents specialize in pain medicine.
- Outline a curriculum for medical students, primary care physicians, neurologists, and pain specialists that will define specific information to help each medical professional accurately diagnose and appropriately treat or refer pain patients.
- Establish centers of excellence for training neurologists in pain medicine.

Visibility Goals:

- Create a campaign for research funding. Find champions for pain neurology, from both the public and private sectors.
- Learn from the successes of other once-emerging fields of neurology, such as Alzheimer's disease and multiple sclerosis research.
- Consider temporary financial support by philanthropic grants until a nascent area of research gains enough visibility for NIH funding.
- Establish an award for neurologic pain research through the American Academy of Neurology to demonstrate its legitimacy to the general neurology community.



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