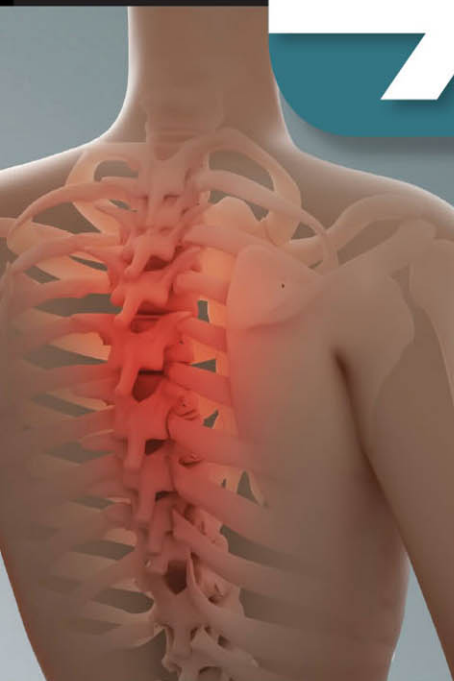


SECOND EDITION

# PAIN MEDICINE & MANAGEMENT



## JUST THE FACTS



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PETER S. STAATS  
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# PAIN MEDICINE AND MANAGEMENT

*Just the Facts*

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# PAIN MEDICINE AND MANAGEMENT

*Just the Facts*

*Second Edition*

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We would like to dedicate this book to the millions of patients suffering from pain worldwide, and the physicians and health care providers who care for them. We would also like to make a special thank you to the authors of this text. In drafting our wish list for authors, we searched for experts around the globe to help us gather the most relevant information on the management of pain. Many of you helped us with the first edition of this book, and your dedication has made the process seamless. We intend for this book to be a broad resource on the management of pain, as well as a tool for those studying for their board examination or seeking to further their knowledge base in pain management.

There are so many influential leaders who have contributed to the advancement of caring for patients with pain. While we cannot list everyone who has helped or influenced us, we would like to make a special thank you to our leaders and mentors in the field of pain for their sage counsel and advice over the years. Two great men, Dr. Sam Hassenbusch and Dr. John Oakley, deserve special mention. They were great friends and leaders, true heroes of pain management, and both gave tirelessly to the field of pain management. Tragically, we lost them both much too early. Sam and John, while you are no longer physically with us, your influence is still felt across the globe. We thank you and miss you.

*To our parents:* You gave us the foundation and compass to begin this journey, along with continued love and support along the way. We understand, now that we are parents, all the sacrifices and care you provided, and are truly appreciative.

*To our spouses, Nancy and Anne:* You will never know how deeply we need your support and counsel. We appreciate all that you do for us to try to do something that matters to improve the care of patients across the globe.

*To our children, Alyssa, Dylan, Rachel, Zachary, and Dominick, the next generation:* You are entering such an exciting time in the evolution of medicine and the history of mankind. The advances that will come during your lifetime will seem almost like magic to a previous generation. We encourage you to embrace your dreams and hopes, and use your energy to improve the lives of others and the world in some way.

*Peter S. Staats, MD, MBA*

*Mark S. Wallace, MD*

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# PREFACE

We edited the first *Pain Medicine and Management: Just the Facts* over ten years ago, and it has served as a valuable tool for physicians who need a brief review on a topic, and those studying for the examination process. Over the past ten years a tremendous amount has changed in the health care arena, while some things have remained largely unchanged. Pain remains one of the greatest health care crises affecting American citizens and citizens of the world. Uncontrolled pain remains a major cause of disability, lost productivity, increased health care costs, and decreased quality of life. In 2011, the Institute of Medicine (IOM) published their landmark report “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.” The fact that the IOM took on this effort speaks to the growing public opinion on the impact chronic pain has on everyday life. The report led to the National Pain Strategy (NPS) charged with providing the Secretary of Health recommendations on the future of pain care in America. One likely focus of the report will be on the importance of using a biopsychosocial approach to pain management. Like our first edition, the second edition of *Pain Medicine and Management: Just the Facts* has a chapter devoted to this topic.

