

## Review Article

*Medical Progress*

## GASTROINTESTINAL TOXICITY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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ONE hundred years have passed since Felix Hoffman, working at Bayer Industries, reported the successful synthesis of acetylsalicylic acid as the first nonsteroidal antiinflammatory drug (NSAID).<sup>1,2</sup> At the suggestion of Hermann Dreser, Bayer's chief pharmacologist at the time,<sup>3</sup> the compound was called "aspirin" and was purported to represent a convenient mechanism for the delivery of salicylic acid in the treatment of rheumatic diseases, menstrual pain, and fever.<sup>2</sup> Approximately 40 years elapsed before Douthwaite and Lintott<sup>4</sup> provided endoscopic evidence that aspirin could cause gastric mucosal damage. Numerous reports have corroborated this observation,<sup>5-8</sup> and the introduction of more potent agents with an even greater propensity for toxic effects has increased the awareness of NSAID-induced gastroduodenal ulcer and provided impetus for the development of effective NSAIDs with a more favorable safety profile.

Starting in the early 1970s, numerous new NSAIDs were developed that were initially believed to be devoid of gastrointestinal toxicity, but few, if any, are entirely harmless. These agents constitute one of the most widely used classes of drugs, with more than 70 million prescriptions and more than 30 billion over-the-counter tablets sold annually in the United States.<sup>9</sup> Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients, resulting in substantial morbidity and mortality.

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## EPIDEMIOLOGY OF GASTROINTESTINAL COMPLICATIONS

Because of the broad and nonspecific definitions of gastrointestinal disorders caused by the use of NSAIDs, as well as differences in patient populations, drugs, dosages, and periods of use, estimates of the prevalence of adverse effects vary greatly. In general, at least 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent.<sup>10,11</sup> Within a six-month period of treatment, 5 to 15 percent of patients with rheumatoid arthritis can be expected to discontinue NSAID therapy because of dyspepsia.<sup>11</sup>

According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication. The risk in patients with osteoarthritis is somewhat lower (7.3 per 1000 patients per year).<sup>12</sup>

The rate of NSAID-related serious gastrointestinal complications requiring hospitalization has decreased in recent years. The decrease may be due, at least in part, to extensive medical-education campaigns that have persuaded physicians to use newer, less toxic NSAIDs and non-NSAID analgesics in populations at high risk.<sup>12</sup>

The mortality rate among patients who are hospitalized for NSAID-induced upper gastrointestinal bleeding is about 5 to 10 percent.<sup>13</sup> An analysis of data from ARAMIS has shown that the mortality rate attributed to NSAID-related gastrointestinal toxic effects is 0.22 percent per year, with an annual relative risk of 4.21 as compared with the risk for persons not using NSAIDs.<sup>12</sup> Although the annual mortality rate is low, it must be emphasized that because a large number of patients are exposed to NSAIDs, often for extended periods of time, the risk over a lifetime is substantial. In the United States, for instance, it is estimated that NSAIDs are used regularly by at least 13 million people with various arthritides. On the basis of these conservative figures and ARAMIS data, the annual number of hospitalizations in the United States for serious gastrointestinal complications is estimated to be at least 103,000. At an estimated cost of \$15,000 to \$20,000 per hospitalization, the annual direct costs of such complications exceed \$2 billion.<sup>14</sup>

It has been estimated conservatively that 16,500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States. This figure is similar to the number of deaths from the acquired immunodeficiency

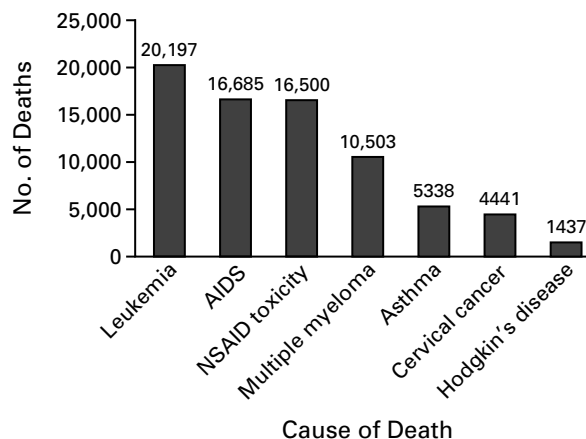
syndrome and considerably greater than the number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease (Fig. 1).<sup>12,15</sup> If deaths from gastrointestinal toxic effects of NSAIDs were tabulated separately in the National Vital Statistics reports, these effects would constitute the 15th most common cause of death in the United States. Yet these toxic effects remain largely a "silent epidemic," with many physicians and most patients unaware of the magnitude of the problem.<sup>12</sup> Furthermore, the mortality statistics do not include deaths ascribed to the use of over-the-counter NSAIDs.

