CONTENTS

Preface
Kenneth D. Brandt ix

Aging or Osteoarthritis: Which is the Problem?
Richard F. Loeser and Najia Shakoor 653

Osteoarthritis (OA) is not an inevitable consequence of aging. Rather, aging-related changes in the musculoskeletal system increase the risk of developing OA when other factors that incite the disease are also present. Factors that contribute to the development of pain and loss of joint function include those associated with aging, those associated with underuse or misuse of the musculoskeletal system, and those associated directly with the development of OA. These factors and their complex interrelationships are discussed in this article.

Microfractures and Microcracks in Subchondral Bone: Are They Relevant to Osteoarthritis?
David B. Burr and Eric L. Radin 675

Although it has been suggested that stiffening of subchondral bone, due to microfractures, is of primary pathogenetic importance in the breakdown of overlying articular cartilage in idiopathic osteoarthritis (OA), recent data suggest that stiffening of subchondral bone in early OA plays little role in the etiology of the disease. On the other hand, microcracks in the subchondral plate and calcified cartilage with subsequent reactivation of the secondary center of ossification appear to be a significant pathophysiologic mechanism in idiopathic OA. Microcracks seem to be capable of causing (or at least contributing to) the articular cartilage loss that is characteristic of the arthrotic process. Microcracks in the subchondral plate and calcified cartilage may serve as a focus for the initiation of targeted remodeling.
What is Important in Treating Osteoarthritis? Whom Should We Treat and How Should We Treat Them?
Paul Dieppe and Kenneth D. Brandt

Many options exist for the treatment of osteoarthritis (OA), ranging from doing nothing through community programs for prevention to total joint replacement surgery. This article outlines the range of options available for prevention and treatment of OA, considers some theoretical targets for therapy, and reviews some of the most frequently used current treatments. The authors conclude that much can be offered today to help people with this common disease, but that access to good treatment and progress in research are impeded by the dominating agendas of the pharmaceutical industry. Similarly, priorities of manufacturers of prosthetic joints and researchers in academia may not always be congruent with those of patients with OA.

Guidelines for Management of Osteoarthritis Published by the American College of Rheumatology and the European League Against Rheumatism: Why are They so Different?
Edward Roddy and Michael Doherty

Recommendations for the management of osteoarthritis were published in 2000 by the American College of Rheumatology and the European League Against Rheumatism. Despite similar objectives, these guidelines differ in several respects. This article explores how the two sets of recommendations differ and considers how such differences arose.

Mechanism of Action of Analgesics Used to Treat Osteoarthritis Pain
Robert B. Raffa

Pain associated with osteoarthritis (OA) often originates from multiple sources such as the synovial membrane, joint capsule, ligaments, periarticular muscle, periosteum, and subchondrial bone. It also involves multiple types of pain (e.g., inflammatory and noninflammatory) and multiple pain transmission pathways. Hence, an understanding of the differences in the mechanisms of action of the commonly available analgesics is helpful for the judicious selection of the optimal agent. Because of the multifaceted nature of most OA pain, treatment often requires a combination of approaches.

Self-Efficacy in Management of Osteoarthritis
John P. Allegrante and Ray Marks

Self-efficacy, a psychologic construct defined as one's confidence in performing a particular behavior, is a significant predictor of psychologic well-being, adherence to prescribed treatments, and
pain coping mechanisms in persons who have arthritis. This article reviews the theory of self-efficacy, describes application of self-efficacy to the management of osteoarthritis (OA), and presents approaches to enhancing the patient’s self-efficacy in management of OA and prevention of OA-related disability.

Gastroprotection by Coxibs: What Do the Celecoxib Long-Term Arthritis Safety Study and the Vioxx Gastrointestinal Outcomes Research Trial Tell Us?
Jaime A. Oviedo and M. Michael Wolfe

On the basis of their reduced capacity to injure the gastroduodenal mucosa, cyclo-oxygenase-2 selective inhibitors (coxibs) were developed as a safer alternative to traditional nonsteroidal anti-inflammatory drugs. Two landmark studies, the Celecoxib Long-Term Arthritis Safety Study (CLASS) trial and the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, have addressed the associated risk of gastrointestinal complications caused by coxibs. This article reviews the evidence obtained in these important trials.

Why are Clinical Trials of Glucosamine No Longer Uniformly Positive?
Tim McAlindon

In contrast to earlier industry-funded trials of knee osteoarthritis, recent placebo-controlled studies of glucosamine have generated negative results. Although there is a tendency to assume that these studies were negative because of the absence of conflicts of interest, interpretation of the negative studies is complicated by cohort differences, methodological issues, and absence of standardization of the test compounds. It also remains unclear how glucosamine actually works. One possibility is that its efficacy as mediated by the sulfate, rather than the glucose, moiety, which further complicates the interpretation of available data. It is clear that more work needs to be done to illuminate the issues surrounding the efficacy and utility of glucosamine compounds.

Biochemical/Immunochemical Biomarkers of Osteoarthritis: Utility for Prediction of Incident or Progressive Osteoarthritis
A. Robin Poole

This article reviews new methodologies that are being developed for the detection of incident osteoarthritis (OA) and the progression of established OA. These tests are based mainly upon serum or urine assays of biomarkers that are products of defined tissue-specific molecular events related to joint damage. These biomarkers can now be detected by sensitive and specific immunoassays. Recent studies in animal models and in humans
with knee OA have revealed that these tests are of value in detecting early OA and can discriminate between populations that differ with respect to the progression of joint damage. These assays may also be of value in clinical trials of disease-modifying OA drugs.

Is Knee Radiography Useful for Studying the Efficacy of a Disease-Modifying Osteoarthritis Drug in Humans? 819
Steven A. Mazzuca and Kenneth D. Brandt

Recent research on radiographic imaging of subjects with knee osteoarthritis (OA) has elucidated the features of imaging protocols that contribute to an accurate representation of disease severity and to sensitive detection of disease progression. Poor reproducibility of positioning of the knee in the conventional standing anteroposterior (AP) view has been shown to obscure the true rate and variability of joint space narrowing in patients with knee OA. Moreover, the standing AP view may be susceptible to systematic bias. The longitudinal studies published to date suggest that fluoroscopic positioning methods are superior to nonfluoroscopic methods with respect to reproducing the position of the knee in serial examinations performed over intervals ranging from 1 to 2.5 years.

Is Time to Joint Replacement a Valid Outcome Measure in Clinical Trials of Drugs for Osteoarthritis? 831
Jean-Francis Maillefert and Maxime Dougados

The rate of radiographic joint space narrowing is commonly used today as a structural outcome measure in clinical trials evaluating potential disease-modifying drugs in patients with hip osteoarthritis, but this results in a continuous variable. Among the methods proposed to circumvent this problem, it has been suggested that the incidence of total hip arthroplasty (THA) provides a "hard" outcome measure. It is a dichotomized variable, easy to measure and sensitive to change, with acceptable intrinsic validity. However, because this measure is limited by the variability of factors underlying the decision to perform surgery and the length of waiting lists, it has been suggested that "time to fulfill criteria for considering THA" may be a more appropriate endpoint.