Over these past ten years we have also learned that opioids, while they may control some pains, can be fraught with problems including overutilization, abuse, diversion, and addiction. In 1995, the American Pain Society voiced that pain should be considered *the fifth vital sign*. In 1999, noting the tremendous problem with pain, the JCAHO endorsed the fifth vital sign as a mandatory component of a patient’s evaluation. As an outgrowth, physicians were told that they must treat pain, and hospitals depend on patient satisfaction scores to determine reimbursement rates. While this may seem like a progressive and appropriate approach at first glance, unfortunately, no clear evidence-based algorithm was provided to physicians or hospitals. Uncontrolled pain soon became equated with “give more opiates.” Opioid treatment guidelines were initially intended for acute pain management, but guidelines emerged for their use in chronic pain and rapidly became the standard for (chronic and cancer) outpatient settings as well. Without adequate training, physicians relied on increased use of opioids, believing that opioids were uniformly effective. This approach has recently been challenged, and a more thoughtful risk-benefit analysis has been advocated as it relates to opioid management with more emerging evidence favoring harm than benefit. In order to help address these concerns, a specific chapter on

the clinical role of opiates in chronic pain was added to this edition, along with updates on substance abuse and the roles of urine toxicology and appropriate monitoring. Many alternatives to opiates are also provided throughout the text and are in line with the long favored biopsychosocial approach to chronic pain.

In addition, the Affordable Care Act has improved access to care for many, which of course every physician wants; however, there may be unintended consequences as well. If physicians are not provided adequate resources and tools to provide that care, we may see problems with overutilization of pharmaceutical drugs or inappropriate referrals for more invasive procedures. Insurance companies have been given unparalleled power to deny appropriate care, which frequently involves interventional care. Ironically, in some settings this drives physicians to more expensive or possibly riskier pharmacologic strategies. This text is intended to be one of many tools that physicians can use to help diagnose and manage their patients with chronic pain.

This second edition of *Pain Medicine and Management: Just the Facts* includes 14 new chapters and 66 updated chapters that reflect the evolving practice of pain medicine. We omitted six chapters that were out-of-date. Each chapter is not intended to be an exhaustive, reference-based source, rather a quick resource to help health care providers and their patients with appropriate strategies. Although each chapter presents individual topics, it should not distract from the integration of multidisciplinary assessment and treatment using a biopsychosocial model. Whether brief or extensive, we believe that all chronic pain patients need to be evaluated in this context before initiating treatment.

## Section 1

# TEST PREPARATION AND PLANNING

## 1 TEST PREPARATION AND PLANNING

*Stephen E. Abram, MD*

### SUBSPECIALTY CERTIFICATION EXAMINATION IN PAIN MEDICINE

- There are several examinations from several organizations
    - The American Board of Anesthesiology (ABA)
      - A written examination in pain medicine designed to test the presence of knowledge that is essential for a physician to function as a pain medicine practitioner.
      - The only board examination that is recognized by the American Board of Medical Specialties.
      - The only board that requires completion of an American Council on Graduate Medical Education Accredited Pain Fellowship.
      - Serves as the Pain Medicine subspecialty examination for the American Board of Physical Medicine and Rehabilitation (ABPMR) and for the American Board of Psychiatry and Neurology (ABPN).
      - Certification awarded by these Boards on successful completion of the examination is time limited and expires in 10 years, and a pain medicine recertification examination is offered to provide maintenance of certification as well.
      - As of the year 2012, nearly 5000 ABA, over 1500 ABPMR, and nearly 300 ABPN diplomates have received initial certification, and over 2500 physicians have completed the recertification process.
      - In 2010, the program of Maintenance of Certification in Anesthesiology for Subspecialties (MOCA-SUBS) was initiated.
    - Beginning in 2017, all ongoing certification will be carried out through the MOCA-SUBS process for all of the specialties involved in the certification process.
    - As of the writing of this chapter in 2013, the process for the three specialties has not been completely defined, but it is likely that a recertification examination will continue to be part of the process.
  - American Board of Pain Medicine
    - Offers a Pain Medicine board examination through the American Academy of Pain Medicine
  - American Board of Interventional Pain Physicians (ABIPP)
    - Offers an examination process for interventional pain physicians through the American Society of Interventional Pain Physicians (ASIPP).
  - The World Institute of Pain (WIP) offers an examination for international physicians who are not eligible for the United States ABME-approved fellowship training.
- The examination required for the Certificate of Added Qualifications in Pain Management was initially offered in 1993 by the ABA, 1 year after the Accreditation Council for Graduate Medical Education approved the first accredited pain fellowship programs. Entrance into the examination up until 1998 was dependent on either completion of a 1-year fellowship in pain management or the equivalent of at least 2 years of full-time pain management practice. Subsequent to the 1998 exam, ABA diplomates were required to complete an ACGME-approved pain fellowship. The name of the certification process has recently been changed to Subspecialty Certification in Pain Medicine.
  - Beginning with the year 2000 examination, the ABA Pain Medicine Examination was made available to diplomates of the ABPN and the ABPMR. For a