In a recent survey of 4799 Americans, 807 were identified who had taken NSAIDs (prescribed or over-the-counter drugs) at least twice in the past year for five or more consecutive days.<sup>12</sup> Approximately 45 percent of the group took NSAIDs for five or more consecutive days at least once per month, and 40 percent took both over-the-counter and prescribed NSAIDs. Nearly 75 percent of those who used NSAIDs regularly were either unaware of or unconcerned about possible gastrointestinal complications. In addition, almost two thirds of the regular users indicated that they would expect warning signs before the development of serious NSAID-induced complications. Only a minority of patients who have serious gastrointestinal complications report any antecedent dyspepsia.<sup>11,13</sup> In a study of patients with serious gastrointestinal complications, Singh et al.<sup>11</sup> found that although the proportion of patients with prior symptoms was only slightly higher than the proportion with no prior symptoms (2.7 percent vs. 2.0 percent), 81 percent of the patients reported no antecedent dyspepsia.

### RISK FACTORS FOR GASTROINTESTINAL COMPLICATIONS

Because dyspeptic symptoms are not a reliable warning sign, it is important to identify factors that increase the risk of serious gastrointestinal complications and to determine methods for reducing this risk. A number of studies have been designed to identify patients who are most likely to have adverse effects of NSAID therapy (Table 1).

Advanced age has been consistently found to be a primary risk factor for adverse gastrointestinal events. The risk increases linearly with age.<sup>15-20</sup> Although previous reports suggested that the risk diminishes over time, a recent study indicates that the risk of NSAID-associated gastrointestinal hemorrhage remains constant over an extended period of observation.<sup>12</sup> Other risk factors that have been identified in multiple studies are higher doses of NSAIDs (including the use of two or more NSAIDs), a history of gastroduodenal ulcer or gastrointestinal bleeding, concomitant use of corticosteroids, serious coexisting conditions, and concomitant use of anticoagulants.<sup>20-27</sup> However, many of these studies are based



**Figure 1.** U.S. Mortality Data for Seven Selected Disorders in 1997. A total of 16,500 patients with rheumatoid arthritis or osteoarthritis died from the gastrointestinal toxic effects of NSAIDs. Data are from the National Center for Health Statistics and the Arthritis, Rheumatism, and Aging Medical Information System.<sup>12</sup>

**TABLE 1.** RISK FACTORS FOR THE DEVELOPMENT OF NSAID-ASSOCIATED GASTRODUODENAL ULCERS.\*

#### Established risk factors

Advanced age (linear increase in risk)  
 History of ulcer  
 Concomitant use of corticosteroids  
 Higher doses of NSAIDs, including the use of more than one NSAID  
 Concomitant administration of anticoagulants  
 Serious systemic disorder

#### Possible risk factors

Concomitant infection with *Helicobacter pylori*  
 Cigarette smoking  
 Consumption of alcohol

\*Information on risk factors is from Singh and Triadafilopoulos,<sup>12</sup> Bjorkman,<sup>16</sup> Longstreth,<sup>17</sup> Greene and Winickoff,<sup>18</sup> Gabriel et al.,<sup>19</sup> Griffin et al.,<sup>20</sup> Langman et al.,<sup>21</sup> Garcia Rodriguez and Jick,<sup>22</sup> Hallas et al.,<sup>23</sup> Silverstein et al.,<sup>24</sup> Hochtain et al.,<sup>25</sup> Piper et al.,<sup>26</sup> Shorr et al.,<sup>27</sup> and Barkin.<sup>28</sup>

on univariate analysis and do not consider the interactions among multiple factors and coexisting conditions.

The identification of *Helicobacter pylori* infection as a factor in the development of peptic ulcer has raised the question of a possible synergistic relation between the presence of *H. pylori* infection and NSAID use. Although several studies<sup>29-32</sup> have found these two factors to be independent, two prospective studies have suggested a synergistic relation. Bianchi Porro et al.<sup>33</sup> used the combination of amoxicillin and omeprazole to treat NSAID users infected

with *H. pylori*. They found that the eradication of *H. pylori* did not affect the rate of ulcer healing. However, six months after the end of combination therapy, the cumulative rate of recurrent ulcers was 31 percent among the patients in whom *H. pylori* had been eradicated and 46 percent among those who were still infected. This difference was not statistically significant.

Chan et al.<sup>34</sup> found that the use of a regimen that included bismuth subcitrate to eradicate *H. pylori* significantly decreased the rate of ulcer development associated with the use of naproxen. In this study, gastroduodenal ulcers developed in 26 percent of *H. pylori*-infected persons, but in only 7 percent of those in whom the organism had been eradicated. The inclusion of bismuth in the drug regimen, however, makes the findings somewhat ambiguous, because bismuth can accumulate in the gastric mucosa and stimulate prostaglandin synthesis.<sup>28</sup> Most recently, Hawkey et al.<sup>35</sup> randomly assigned 285 patients with current ulcers or a history of ulcers who were using NSAIDs to combined treatment with omeprazole, clarithromycin, and amoxicillin or to treatment with omeprazole alone. They found that the eradication of *H. pylori* did not affect the rate of recurrent ulcer; in addition, ulcer healing was impaired even in the patients who were successfully treated with antibiotics for *H. pylori* infection. It thus appears that infection with *H. pylori* increases the risk of gastroduodenal mucosal injury associated with NSAID use only minimally, if at all.<sup>28</sup>

