OSTEOARTHRITIS, also known as degenerative joint disease, almost uniformly accompanies ageing. Generally it has an insidious onset and a variable relationship of symptoms and functional impairment with slowly accumulating radiographic and pathologic evidence of its presence. As yet, there is no clinical evidence that treatment changes its course. The characteristics, manifestations, and outcomes of its clinical subtypes, e.g. Heberden’s nodes, OA of hips and knees, OA of the spine etc., differ so much that clinical trials must be limited to single subtypes [1, 2]. Further complicating clinical trials are acute exacerbations of symptoms in OA joints, that may be related to intercurrent trauma or to co-existing calcium crystal deposition disease. Nevertheless, millions of persons desire relief from the annoying stiffness and discomfort associated with OA, and hundreds of thousands would welcome a medical therapy that could prevent the progression of OA to the point where surgical joint replacement is needed.

Appropriate goals for the development of drug therapies for OA include: (1) more effective and better-tolerated drugs (than the currently available NSAIDs and analgesics) to relieve the annoying symptoms of OA; (2) a treatment to arrest, or at least to slow the progression of the pathologic changes in osteoarthritic joints. No available treatments have been proven to alter OA progression, but it is conceivable that inhibition of enzymes that promote cartilage degradation, such as neutral metalloproteinases, proteoglycanases, or collagenolytic enzymes either directly through pharmacologic inhibition of these enzymes or indirectly through upregulation of natural inhibitors such as tissue inhibitor of metalloproteinases (TIMP) [3, 4], could prevent progressive cartilage damage in OA; (3) even more useful would be a treatment such as a growth factor or a growth-factor inhibitor (e.g. IL-1 inhibitor) that reversed the pathologic process, normalizing the misdirected attempts at bone and cartilage repair that produce functionless cartilage-covered bony osteophytes, and resulting in a more normal, more functional, ‘younger’ joint [5].

NSAIDs have been studied with in vivo animal models and in vitro models of pathogenic factors of OA, with sometimes disparate findings. For example, in studies of normal cartilage slices salicylate inhibited proteoglycan synthesis, whereas piroxicam had no appreciable effect, and benoxaprofen increased proteoglycan synthesis. In osteoarthritic articular cartilage explants salicylate inhibited proteoglycan synthesis to an even greater extent than that seen in salicylate-treated normal cartilage explants [6, 7]. Dogs with experimentally induced OA demonstrated more depletion of cartilage proteoglycan when treated with therapeutic doses of aspirin compared to untreated control animals. Similar discrepancies have been noted among and between various NSAIDs in other experimental studies [8–11].

Numerous clinical trials of a few weeks to several months duration have demonstrated that various NSAIDs are more effective than placebo for the short-term relief of OA symptoms, and have been the basis for approval of these drugs to treat OA [12]. However, a well-designed 4-week randomized comparison of paracetamol 4 g/day, ibuprofen 1200 mg/day and ibuprofen 2400 mg/day in 184 patients with OA of the knee found statistically equal, modest improvement in all measures except pain at rest, which in a dose-related manner improved more with ibuprofen [13] suggesting that ‘anti-inflammatory’ doses of NSAIDs may not always be needed to relieve OA symptoms.

If a future ‘chondroprotective’ agent is hypothesized to retard the progression of pathologic and radiographic changes in OA, its evaluation will require a clinical trial that is long enough to permit significantly greater progression of radiographic damage in a control group than in the experimental treatment group. Although potentially chondroprotective agents are undergoing pre-clinical development, as yet there have been only a few controlled clinical trials of sufficient duration to provide guidance in the design of, and sample size estimations for, a clinical trial of such an agent. The two-year study by Dieppe et al. in this issue [14] and a two-year study by the United States multiclinic Cooperative Systematic Studies of Rheumatic Diseases (CSSRD) group [15] are quite similar in design and findings. The Dieppe study compared diclofenac 100 mg daily with ‘placebo’ (plus up to 4 g of paracetamol daily if needed) in a double-blind, randomized study of 89 patients with established symptomatic OA of the knee. The CSSRD studied 178 patients with symptomatic grade II or III OA of the knee who were randomized to receive either 750 mg/day of naproxen or 2600 mg/day of paracetamol.