- period of 5 years, physicians from these specialties were admitted to the examination system on the basis of temporary criteria similar to the process in place for ABA diplomates during the first 5 years of the examination system. Since 2005, successful completion of an ACGME-approved fellowship in pain medicine has been required. Candidates from the ABPN and the ABPMR are awarded subspecialty certification by their respective boards, not by the ABA, on successful completion of the examination. The ABPMR offers subspecialty certification to any physician who is a diplomate of an American Board of Medical Specialties (ABMS)-approved board, and who has completed an ACGME-approved pain fellowship training program. This process has provided the opportunity for physicians in any discipline, including primary care physicians, to obtain certification in pain medicine, provided they are able to obtain fellowship training. With the expansion of the examination system to diplomates of the other boards, there was a broadening of the scope of the examination. Question writers and editors from Neurology, Psychiatry, and PM&R were added to the examination preparation process. Although previous examinations included material from all aspects of pain management practice, the infusion of new expertise produced a more diverse question bank. The examination should, and does, contain information from all the disciplines involved in the multidisciplinary treatment of pain. The areas of knowledge that are tested can be found in the ABA Pain Medicine Certification Examination Content Outline. This document is revised periodically and can be found on the ABA website, <http://www.abanes.org>.
- The ABA Pain Medicine Certification Examination is a comprehensive 200-question exam, administered by computer. The examination now uses only the A-type question format. The A-type question is a “choose the best answer” format with four or five possible answers.
  - The ABA, ABPMR, and ABPN certificates in pain medicine are limited to a period of 10 years, after which diplomates are required to pass a recertification examination. The recertification process uses the 200-question certification exam. The success rates for ABA diplomates from 2005 through 2012 are as follows:

	2005	2006	2007	2008	2009	2010	2011	2012
Certification	83%	86%	78%	89%	89%	89%	80%	86%
Recertification	93%	88%	89%	92%	86%	91%	100%	77%

The pass rate for ABPMR diplomates for 2012 was 86% for initial certification and 85% for recertification. For ABPN diplomates, it was 91% for initial certification and 85% for recertification.

- The ABA began offering a Pain Medicine In-Training Examination in 2013. This is a 3-hour, 150-question examination that offers Pain Medicine Fellows the opportunity to experience this type of computer-based examination in their subspecialty and gives them information regarding their areas of knowledge strengths and weaknesses. It also provides fellowship training programs some feedback on how well they are preparing their trainees for exam preparation.

## PREPARING FOR THE EXAM

- A reasonable first step in the study process is to identify areas of weakness.
- The ABA Content Outline (available through the ABA website or through each of the other two primary boards).
  - Provides a detailed and comprehensive list of topics that pain fellows need to study in order to understand the scientific basis of pain management, to provide good patient care, and to do well on the certification exam.
  - The order of topics is not designed to be a curriculum to be followed for the year of fellowship training. Rather the Content Outline is useful in assuring that all of the areas of knowledge are adequately covered during the fellowship and as a study guide for exam preparation.
  - This text covers a large portion of the required knowledge base for successful completion of the examination.
- Selection of study materials is always a dilemma.
  - A useful source is the *Core Curriculum for Professional Education in Pain*, published by the International Association for the Study of Pain (IASP).
    - Available for purchase through the IASP website ([www.iasp-pain.org](http://www.iasp-pain.org)) and is also available as PDF downloads at that site.
    - It is organized somewhat differently than the ABA Core Curriculum, and has a less extensive list of topics.
    - Emphasizes the important aspects of each area of study, and provides concise information about each target area as well as extensive bibliographies for each section.
    - The latest version is the third edition, published in 2005.
    - While some of the references will be out of date and supplanted by more recent publications, there are many classic references that are still quite relevant.
  - There are a growing number of textbooks on pain medicine, each with its own strengths and weaknesses.