Singh et al.<sup>36</sup> recently proposed a simple, point-based algorithm that patients and their physicians can use to estimate the risk of an NSAID-related gastrointestinal complication. If confirmed by other investigators, this tool may help guide decisions about prescriptions for specific NSAIDs, the use of prophylactic agents, and the need for and frequency of patient monitoring.<sup>36</sup>

#### PATHOGENESIS OF NSAID-INDUCED GASTRODUODENAL MUCOSAL INJURY

Gastroduodenal mucosal injury develops when the deleterious effect of gastric acid overwhelms the normal defensive properties of the mucosa. Concepts about NSAID-induced gastroduodenal mucosal injury have evolved from a simple notion of topical injury to theories involving multiple mechanisms with both local and systemic effects (Fig. 2). The systemic effects are largely the result of the inhibition of endogenous prostaglandin synthesis.<sup>37</sup> Prostaglandin inhibition, in turn, leads to decreases in epithelial mucus, secretion of bicarbonate, mucosal blood flow, epithelial proliferation, and mucosal resistance to injury.<sup>38,39</sup> The impairment in mucosal resistance permits injury by endogenous factors, including acid, pepsin, and bile salts, as well as by exogenous factors such as NSAIDs and possibly ethanol and other noxious agents.

#### Topical Injury

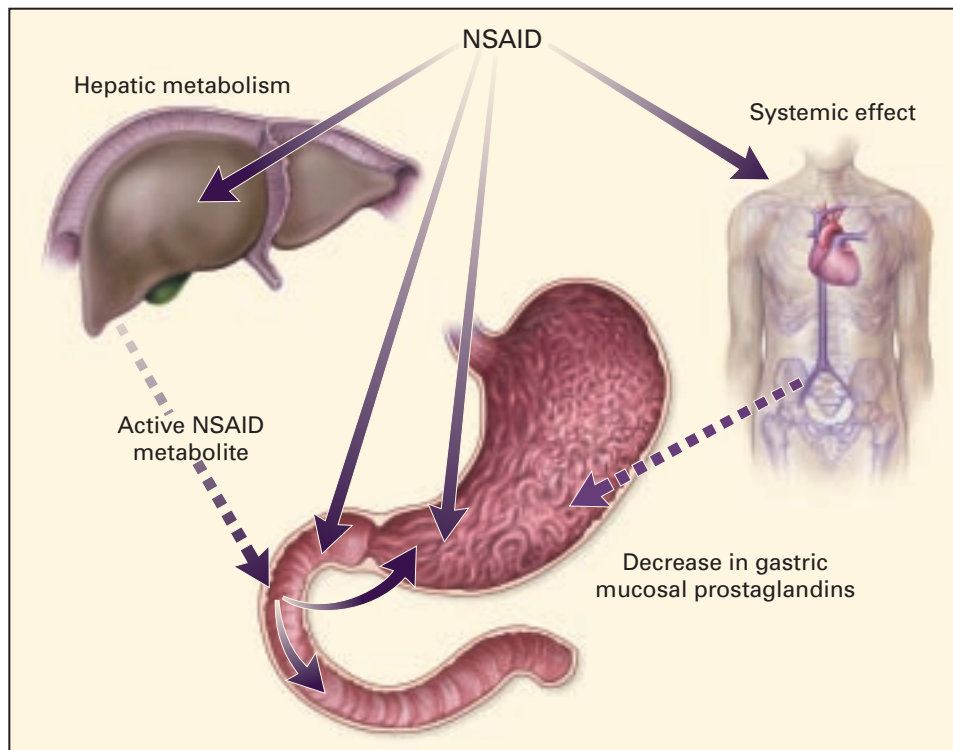
Mucosal injury is initiated topically by the acidic properties of aspirin and many other NSAIDs. Because of a low dissociation constant, which varies according to the particular agent, these weak acids remain in their nonionized lipophilic form in the highly acidic gastric lumen. Such conditions favor migration through the gastric mucus across plasma membranes and into surface epithelial cells, where NSAIDs are dissociated into the ionized form, resulting in trapping of hydrogen ions.<sup>37</sup> NSAIDs can also cause topical mucosal damage by diminishing the hydrophobicity of gastric mucus, thereby allowing endogenous gastric acid and pepsin to injure the surface epithelium.<sup>39</sup> In addition, topical mucosal injury may occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.<sup>40,41</sup> For example, although sulindac is administered as a non-toxic prodrug, its active metabolite, sulindac sulfide, is excreted into the bile. On entry into the duodenum, sulindac sulfide causes topical injury to the mucosa by virtue of its acidic properties.