Both studies had major problems retaining patients to the end of the 2-year trials; 69% of those randomized to diclofenac completed 2 years and only 45% in the placebo (plus ad lib paracetamol) group, 39% of those assigned to naproxen and 31% of those in the paracetamol 2600 mg/day group completed the 2-year studies. In both studies withdrawals for lack of efficacy were more common in the paracetamol (or placebo plus ad lib paracetamol) group than in the NSAID group. Statistical analyses of those who completed the 2-year

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studies showed only minimal differences between treatment groups, and there was no progression of radiographic findings in about 70% of completers in both studies, regardless of treatment assignment. Both studies detected a subgroup of patients who appeared to benefit more from the NSAID than from paracetamol/placebo; in the CSSRD study, this subgroup consisted of patients with more severe OA at entry, when measured by limitation of knee flexion. No acceleration of radiographic damage by NSAID administration was noted in either study. Dieppe et al. conclude that 2 years is too short a time to detect significant change in knee structure and function using conventional clinical and radiographic methods, but neither study continued to obtain radiographs after patients had withdrawn from the study.

Can the experience in these studies be used to assist in the design of future trials of potentially effective chondroprotective therapies for OA patients? Are placebo control groups ethical or necessary? The possibility that some NSAIDs could accelerate cartilage degradation (as suggested by some in vitro work) and the greater toxicity of NSAIDs relative to paracetamol and other analgesics, emphasize the need to clarify in a controlled manner the long-term effect(s) of NSAIDs on cartilage. Because the cited studies [13–15] show no difference in the symptomatic or radiographic progression of OA patients treated with ibuprofen, diclofenac, naproxen, paracetamol or ‘placebo/paracetamol’, randomly depriving OA patients of NSAIDs does not appear to cause irreparable harm. Provision of paracetamol, either by randomized blind assignment or as an ‘as needed’ supplement provided adequate symptomatic relief for those patients who completed the 2-year studies. Thus, a ‘chondroprotection’ study could ethically compare the experimental agent with placebo if ad lib supplemental paracetamol or NSAID were allowed to control symptomatic exacerbations during the trial. Alternatively, all patients could continue to receive a standardized background NSAID or paracetamol, with placebo or the experimental agent randomly added, a design similar to that of most studies of slowly acting anti-rheumatic drugs.

The minimum duration needed for a ‘chondroprotective’ trial is not clear. Only 25.5% and 30% of the patients who completed the cited trials [14, 15] showed radiographic progression after 2 years. However, radiographic progression in the many withdrawals who did not complete the trials is not known, and probably was greater than that in those who were able to complete 2 years of study. The power of future studies could be increased by continuing radiographic follow-up of all drop-outs for the full duration of the study, regardless of post-drop-out therapy. Since no available therapy has any proven chondroprotective benefit, an intent-to-treat analysis of the ultimate available therapy has any proven chondroprotective study, regardless of post-drop-out therapy. Since no

Selection of a uniform OA population based on clinical characteristics, genetic or biochemical markers of disease activity and perhaps advanced imaging techniques, might also strengthen the observations made in future OA trials. Ideally for the analysis of potential chondroprotective agents, patients would be selected who have relatively early joint changes, with theoretically responsive cartilage, but who are advanced enough to have detectable radiographic changes over a time course of several years. Alternatively, metabolic products of OA cartilage or collagen may prove to be useful surrogate markers of disease activity and may help to identify promising chondroprotective agent in trials that are too brief to demonstrate radiographic progression.

In conclusion, efficient clinical evaluation of potentially chondroprotective therapies of OA will be challenging. The 2-year Dieppe et al. [14] and CSSRD [15] studies provide essential quantitative background data that should facilitate the design of these future clinical trials.