- It is reasonable to use comprehensive textbooks as a study source, keeping in mind that, by definition, information is somewhat outdated by the time a large textbook is printed and that there are strong and weak chapters in any given textbook.
- While the examination tends not to use extremely new findings, there is an effort to keep information current, particularly if there are strong data from multiple sources.
- It may be helpful to supplement the use of textbooks with recent review articles, particularly for topics in fields that are changing rapidly, such as the basic sciences related to pain.
  - Available through medical literature search instruments, such as Medline, which can be limited to English language, review articles, and, where appropriate, discussions of human subjects or patients.
- Some students retain information best from written material, others from spoken lectures.
  - A combination of both sources results in the most effective retention.
  - Participation in pain medicine review courses provides both visual and auditory inputs.
    - Offered by:
      - ◆ American Pain Society
      - ◆ IASP
      - ◆ American Society of Regional Anesthesia and Pain Medicine
      - ◆ American Academy of Pain Medicine. Many of the specialty societies offer topics in acute, chronic, and cancer pain management at their annual meetings as well.
      - ◆ ASIPP annual meeting
    - High-quality courses are also offered by both academic and private practice groups.
    - Many review courses offer audio tapes of lectures. A major advantage of this medium is the ability to use commuting time to review pertinent topics. Hearing material that has previously been read tends to solidify one's learning.
- Perhaps the best learning method is to review the available information regarding a patient one is currently managing.
  - For many practitioners, application of this knowledge in the clinical setting is the best way to learn new information and to retain knowledge.
  - Review the available literature on a given condition in anticipation of a particular patient coming into the clinic or hospital with that condition or shortly after seeing a patient with the condition.
- Problem-based learning sessions, which are becoming more prevalent in clinical meetings and symposia, are also effective in focusing on a clinical condition and linking that clinical situation to a knowledge base.
  - Question-and-answer textbooks may be helpful in identifying gaps in knowledge and, if self-testing is done periodically, may be a measure of study progress. Practice examinations increase one's confidence in the test-taking process and increase familiarity with the format.

## GENERAL STUDY TECHNIQUE

### PLANNING MATERIAL TO COVER

- The material to be studied will depend to a great extent on the range and depth of material covered in residency and fellowship training, and the time period from which training has been completed.
- Study of material covered in depth during training need only be reviewed briefly, while material covered only superficially needs to be studied in depth. Much of this decision is dictated by the candidate's specialty.
  - An anesthesiologist probably needs to spend considerable time on headache management or rehabilitation of the spinal cord-injured patient, while a neurologist needs to study indications of and techniques for nerve blocks.
  - As noted above, a grid, such as the ABA Core Curriculum, can be used to select topics for review versus in-depth study.

### PLANNING STUDY TIME

- Once you begin the study process, it is helpful to evaluate the amount of time available for study and to schedule your available time.
  - Very short study sessions tend to be ineffective, whereas 1- to 2-hour sessions are probably optimal.
  - Daily sessions of an hour or two are more productive than weekly sessions of 5 or 6 hours.
  - According to Sherman and Wildman, the best schedule is an hour or two daily for many days, ending in a concentrated review session shortly before the examination.
  - Early in the study process, considerable time should be devoted to surveying the material to be learned, whereas later in the process, reading and reviewing material should be used more frequently.
  - It is helpful to develop a routine for each study session. An example follows:
    - Briefly review previously studied material.
    - Survey new material to study.
    - Review study questions on the topic, or create study questions.
    - Study the material.
    - Review the material studied.