#### The Role of Prostaglandins

Topical injury caused by NSAIDs contributes to the development of gastroduodenal mucosal injury. However, the systemic effects of these agents appear to have the predominant role,<sup>37,42,43</sup> largely through the decreased synthesis of mucosal prostaglandins.<sup>44</sup> The use of enteric-coated aspirin preparations<sup>44</sup> and parenteral<sup>45</sup> or rectal<sup>46</sup> administration of NSAIDs in order to prevent topical mucosal injury has also failed to prevent the development of ulcers. Moreover, doses of aspirin as low as 30 mg are sufficient to suppress prostaglandin synthesis in the gastric mucosa.<sup>47</sup>

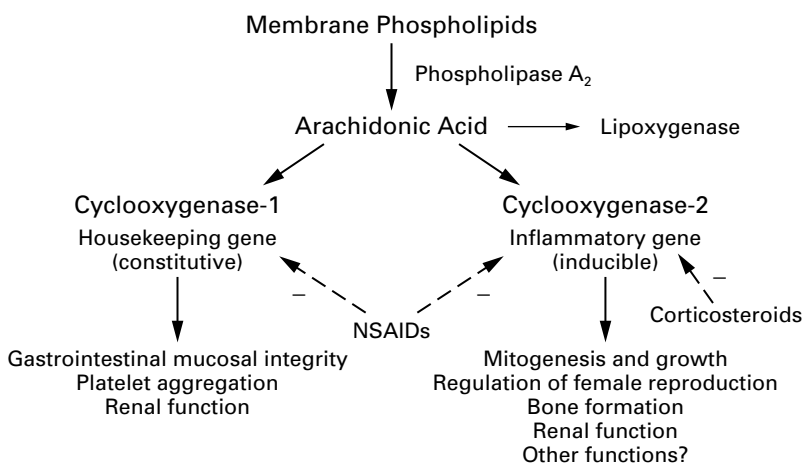
Prostaglandins are derived from arachidonic acid, which originates from cell-membrane phospholipids through the action of phospholipase A<sub>2</sub> (Fig. 3). The metabolism of arachidonic acid to prostaglandins and leukotrienes is catalyzed by the cyclooxygenase pathway and the 5-lipoxygenase pathway, respectively.<sup>1,37</sup> Two related but unique isoforms of cyclooxygenase, designated cyclooxygenase-1 and cyclooxygenase-2, have been demonstrated in mammalian cells.<sup>48,49</sup> Despite their structural similarities, they are encoded by distinct genes and differ with regard to their distribution and expression in tissues.<sup>50,51</sup> The cyclooxygenase-1 gene contains a promoter region without a TATA sequence and is primarily expressed constitutively. In contrast, the cyclooxygenase-2 gene is thought to be the inducible form that is nearly undetectable in most (but not all) tissues under normal physiologic conditions.

Cyclooxygenase-1 appears to function as a "house-keeping" enzyme in most tissues, including the gastric mucosa, the kidneys, and the platelets, whereas the expression of cyclooxygenase-2 can be induced



**Figure 2.** Mechanisms by Which NSAIDs Induce Gastroduodenal Mucosal Injury.

According to the dual-injury hypothesis of Schoen and Vender,<sup>37</sup> NSAIDs have direct toxic effects on the gastroduodenal mucosa (solid arrows) and indirect effects through active hepatic metabolites and decreases in mucosal prostaglandins (broken arrows). Hepatic metabolites are excreted into the bile and subsequently into the duodenum, where they cause mucosal damage to the stomach by duodenogastric reflux and mucosal damage to the small intestine by antegrade passage through the gastrointestinal tract. Adapted from Schoen and Vender.<sup>37</sup>



**Figure 3.** Biosynthesis of Prostaglandins through the Cyclooxygenase Pathways.

The immediate precursor of prostaglandins, arachidonic acid, is derived from membrane phospholipids and is catalyzed by the two cyclooxygenase isoenzymes (also designated as prostaglandin H synthase), cyclooxygenase-1 and cyclooxygenase-2. The gene for cyclooxygenase-1, the housekeeping enzyme, is expressed constitutively and maintains the homeostasis of organs, including gastric mucosal integrity. In contrast, the gene for cyclooxygenase-2, the inflammatory enzyme, is inducible. Although both pathways can be variably inhibited by different NSAIDs, only the gene for cyclooxygenase-2 contains a corticosteroid-responsive repressor element in its promoter region. The broken arrows indicate the inhibitory effects of pharmacologic agents.

by inflammatory stimuli and mitogens in many different types of tissue, including macrophages and synovial cells.<sup>43</sup> It has thus been suggested that the antiinflammatory properties of NSAIDs are mediated through the inhibition of cyclooxygenase-2, whereas adverse effects, such as gastroduodenal ulceration, occur as a result of effects on the constitutively expressed cyclooxygenase-1.<sup>43,49</sup> As discussed below, current strategies for developing NSAIDs with an improved safety profile include the selective inhibition of cyclooxygenase-2, with the sparing of cyclooxygenase-1.

