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## Preface

### Analgesia: no pain, lot to gain

Ancient Greeks considered diseases to be penalties sent by gods. Indeed, the English word “pain” has its origin in the Greek word *poine* (“penalty”). The word analgesia is derived from the Greek adjective *analgetos* (“not sensing pain”) that, in turn, stems from the verb *alego*, meaning “to care, look after”. Modern medical dictionaries define analgesia as (1) absence of sensibility to pain, or (2) the relief of pain without loss of consciousness.

Chronic pain is a complex phenomenon, which continues to remain undertreated in the majority of affected patients and thus represents a significant unmet medical need. For any given analgesic drug, the NNT (number needed to treat) number is estimated to be as low as one in seven. Such clinical value (beneficial only in 15% of treated patients) would be unacceptably low for any other disease. Not surprisingly, the medical management of chronic pain remains frustrating both for patients and their clinicians.

Chronic pain is rampant, affecting a major segment of the population. In the US, an estimated 50 million adults are suffering from chronic pain. Chronic pain, however, is not only a health problem. Many patients are in their productive age: the loss of work hours due to pain has grave implications for the economy. As the population is graying, the prevalence of chronic pain is expected to rise. The term “pain epidemic” is hardly unjustified. The US market for treatment of chronic pain is expected to nearly double from today’s \$2.6 billion to \$5.1 billion in the next ten years. This represents opportunities for the pharmaceutical industry but may strain the resources of the healthcare system. The world-wide prevalence of chronic pain is unknown, but the global pain market was reported to generate total sales of \$34 billion in 2007.

Most existing analgesic drugs (painkillers) are derivatives of natural products that had been introduced into clinical practice on a largely empirical basis. The current Decade of Pain Control and Research (2001–2010) has, however, witnessed major changes in analgesia research, progressing from a system level to cellular, subcellular, and molecular. Breakthrough advances in biomedical technologies have allowed us to develop a better understanding of the mechanisms by which pain is generated, transmitted, modulated, and perceived. Genomics (“brain on a chip”) and proteomics have been applied to identify genes and their products that change during pain and thus may represent novel targets for pharmacological manipulation. These genes as pain targets are validated by generation of knockout mice, site-specific mutation, silencing by RNA interference, or knock-down by antisense methods. Cell lines heterologously expressing these genes are generated and used to screen compound libraries for lead analgesic molecules. Then drug candidates are tested in animal models of pain for analgesic activity. Gene transfer by viral vectors represents an attractive alternative strategy for the delivery of antinociceptive substances. Molecular neurosurgery (targeted neurodegeneration by neurotoxins) is another approach for permanent pain relief.

The molecular mechanisms that underlie drug tolerance, dependence, and individual sensitivity are beginning to be understood. Receptor heterogeneity secondary to single nucleotide polymorphism (SNPs) is believed to play an important role. SNPs, however, are not the only source of genetic variability. Copy number variation (CNV) is now emerging as a new source of genomic variation. Indeed, CNVs are now thought to include more nucleotides than SNPs. It is now generally accepted that one size does not fit all: chronic pain patients need individualized therapeutic decisions, a concept popularized in the media as personalized medicine. Enhanced analytic strategies, like microarrays, array-based comparative genomic hybridization and microfluidic chips, may make pain theranostics, the fusion of diagnostics and therapeutics, a reality.

It is hoped that these discoveries will eventually lead to individualized analgesia protocols. Furthermore, new techniques explore low affinity interactions of anesthetics and analgesics with proteins that cannot be detected by traditional binding methodology. Finally, fMRI (functional magnetic resonance imaging) technology creates a unique opportunity for “virtual reality analgesia” by the effects of analgesic drugs on brain functions.

This volume offers comprehensive coverage of molecular analgesia research methods from target discovery through target validation and clinical testing to tolerance and dependence. Emerging receptor classes as targets for analgesic drugs and innovative analgesic strategies are discussed in separate chapters. From the molecular research bench through the animal laboratory to the bed-side, this book is for all those scientists and clinicians who are interested in what the increasingly molecular future has in store for analgesia research.

I used a paraphrase of the title of Robert Herrick’s poem (“No pain, no gain”) in the title of this preface thus it is fitting to close my writing with another poem of his:

96. To Critics  
I’ll write, because I’ll give  
You critics means to live;  
For should I not supply  
The cause, th’ effect would die.

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