## STUDY SKILLS

- Look for the main ideas in what you read.
  - When reading about the management of a specific syndrome, what is the principal treatment modality?
  - For a chronic condition, the primary goal may be regaining strength and flexibility, while many of the specific treatments merely provide the means to achieve this primary goal.
  - Understanding the pathophysiology of a specific condition helps you remember the clinical features and management principles of the disorder. Assess your confidence in your knowledge and understanding of a topic. If you feel good about that material, go on to a different topic. If not, continue to read and review.
  - Write out a brief summary of the material you have studied. Include the main ideas and the most important details.
  - If possible, discuss the material with other trainees or with colleagues. Ask others about their understanding of a topic. If their ideas conflict with yours, reread the material. Read additional material on important topics. This will reinforce learning and may uncover areas where controversy and differences of opinion exist. A variety of techniques have been devised to help us remember important information.
    - One helpful technique is to organize information being learned. The Content Outline can be helpful in organizing information by topic.
    - There are a number of specific techniques for aiding memory and recall.
      - Overlearning refers to the repetitive study of a topic that is already familiar.
      - As stated previously, listening to an audio tape of a lecture subsequent to reading about the topic can reinforce learning.
      - Analogies can be helpful. You can compare a topic being learned to a topic with which one is familiar. For instance, you might think of certain types of neuropathic pain caused by an ectopic focus of nociceptor activity as analogous to a seizure. Such an analogy may be particularly useful, as both conditions may benefit from the same type of drugs.
      - Imagery can be a powerful memory technique. Creation of a visual image that describes a condition, a theory, or a treatment can be a very effective aid to learning and recall.
      - Some students find the use of acronyms helpful. I occasionally find myself using mnemonics and acronyms I learned many years ago in medical school. The ones that are a bit risqué seem to be the easiest to remember.
  - Recitation of material aloud multiple times is an effective way of improving retention. If the recited material rhymes or is connected to a vivid mental picture, it will be still easier to remember.
  - If you are in an academic setting, teaching the material you have just learned to other trainees can be an extremely powerful technique, as it requires organization as well as understanding of the material.
  - Restating information, such as rewriting certain key aspects of a learned topic, can be a powerful tool. Restating a concept in your own words is most effective.
  - Quiz yourself on the material. This is particularly important for auditory learners.
  - Note taking is particularly important for visual learners. Notes should be brief, clear, and succinct. This is much more effective than underlining, and notes can be reviewed shortly after the reading session, and may be used for self-testing.
  - Review should be done immediately after completion of a learning session. Practice should then be repeated periodically.
  - Intent to learn is important.
    - Reading and listening to new information with the active intent to learn is key to the memory process.
    - Some of the techniques stated above should be coupled with this active intent to remember.
  - Attention and interest are critical.
    - As the pain medicine examination covers material that is vitally important to future practice, interest should be given.
    - There may, however, be material outside your proposed area of expertise or practice that stirs little interest.
    - Consider situations in which such material might become important to your practice.
- There are a number of reasons why we forget learned material.
    - We may not have learned the material well. During the learning process, the material must be given interest and attention.
    - Subsequently, questioning oneself about the material and periodically reviewing are critical.
      - Disuse leads to loss of memory.
        - We forget the most in the first 24 hours after learning, and it is during this period that review is most helpful.
        - Interference is another source of forgetting.
          - ◆ Interference may be related to anxiety, distraction, emotional disturbance, and intellectual interference.

- ◆ Intellectual interference, or mental overcrowding, is related to loss of memory during subsequent intellectual activity.
- ◆ This can be minimized by reflecting on what has just been learned, and by synthesizing and organizing the material before moving on to other topics.
- Another strategy is to follow a learning session with sleep or nonintellectual activities, such as exercise, and recreation.
- A lack of attention or effort during the learning process is very detrimental. There must be concentration without distraction during the learning process, and a conscious effort to learn and remember.

## STRESS AND ANXIETY

- Stress that occurs during preparation for an exam is related primarily to anxiety over the possibility of failing the exam and the consequences of that failure. The best way to deal with this is through adequate preparation and the use of practice tests to demonstrate preparedness.
- There are a number of techniques for dealing with the remaining anxiety and stress.
  - If anxiety interferes with the study process, meditation, relaxation exercises, and massage can be helpful.
  - Many individuals find that aerobic exercise works best.
  - If you begin to panic during test preparation or the test itself, it is helpful to focus your attention away from the anxiety-provoking topic.
  - Breathing exercises, with concentration on breathing alone, can be beneficial.
- Another technique is to concentrate on a muscle group, first contracting then relaxing those muscles. Make a tight fist, hold it for a few seconds, then open and relax your hand, watching the blood return to the palm. Negative thoughts about the exam or about poor performance (“catastrophizing”) can increase anxiety and fear, increase catecholamine levels, and interfere with performance.
  - Mental practice or mental rehearsal, a technique often used by athletes, can replace negative thoughts, and can be adapted to the examination process.
  - Visualize yourself sitting in the exam setting calmly and confidently, focusing all your attention on the examination. You will thus create a vivid mental image of positive outcomes, such as successfully answering a question. The technique needs to be repeated on multiple occasions. It is most successful when it is preceded by relaxation exercises.