Although there is substantial evidence that the suppression of gastric prostaglandins is the fundamental mechanism responsible for the gastrointestinal toxicity of NSAIDs, some studies suggest that other mechanisms may be involved. For example, ulcers do not develop spontaneously in mice with a disrupted cyclooxygenase-1 gene,<sup>52</sup> and Wallace et al.<sup>53,54</sup> reported that NSAID-induced injury occurred in association with enhanced adherence of neutrophils to the gastric vascular endothelium, as the result of an increase in the expression of intercellular adhesion molecule 1 in the basal endothelium.<sup>55-58</sup> Neutrophil adherence, in turn, causes mucosal injury through the release of oxygen-derived free radicals and proteases.<sup>1</sup>

#### CLINICAL SPECTRUM OF INJURY

In the majority of patients, NSAID-induced gastroduodenal mucosal injury is superficial and self-limited. However, peptic ulcers develop in some patients, and they may lead to gastroduodenal hemorrhage, perforation, and death. Serious complications of NSAID use that are less commonly recognized include pill esophagitis, small-bowel ulceration, small-bowel strictures, colonic strictures, diverticular disease, and exacerbations of inflammatory bowel disease.<sup>9</sup>

The spectrum of NSAID-related gastroduodenal injury includes a combination of subepithelial hemorrhages, erosions, and ulcerations that is often referred to as NSAID gastropathy. The distinction between erosions and ulcerations depends on pathological definitions, with ulcers defined as lesions that penetrate to the level of the submucosa and erosions defined as lesions confined to the mucosa. For practical purposes, an endoscopic definition is used, which is based on a subjective assessment of the size, shape, and depth of the lesion. Erosions are likely to be small and superficial, whereas ulcers tend to be larger (more than 5 mm in diameter) and deeper.<sup>9</sup>

After ingestion of an NSAID, ultrastructural damage to the gastric surface epithelium occurs within minutes, and gross, endoscopically detectable hemorrhages and erosions in the gastroduodenal epithelium occur within several hours.<sup>59</sup> However, mucosal adaptation appears to occur in response to long-term administration of aspirin in most persons.<sup>60,61</sup> No area of the stomach is resistant to NSAID-induced

mucosal injury; the most frequently and severely affected site is the gastric antrum.<sup>59</sup> Although the prevalence and severity of acute injury vary according to the drug formulation,<sup>62-64</sup> the acute injury commonly observed during short-term administration of NSAIDs is not closely correlated with the subsequent development of the more clinically relevant process of mucosal ulceration<sup>20,21,65,66</sup> or with serious complications.<sup>10,67,68</sup> Duodenal mucosal injury occurs less commonly than gastric damage; however, ulcer complications associated with NSAIDs occur with nearly equal frequency in these two sites.<sup>51,66</sup> Prospective, cross-sectional endoscopic studies have shown that the combined prevalence of gastric and duodenal ulcers is 10 to 25 percent in patients with chronic arthritis treated with NSAIDs,<sup>10,67</sup> which is 5 to 15 times the expected prevalence in an age-matched healthy population.

#### TREATMENT OF NSAID-RELATED DYSPEPSIA

At least 10 to 20 percent of patients have dyspeptic symptoms during NSAID therapy.<sup>10,11</sup> However, such symptoms are poorly correlated with the endoscopic appearance and severity of mucosal injury, since up to 40 percent of persons with endoscopic evidence of erosive gastritis are asymptomatic,<sup>10,68</sup> and conversely, as many as 50 percent of patients with dyspepsia have normal-appearing mucosa.<sup>10</sup>

##### Histamine H<sub>2</sub>-Receptor Antagonists

Several studies using different methods have shown an improvement in dyspeptic symptoms when histamine H<sub>2</sub>-receptor antagonists are given to patients taking NSAIDs.<sup>69-73</sup> A recent prospective, observational cohort study by Singh et al.,<sup>11</sup> however, found that asymptomatic patients with rheumatoid arthritis who were taking H<sub>2</sub>-receptor antagonists had a significantly higher risk of gastrointestinal complications than those not taking these drugs. The explanation for this surprising observation is unknown, but it might be due to the masking of dyspeptic symptoms associated with mucosal injury. Therefore, although H<sub>2</sub>-receptor antagonists are effective in reducing NSAID-related dyspepsia, their routine use in asymptomatic patients taking NSAIDs cannot be recommended. Patients receiving H<sub>2</sub>-receptor antagonists for the treatment of dyspepsia must be monitored carefully for the development of serious complications. The initial dose should generally be low (e.g., 400 mg of cimetidine, 150 mg of ranitidine or nizatidine, or 20 mg of famotidine, administered twice daily in each case), and the dose should be tailored to the needs of each patient.