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**IMPROVING PRESCRIBING OF NON-STERoidal ANTI-
INFLAMMATORY DRUGS**

Cost containment of pharmaceuticals is topical. The UK’s current drugs bill is £3 billion, and after staff costs, drugs are the next biggest item in the £33 billion health budget [1]. On a national basis many different approaches to reducing expenditure have been tried. These include the Government’s limited lists which currently extends to seven therapeutic categories, the encouragement from the Department of Health to pre-
scribe generics, expanding the number of drugs that can be sold in pharmacies without prescription and the introduction of indicative prescribing budgets [2]. Hos-
pital-based initiatives have included the setting up of Drug and Therapeutics Committees and the introduction of formularies [3] with reductions in the quantities of medicines supplied at discharge and to outpatients. General Practitioners are being encouraged to develop their own formularies through local agreement and to draw up common prescribing policies [4].

In 1991, pharmaceutical costs accounted for 11.6% of National Health Service expenditure, and this com-
pares favourably with other countries in the EEC [5]. Currently the UK drug bill is increasing by approximately 14 per cent per annum [6], an increase which is causing the Government concern. However, the increase in costs for drugs should be considered in line with the advance in therapeutics and the introduction of expensive new products. Medicines introduced in the UK in the past 5 years account for 69% (£143 million) of the £207 million growth in drug costs [7].

The ‘drug bill’ is often targeted by hospital managers seeking to control and reduce overall hospital costs. The quality of information available about the use of pharmaceuticals and their costs is generally very good, making this area of expenditure an easy target for quick-fix management. However, in the hospital setting the discerning manager would probably find greater savings by reviewing other areas of expenditure such as waste in X-rays, haematology and chemical pathology tests and delays in patient discharge due to poor planning during the hospital stay.

Why are pharmaceutical costs generally well-con-
trolled in the hospital setting? Local prescribing poli-
cies and drug formularies are tried, tested and proven means of controlling drug expenditure. The paper in this issue by Sutters and colleagues [8] amply demon-

strates that a collaborative approach by pharmacists and physicians, involved in educating colleagues can improve the quality of prescribing and result in cost reductions. Improving the quality of prescribing, to consider the most cost-effective therapy, does not always mean using the cheapest drugs. Local prescrib-
ing policies which rationalize the selection of medicines based on an educational approach rather than cost alone, can improve the quality of prescribing. Collab-
oration and co-operation between pharmacists and physicians extends far beyond cost containment; into direct patient care. The profession of pharmacy has undergone significant growth and development over the past 20 years. Pharmacy entered the twentieth cen-
tury performing the role of social apothecary. This tra-
ditional role began to wane as the preparation of medicines was passed to the pharmaceutical industry. Clinical pharmacy practice started its development in the 1970s and pharmacists moved closer to the bedside to practice more patient-oriented pharmacy. The emergence of pharmacy as a clinical profession has given pharmacists the skills and knowledge to improve the outcome of drug therapy [9].

The mission of pharmacy is to service society as the profession responsible for the appropriate use of medi-
cines to achieve optimal therapeutic outcomes [10].

A priority for patient care today for physicians and pharmacists, is to improve the quality of our use of drugs by preventing drug-related morbidity and mor-
tality. Although drugs are administered for the pur-
pose of achieving definite outcomes that improve the patient’s quality of life, the potential for outcomes that diminish the quality of life is always present [11]. The outcome of care for the patient may be less than optimal as a result of poor use of medicines. This can occur through inappropriate prescribing of a medicine, for example by not considering the patients hepatic and renal function or the other medicines the patient is taking. Poor delivery of the medicines to the patient through incorrect administration volumes or diluent or speed of administration. Idiosyncrasies of the patient may also result in morbidity from drug treatment. The patients themselves may cause their own morbidity through inappropriate behaviour resulting in excessive dosing or under-dosing—and so drug morbidity is multifactorial.