CLINICAL INVESTIGATION INSTITUTE

Pain, from bench to bedside

There has been substantial progress in understanding the neurobiological basis of pain, but these advances have yet to translate into new and improved analgesics.

Pain is so commonplace an experience that one tends not to think about it as a pathological condition. Yet, pain, in its many guises, is a serious health problem that affects the quality of life of millions of people worldwide and, unfortunately, remains challenging to treat.

With this in mind, we decided to devote our 2010 Frontiers in Clinical Investigation Symposium which we proudly organize in collaboration with the Clinical and Translational Research Institute of UCSD, to the field of pain. This collection of reviews, written by some of the participants at the meeting and by other renowned experts, is meant to complement the Symposium by providing an up-to-date, authoritative view on some of the topics that will be discussed at the meeting.

An early, simplistic view of pain treated it as a somewhat static entity—poorly myelinated Aδ and C fibers transmit painful inputs to the spinal cord, information that then finds its way to the thalamus via the anterolateral system before reaching the somatosensory cortex. This picture has gradually made way for a much more sophisticated outlook that takes into account developments in disciplines as diverse as genetics, systems neuroscience and even immunology.

Thus, advances in molecular biology have led the field to develop a more realistic view of the complexity of peripheral nociceptors, reviewed here by Michael Gold and Gerald Gebhart. Taking stock of the panoply of receptors and downstream mechanisms that initiate pain is a good starting point in the search for new ways to combat the disorder.

The pathophysiological bases of pain in the central nervous system are also much more complex than early anatomical studies indicated. Neurophysiological studies, discussed by Rohini Kuner for this collection, have led researchers to develop an appreciation for the importance of plastic changes at the synapse as a key anatomical substrate of chronic pain. Equally important to understanding the central mechanisms of pain are the imaging studies, reviewed by Irene Tracey, showing that patients' expectations may affect their response to an analgesic. As she discusses, this observation has profound implications for how we assess pain relief in patients.

One can argue that medical practitioners have known of a connection between the immune system and pain since the first century AD, when Celsus identified the four classical signs of inflammation—*calor*, *dolor*, *rubor* and *tumor*. Indeed, the immunological basis of pain has already provided evidence of their therapeutic potential—consider, for example, cyclooxygenase inhibitors and nonsteroidal anti-inflammatory drugs. However, this potential remains largely unrealized while the relationships between immune cells, neurons and glia in the context of pain become increasingly intricate, as Ke Ren and Ronald Dubner discuss in their review.

Despite the advances on all of those fronts, there is a profound paucity of new drugs to combat pain. In his contribution, Clifford Woolf analyzes the challenges—target validation, intellectual property, clinical-trial design, regulatory hurdles and others—that must be overcome to develop new analgesics. This article will be useful reading for those trying to move the biology of pain from the bench to the bedside.

The final two pieces in this collection focus on two serious challenges of translational research on pain—animal models and clinical trials. First, as in nearly every field of biomedicine, the usefulness of animal models in pain research has recently come under close scrutiny. What is the relationship of the pain readouts that one measures in mice and other species to actual pain in humans? Which preclinical models, if any, are more predictive of clinical efficacy? In an intriguing News Feature, *Nature Medicine*'s Elie Dolgin reports on some of the difficulties in modeling pain in animals.

Last, validating a target and identifying a potentially good analgesic are difficult tasks that are often wasted in poorly designed clinical studies. In his article, John Farrar considers the problematic of conducting clinical trials for pain relievers, pointing to the principles that should be observed when designing and interpreting data from clinical studies.

We hope that the articles in this collection will stir debate and feed the imaginations of our readers. We sincerely thank Cadence Pharmaceuticals for their financial support to produce this focus. As usual, *Nature Medicine* takes full editorial responsibility for the content of these pages.