##### Proton-Pump Inhibitors

In two recent studies, the proton-pump inhibitor omeprazole was compared with ranitidine<sup>74</sup> or mi-

soprostol,<sup>75</sup> a prostaglandin E<sub>1</sub> analogue, for the treatment and prevention of NSAID-related gastroduodenal ulcers. A secondary goal in both of these multicenter trials was to assess the effects of therapy on dyspeptic symptoms. In both studies, although different methods were used to assess the clinical response, omeprazole provided greater symptomatic relief. After four weeks, only 6 percent of patients treated with omeprazole had moderate-to-severe symptoms, as compared with 52 percent at base line, whereas 12 percent of those treated with ranitidine had such symptoms, as compared with 50 percent at base line.<sup>74</sup> A quality-of-life evaluation showed that the patients receiving omeprazole had significantly greater improvement in scores on the Gastrointestinal Symptom Rating Scale than the patients receiving misoprostol.<sup>75</sup> Because proton-pump inhibitors represent a suitable means of preventing the development of gastroduodenal ulcers associated with the use of NSAIDs,<sup>76</sup> they appear to provide a safe and effective form of therapy for NSAID-associated dyspepsia.

#### MANAGEMENT OF NSAID-RELATED GASTRODUODENAL ULCERS

The optimal treatment for patients with NSAID-induced gastroduodenal ulcers should include the elimination of any potentially aggravating factors. Nontoxic analgesics such as acetaminophen should be substituted for NSAIDs when possible, and in patients with inflammatory arthritides, disease-modifying (or slow-acting) antirheumatic drugs have been recommended as first-line treatment. If NSAID therapy is discontinued, effective treatment aimed at healing the acute ulcer can be instituted with one of several antisecretory agents or with sucralfate. If the use of NSAIDs must be continued, ulcer healing is entirely dependent on the specific agent chosen for ulcer treatment.

##### Mucosal Protective Agents

Sucralfate, a basic aluminum salt of sucrose octasulfate, is effective in the treatment of both NSAID-related duodenal ulcers and those unrelated to NSAIDs, and the agent appears to be as effective as H<sub>2</sub>-receptor antagonists in the healing of non-NSAID-related gastric ulcers.<sup>77</sup> However, sucralfate has no proven benefit in the treatment or prevention of NSAID-related gastric ulcers. Prostaglandins exert their therapeutic effects both by enhancing mucosal defensive properties and by inhibiting gastric-acid secretion.<sup>39</sup> Although they are effective in preventing NSAID-induced gastroduodenal mucosal injury, their role in the treatment of NSAID-associated ulcers is unclear. Hawkey et al.<sup>75</sup> recently compared the capacity of misoprostol (200 µg given four times daily) and omeprazole (20 mg or 40 mg given once daily) to heal gastroduodenal ulcers in patients receiving on-

going NSAID therapy. After eight weeks of therapy, 89 percent of the patients with duodenal ulcers who received omeprazole at either dose had healing, as compared with only 77 percent of those with duodenal ulcers who received misoprostol. Among the patients with gastric ulcers, healing was detected in 80 percent of those receiving 40 mg of omeprazole, in 87 percent of those receiving 20 mg of omeprazole, and in 73 percent of those receiving misoprostol.<sup>75</sup>

##### Antisecretory Drugs

The efficacy of H<sub>2</sub>-receptor antagonists in the treatment of NSAID-related ulcers has not been assessed extensively. Both open, uncontrolled, nonrandomized studies<sup>78</sup> and prospective, randomized studies<sup>79</sup> have suggested that treatment with conventional doses of H<sub>2</sub>-receptor antagonists for 6 to 12 weeks results in the healing of approximately 75 percent of gastric ulcers (range, 50 to 88 percent) and 87 percent of duodenal ulcers (range, 67 to 100 percent), despite the continued use of NSAIDs. When the use of NSAIDs is continued, healing appears to be delayed and is largely dependent on the initial size of the ulcer. O'Laughlin et al.<sup>80</sup> reported a 90 percent healing rate for small gastric ulcers (less than 5 mm in diameter) after an eight-week course of treatment with cimetidine, whereas only 25 percent of larger ulcers healed.

In a multicenter trial that included a small subgroup of patients with NSAID-related gastric ulcers, Walan et al.<sup>81</sup> reported that among the patients who continued to receive NSAIDs, the healing rate was higher for those treated with omeprazole than for those treated with ranitidine. A more recent multicenter trial by Yeomans et al.<sup>74</sup> also demonstrated the superiority of omeprazole over ranitidine in the treatment of NSAID-related gastroduodenal ulcers. In this study, the rates of ulcer healing at eight weeks were 79, 80, and 63 percent in the groups receiving 40 mg of omeprazole, 20 mg of omeprazole, and 150 mg of ranitidine twice a day, respectively. A study by Agrawal et al.<sup>82</sup> compared the efficacy of lansoprazole with that of ranitidine in the healing of gastric ulcers during continued NSAID therapy. After eight weeks, ulcers were healed in 57 percent of the patients receiving 150 mg of ranitidine twice daily, whereas ulcers were healed in 73 percent of those receiving 15 mg of lansoprazole once daily and 75 percent of those receiving 30 mg of lansoprazole once daily. These observations suggest that proton-pump inhibitors can heal gastroduodenal ulcers more effectively than H<sub>2</sub>-receptor antagonists, whether or not NSAIDs are continued.