## TAKING THE EXAM

- Reviewing of important information the day before the exam can be beneficial, but keep the sessions to an hour or two and do not let them compete with needed recreation, relaxation, and sleep.
- Eat regular, moderate-sized meals.
- Use stress-reducing techniques.
- If you do aerobic exercise regularly, continue it the day before the exam.
- On the day of the exam, avoid last-minute cramming. It is probably best not to study at all in the last hours before the exam.
- You may want to avoid caffeine, even if you use it regularly, as the combination of examination anxiety and caffeine may produce over-stimulation.
- Arrive at the examination site early enough that you are not rushed or stressed.
- Assess the number of questions on the exam and calculate the amount of time you can spend per question. Read the directions carefully.
- Computer-based exams usually provide a brief practice exam that can be used prior to the start of the actual exam. Be sure to participate in this exercise.
- Read each question or stem carefully. Note questions asking for “all are correct **except**” answers.
- Think of your own answer or answers to the questions before reading the examination answers and choose responses that are closest to yours.
- Eliminate choices that you know are incorrect.
- Read all the possible responses before selecting an answer. Some questions ask for the *best* answer among responses that may have more than one correct answer.
- For examinees who are prone to test anxiety, it may be helpful to read through but not answer difficult questions initially, answering the easier questions first. This technique provides momentum and confidence to complete the exam initially. Later items may provide cues for answering skipped items.
- Answer all the questions unless there is a penalty for wrong responses (this should be made clear from the test instructions).
- Use all of the allotted time.
- Rework difficult questions and look for errors on easy questions, such as selection of the wrong letter or misreading of the stem.

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*University of Minnesota Learning and Academic Skills Center*  
<http://www.ucs.umn.edu/lasc/OnlineLearn.htmlx>  
*University of New Mexico Center for Academic Program Support*  
<http://www.unm.edu/~caps/strategies.html>  
*University of South Australia Learning Connection* <http://www.unisanet.unisa.edu.au/learningconnection/students.htm>  
<http://www.unisanet.unisa.edu.au/examsuccess/>

## ONLINE RESOURCES

*Dartmouth Academic Skills Center* <http://www.dartmouth.edu/admin/acskills/>  
*Study Skills Assessment Instrument* [http://www.hhpublishing.com/\\_assessments/LASSI/index.html](http://www.hhpublishing.com/_assessments/LASSI/index.html)

## Section 2

# BASIC PRINCIPLES

## 2

### A BRIEF REVIEW OF THE BASIC PHYSIOLOGY OF PAIN PROCESSING

*Linda S. Sorkin, PhD*

*Tony L. Yaksh, PhD*

#### PAIN—MULTIPLE FACETS

- “Pain” as defined by the International Association for the Study of Pain: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”
- The psychophysical experience of pain may be divided into sensory-discriminative (“I hurt here on a scale of 1–10”) and motivational-affective (“I really don’t like this experience and will try to avoid it in the future”) components.
- The so-called prefrontal lobotomies carried out in the last century had no effect upon sensations associated with chronic pain (eg, head and neck cancer), but altered the affective component of the pain state. This is taken as support of this orthogonal dichotomy.

#### NOCICEPTIVE PAIN

##### BEHAVIORAL CHARACTERISTICS

- “Nociceptive pain” is secondary to real or threatened damage to non-neural tissue and subsequent nociceptor activation.
- The nociceptive message is initiated by high intensity, potentially tissue-injuring stimuli (thermal, mechanical, and/or chemical products, including both endogenous locally derived agents, eg, kinins, prostaglandins (PGs), and exogenous chemical products)

applied to or released near non-neural tissues (skin, muscle, viscera, etc.).

- A nociceptive stimulus typically evokes a constellation of responses with increasingly complex levels of organization:
  - local flexion (withdrawal) of the stimulated limb, which may be spinally mediated (local reflexes);
  - autonomic responses (increased pituitary-sympathetic outflow, respiratory rate/blood pressure/heart rate) mediated by outflow organized at the brainstem level;
  - organized escape behavior; and
  - emotive/affective expressions organized at the cortical level.

##### NOCICEPTIVE PAIN PATHWAYS

- As spinal cord lesions restricted to one side produce deficits in contralateral pain (the Brown Sequard syndrome and identified by William Gower to be important for pain in humans), pain is said to be a “crossed pathway.” (This is the basis for the classic ventrolateral cordotomy for pain.)
- The simplest anatomic pathway underlying the encoding of the nociceptive stimulus involves three neurons:
  - Primary afferent neuron that goes from skin to spinal cord with the cell body in the dorsal root ganglia (DRG),
  - Spinal cord projection neuron with the cell body in the dorsal horn that projects to the contralateral lateral thalamus via the ventrolateral quadrant (eg, the spinothalamic), and
  - Thalamocortical neuron that projects to the ipsilateral primary somatosensory cortex.
- This three-neuron system displays a high degree of somatotopic organization: for example, stimulation of the left big toe activates specific neuronal populations

in the ipsilateral spinal cord and contralateral thalamic and cortical levels. This system is thought to underlie the sensory discriminative component of the nociceptive experience.

