lipid concentration in the serum. The rareness of this entity is corroborated by one of us (I.R.) who has been examining synovial fluid for crystals for over 15 years and has never seen this form of crystal before.

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Coxibs and cardiovascular risk

Jill Cotter and Eric Wooltorton[1] highlight the importance of differences in cyclooxygenase 2 (COX-2) selectivity as a potential explanation for the prothrombotic effects of coxibs. However, they neglect important evidence that celecoxib might not share the same cardiovascular (CV) risk as rofecoxib.

An increased thrombotic risk with celecoxib has been demonstrated only in the APC (Adenoma Prevention with Celecoxib) study.[2] On the other hand, data from the CLASS trial[3] and a meta-analysis of multiple controlled trials[4] have not uncovered any prothrombotic effect of celecoxib compared with either conventional NSAIDs or placebo. This is consistent with many observational studies that found increased CV risk with both high and low doses of rofecoxib but not with celecoxib.[5-7]

It is noteworthy that the APC trial demonstrated a trend toward increased CV risk of celecoxib among ASA users. Celecoxib might have caused this effect by interference with ASA-induced inactivation of platelet COX-1, which can occur at significantly lower concentrations of celecoxib than are necessary for inhibition of platelet COX-1 activity.[8] This notion does not contradict our previously stated view that ASA might mitigate CV risk associated with coxibs.[9] However, a recent case–control study showed that the risk-modifying effects of ASA were seen only at a low dose but not at a high dose of rofecoxib.[7] We have, therefore, suggested that higher doses of coxibs could also interfere with the anti-inflammatory effects of ASA mediated by COX-2.[10]

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Jill Cotter and Eric Wooltorton[1] indicated that COX-2 inhibitors appear to increase the risk of cardiovascular adverse events in a dose-related fashion. The CLASS and VIGOR clinical trials of COX-2 inhibitor(s) suggested that both celecoxib and rofecoxib can increase the risk of cardiovascular events.[2] The VIGOR trial compared rofecoxib with the NSAID naproxen in patients with rheumatoid arthritis[3] and indicated a 5-fold increase in the relative risk of developing serious cardiovascular events between the rofecoxib group and the naproxen group.

Clinical data have shown that expression of COX-2 is upregulated by inducible nitric oxide synthase (iNOS) that might play a protective role in the

cardiovascular system.[4] However, the COX-2 enzyme might be exerting detrimental effects elsewhere, because analysis of protein extracts from normal arteries has revealed constitutive COX-1 only, but atheromatous lesions contained both COX-1 and COX-2 protein.[5] Some studies suggest that prostanoids and nitric oxide may have proatherosclerotic effects[6] resulting from the formation of peroxynitrite species in the affected vessels, possibly involving "cross talk" between the COX-2, iNOS and other enzyme systems, which may generate oxidants including dihydrogen trioxide and even ozone from singlet oxygen and water in atheromatous plaques.[7]

Well-planned basic research is essential to show whether COX-2 activity is beneficial or harmful for the cardiovascular system in different sites or in cardiovascular disease and to exploit the benefits of COX-2 inhibitor therapy.

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Jill Cotter and Eric Wooltorton suggest an approach to prescribing COX-2 inhibitors that includes estimating cardiac risk, using the lowest doses for short periods, and discussing the risks and benefits of long-term use. They provide evidence for the cardiovascular risks of celecoxib.[1] Regarding the benefits, it is helpful to review the results of the CLASS trial,[2] which was designed to evaluate the efficacy of celecoxib in reducing clinically significant upper gastrointestinal (GI) adverse events.

CLASS reported the pooled results of 2 trials comparing celecoxib, 400 mg twice a day, with diclofenac, 75 mg twice a day, and ibuprofen, 800 mg three times a day. The study protocol prespecified that the results would be pooled, but an FDA report[3] gave the results separately for diclofenac and ibuprofen, for the full length of the 2 studies, 12 months and 15 months, whereas the published CLASS study reported 6-month data.

The FDA report concludes that the CLASS trial was a robust testing of the safety of celecoxib at doses 2 and 4 times those currently labelled for rheumatoid arthritis and osteoarthritis, respectively; celecoxib does not appear to be more effective for treating the signs and symptoms of osteoarthritis or rheumatoid arthritis than the NSAID comparators; and celecoxib did not show statistically significant superiority to diclofenac at any point in the trial regardless of ASA use or end point (including the primary end point of clinically significant upper GI events, namely, upper GI bleeding, perforation, or gastric outlet obstruction alone or with gastroduodenal ulcers).

With little indication of benefit in symptom control or reduction of adverse events, it is questionable whether there is a need to prescribe celecoxib at all.

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The wrong stuff

If Dr. Ursus gets upset and anxious, indeed paranoid, about misdiagnosing the very early manifestations of an extraordinarily rare disorder such as Guillain–Barré syndrome,[1] he won't last long in this job.

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