#### PREVENTION OF NSAID-ASSOCIATED GASTRODUODENAL ULCERS

Because of the prevalence and severity of NSAID-related gastrointestinal complications, recent efforts

have been directed at the prevention of mucosal injury induced by NSAIDs. As discussed above, the best way to prevent mucosal injury is to avoid the use of NSAIDs and to substitute an agent less toxic to the gastroduodenal mucosa, such as acetaminophen, salsalate, or magnesium salicylate. Nevertheless, a potent NSAID is commonly preferred, and two strategies have been used to improve their safety: the administration of concomitant medication to protect the gastroduodenal mucosa from injury and the development of safer antiinflammatory agents.

### Concomitant Therapy

#### *Sucralfate*

Early, small studies suggested that sucralfate might reduce gastroduodenal mucosal injury associated with the use of NSAIDs.<sup>83</sup> However, a large, controlled, randomized trial conducted by Agrawal et al.<sup>84</sup> showed no significant benefit of sucralfate in preventing gastric ulcers in patients with osteoarthritis who were receiving NSAID therapy.

#### *H<sub>2</sub>-Receptor Antagonists*

Two large, placebo-controlled, prospective trials investigated the protective effect of ranitidine in patients with arthritis who were receiving NSAID therapy.<sup>85,86</sup> Ranitidine (150 mg given twice a day) was effective in preventing duodenal ulcers, which developed in 0 percent and 1.5 percent of the ranitidine-treated patients in the two studies, as compared with 8 percent of the placebo-treated patients in both studies. In contrast, the same dose of ranitidine was ineffective in preventing gastric ulcers in both studies. Taha et al.<sup>73</sup> recently reported a benefit of high-dose famotidine (40 mg given twice a day), as compared with placebo, in preventing both gastric and duodenal ulcers in patients with arthritis who received NSAIDs for 24 weeks. Symptomatic relief was also observed in the group randomly assigned to famotidine, but the benefit, although statistically significant, was only moderate, and the cost of such doses of H<sub>2</sub>-receptor antagonists is considerable. Thus, the use of H<sub>2</sub>-receptor antagonists for the prevention of NSAID-associated ulcers cannot be recommended.

#### *Proton-Pump Inhibitors*

Although proton-pump inhibitors had previously been demonstrated to heal gastroduodenal ulcers effectively in NSAID users,<sup>81</sup> until recently only two small studies<sup>87,88</sup> had systematically examined their effectiveness in preventing NSAID-related gastroduodenal mucosal injury. A recent study compared omeprazole and ranitidine for the prevention of recurrent gastroduodenal ulcers in a large number of patients with arthritis in whom NSAID therapy could not be discontinued.<sup>74</sup> After six months of treatment, 16.3 percent of the patients treated with ranitidine had gastric ulcers, and 4.2 percent had

duodenal ulcers. In the omeprazole group, only 5.2 percent of the patients had gastric ulcers, and only 0.5 percent had duodenal ulcers.<sup>74</sup>

Another recent study compared omeprazole (20 mg given once a day) and misoprostol (200 µg given twice a day) for the prevention of recurrent ulcers in patients with arthritis who were receiving NSAID therapy.<sup>75</sup> After six months, 12 percent of the patients receiving placebo and 10 percent of those receiving misoprostol, but only 3 percent of those receiving omeprazole, had duodenal ulcers. Gastric ulcers recurred in 32 percent of the patients receiving placebo, in 10 percent of those receiving misoprostol, and in 13 percent of those receiving omeprazole.<sup>75</sup> These studies suggest that, like misoprostol, proton-pump inhibitors are superior to H<sub>2</sub>-receptor antagonists. Although a prospective analysis of clinical outcomes has not been performed, these agents appear to be effective in preventing the recurrence of ulcers during continued use of NSAIDs.<sup>76</sup>

#### *Prostaglandins*

In their initial study, Graham et al.<sup>67</sup> reported that the prevalence of gastric ulcers in patients with osteoarthritis who were receiving NSAIDs was 1.4 percent in those receiving concomitant treatment with 200 µg of misoprostol four times a day, 5.6 percent in those receiving 100 µg of misoprostol four times a day, and 21.7 percent in those receiving placebo. The efficacy of misoprostol as prophylaxis against duodenal ulcers was confirmed in a subsequent study by Graham et al.<sup>89</sup> Despite the effectiveness of misoprostol in preventing gastroduodenal ulcers, the agent was not associated with any improvement in dyspeptic symptoms in these studies. Furthermore, diarrhea developed in many of the patients receiving the 200-µg dose of misoprostol. Raskin et al.<sup>90</sup> compared three regimens of misoprostol (200 µg given twice, three times, or four times a day) and concluded that although lower doses of misoprostol are better tolerated, the drug needs to be taken at least three times a day to provide effective prophylaxis against NSAID-induced gastric ulcers.