- Spinal neurons also project via the brainstem, medial thalamus, and/or midbrain areas to anterior cingulate gyrus. This system is thought to underlie the affective-motivational component of the nociceptive experience. This system is phylogenetically older, involves more neurons, and is slower than the sensory discriminative pathway.
- There is also a multisynaptic system projecting through the brainstem reticular formation (spinoreticulotact) that is believed to serve in complex pathways contributing to the autonomic response and to spinal-brainstem-spinal loops (see below) for modulation and/or integration of the nociceptive message.

## TISSUE INJURY PAIN—UNDERLYING MECHANISMS

- Nociceptive pain is initiated by tissue injury; it can be secondary to incision (acute trauma), inflammation, or disease.
- As will be reviewed in more detail below, there are several populations of primary afferent fibers, characterized by morphology, conduction velocity, and importantly the nature of the stimulus that can produce activity (action potentials).
- Potentially tissue-damaging stimuli—mechanical, thermal, or chemical—can activate specific populations of primary afferents as determined by their receptors; collectively they are called “nociceptors.” While some nociceptive afferent fibers are specific to one modality (eg, cold or a particular chemical such as histamine or bradykinin), a majority of axon terminals are studded with multiple types of receptors and thus, are “polymodal” and respond to multiple inputs, which “match” their receptors.
- Tissue injury initiates a cascade of local events.
  - Plasma extravasation (capillary leak).
  - Infiltration of inflammatory cells (macrophages, neutrophils, and mast cells).
  - Release of a wide variety of “active factors” from plasma (bradykinin) and from local injured (eg,  $K^+$  and  $H^+$ ) and inflammatory (eg, histamine, cytokines, and prostanoids) cells.
  - Release of peptides from collaterals of activated nociceptive nerve terminals (eg, substance P [sP], calcitonin gene-related peptide [CGRP], and glutamate). These neuropeptides induce vasodilation, increased vascular permeability, and further escape of plasma proteins into the tissue. This

vascular leak causes edema at the injury site and the surrounding flare (indicating precapillary dilation).

- The local chemical; milieu initiates two events:
  - Activation of receptors on peripheral terminals of “pain fibers” (nociceptors), which initiates action potentials, whose frequency is related to local concentrations of inflammatory products.
  - In addition to exciting nociceptors, these products act via second messenger cascades involving several kinases to sensitize nociceptors by lowering the threshold of, or increasing, the open time of individual ion channel containing receptors. If the thermal threshold is reduced such that body temperature or other normal physiological processes initiates neural activity, this would appear to be spontaneous pain. Reduction of thresholds of nociceptors to temperature and pressure within the innocuous range is manifested as allodynia and is also called primary hyperalgesia (eg, a lowering of threshold to produce afferent discharge).

## PRIMARY AFFERENT FIBERS

- Primary afferent fibers are divided into classes based on morphology: myelinated versus unmyelinated and axonal diameter ( $A\beta > A\delta > C$ ) and their corresponding conduction velocities ( $A\beta > A\delta > C$ ).
- Most fibers that transmit acute nociceptive pain are  $A\delta$  (small myelinated) or C (unmyelinated) fibers. Not all  $A\delta$  and C fibers transmit pain information; many code for innocuous temperature, itch, and touch.
- Some afferent fibers, “silent or sleeping nociceptors,” signal only after there has been an overt tissue damage. Chemicals released by injury/inflammation can sensitize these receptors. Accordingly, many of these are thought to play a prominent role in arthritis pain and other diseases associated with tissue damage or chronic inflammation. Viscera contain a particularly large proportion of silent nociceptors.
- Parallel experiments comparing electrophysiological data in single C nociceptive fibers to human psychophysical data show a high correlation between activity in primary afferent fibers and a pain sensation. This suggests that afferent fiber activity mediates pain and that inhibition of this activity diminishes pain.
- In many cases, transduction mechanisms for stimuli activating afferent terminals have been identified. Within the cutaneous C nociceptive fiber population, fibers containing TRPV1 receptors are typically activated by high temperatures ( $>48^\circ\text{C}$ ). Importantly, these channels are also activated by the chemical capsaicin and decreases in pH (acidity). These axons contain a variety of neuropeptides.

- Other C nociceptors are positive for the surface lectin IB4 and are capsaicin-insensitive. The IB4<sup>+</sup> fibers tend to have sensitivity to mechanical stimuli.
- Both classes of C fibers have monosynaptic terminations in laminae I and II of the spinal dorsal horn, with the peptidergic ones being more superficial (see below).
- A $\delta$  nociceptors primarily terminate in laminae I and V of the dorsal horn (see below).
- C fibers have polysynaptic connections with neurons in lamina V as well as with neurons in deeper dorsal horn. Many nociceptive afferents from viscera have monosynaptic input to lamina X around the central canal as well as bilaterally throughout the spinal dorsal horn.

### SPINAL CORD SENSORY ORGANIZATION

- Primary afferent fibers terminate either directly or indirectly through interneurons onto spinal cord transmission cells that convey their information to supraspinal sites. Some neurons project to various midbrain and thalamic nuclei that serve as way stations for the discriminative and affective components of pain. These ascending pathway nuclei are predominantly crossed and ascend in the anterolateral quadrant of the spinal cord contralateral to the cell body and the innervated body part.
- Other neurons project to brainstem autonomic centers in the reticular formation that regulate increases in cardiovascular function and respiration in tandem with affective components of nociceptive transmission; these pathways tend to be bilateral. In addition to ascending pathways, intrinsic pathways in the spinal cord connect to motor neurons that participate in reflex motor activity.
- Given that nociceptive afferent fibers terminate in laminae I and II, it is understandable that the neurons in lamina I are largely activated by high-threshold stimuli and are termed “nociceptive specific.” Conversely, many cells that are found in deeper dorsal horn laminae send dendrites toward the superficial layers and receive high-threshold afferent input on their distal dendrites, but they also receive low-threshold input on their cell bodies and ascending dendrites. These cells thus respond to low-threshold stimuli and to high-threshold input. These cells are said to receive convergent input, in which they fire more action potentials; as the intensity of the stimulation increases, they are called “wide dynamic range (WDR)” neurons.
- In the case of both nociceptive-specific and WDR neurons, action potential firing frequency is dependent upon the intensity of the afferent stimulus, with nociceptive-specific neurons showing an increased discharge starting at noxious stimulus intensities, whereas WDR neurons begin to discharge at low non-noxious stimulus intensities and progressively increase firing rates as intensity rises.
- Interestingly, in the face of high-frequency C-fiber input, many WDRs show a marked increase in their response to a given stimulus intensity. This results in repeated mild stimuli producing a disproportionately high level of discharge, a phenomena called “wind up.”
- Many WDR neurons are multimodal and respond to both mechanical and thermal inputs. Others respond exclusively to noxious heat or cold. There are also cells that respond only to chemical stimulation, including histamine release in the skin (and thus likely mediate itch). A small population of nociception-specific cells is located in deep dorsal horn.
- Convergence of input from the outer body surface (skin) and from viscera onto individual spinal neurons also occurs. Thus, when activity is initiated in viscera, pain is referred to the portion of the body surface that “shares” those neurons. This is one explanation for “referred pain.”

### SPINAL CORD PHARMACOLOGY

- Afferent nociceptive fibers release glutamate and peptides from their central terminals in the spinal cord. Some peptides are released along with the glutamate only when the afferent fibers fire action potentials at high frequencies (equivalent to severe injury). The postsynaptic effects may usefully be thought of as having: (i) acute, (ii) early onset/short duration, (iii) delayed onset/intermediate duration, and (iv) slow onset, long duration.
- *Acute onset postsynaptic events.* Glutamate produces a fast response (depolarization) in the spinal neurons via receptors linked to ion channels. These are called non-*N*-methyl-*D*-aspartate (NMDA)-type glutamate receptors and consist of amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors, which increase membrane permeability to Na<sup>+</sup>, yielding a prominent but transient depolarization. This linkage accounts for the majority of the acute response produced by brief activation of low- and high-threshold afferents.
- As noted, in the face of on-going high-threshold/high-frequency input, the input-output function of dorsal horn neurons is altered. This change in gain may be broadly considered in terms of events that occur acutely, lasting milliseconds to seconds, events that are longer lasting (seconds to minutes), and events that are very long lasting (hours to days).