It must be emphasized that the prevention of endoscopically detectable ulcers as an end point is not necessarily a safeguard against the development of serious ulcer-related complications. To determine whether treatment with misoprostol could affect the incidence of ulcer complications caused by NSAID use, Silverstein et al.<sup>24</sup> conducted the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) study. They reported a 40 percent reduction in the overall rate of complications due to NSAID-associated ulcers in a group of patients receiving 200 µg of misoprostol four times a day, as compared with the patients receiving placebo.<sup>24</sup>

Although misoprostol is highly effective for preventing NSAID-induced ulcers and is the only drug

approved by the Food and Drug Administration as prophylaxis against NSAID-related gastroduodenal ulcers, it has a number of adverse effects. These include diarrhea and abdominal pain associated with the increased generation of cyclic adenosine monophosphate in the small intestine and increased uterine contractility that can lead to spontaneous abortion.

#### Development of Safer NSAIDs

Several modifications in the formulation of NSAIDs have been introduced in recent years to reduce their toxicity. Recent surveillance and endoscopic studies have confirmed that the incidence of gastroduodenal mucosal injury is reduced with the use of nabumetone, etodolac, and meloxicam.<sup>91-93</sup> The improved safety of meloxicam appears to be due to its preferential inhibition of cyclooxygenase-2, with a minimal effect on cyclooxygenase-1. In contrast, nabumetone and etodolac appear to inhibit cyclooxygenase-2 preferentially at low doses, but the preferential inhibition of cyclooxygenase-2 is diminished at higher doses. These agents also have other properties that contribute to their safety. Etodolac has a low level of enterohepatic recirculation and a short half-life; nabumetone is a nonacidic prodrug formulation and has no enterohepatic recirculation.<sup>94</sup>

#### Highly Selective Cyclooxygenase-2 Inhibitors

Highly selective cyclooxygenase-2 inhibitors have recently been developed that, in studies to date, have had a markedly reduced capacity to cause injury to the gastroduodenal mucosa.<sup>95-98</sup> Two of the compounds, celecoxib and rofecoxib, have been studied extensively, and they appear to maintain their selectivity for cyclooxygenase-2 at doses substantially higher than those required to affect inflammation. These agents are more than 100 times as selective in their ability to inhibit cyclooxygenase-2 as the currently available NSAIDs and have been shown to promote the development of gastroduodenal ulcers at a rate not significantly different from that of placebo.<sup>99,100</sup> The selectivity ratios for inhibition of cyclooxygenase-1 and cyclooxygenase-2 of celecoxib, rofecoxib, and other agents have been determined primarily by *in vitro* assays.<sup>101</sup> Although these drugs have similar *in vivo* selectivity, genetic differences among patients may affect the cyclooxygenase-2 selectivity of these drugs. Celecoxib became available for use in the United States in February 1999, and rofecoxib will probably be available very soon.

In spite of enthusiasm for these promising new NSAIDs, some questions remain regarding their highly selective inhibition of cyclooxygenase-2. For example, cyclooxygenase-2 might generate endogenous prostanoids that are biologically important (Fig. 3). Mice in which the gene for cyclooxygenase-2 has been disrupted have defects in renal function and

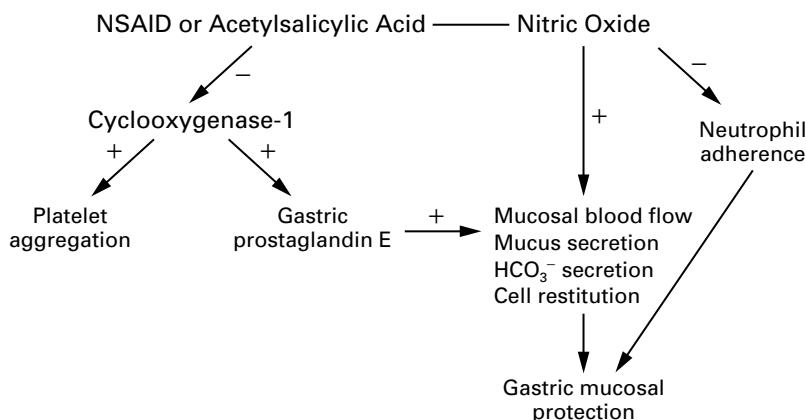
regulation of bone resorption, and female mice have impaired reproductive physiology.<sup>94</sup> Mizuno et al.<sup>102</sup> have suggested that an increase in mucosal cyclooxygenase-2 expression may be necessary for the normal healing of gastroduodenal ulcers. However, non-selective NSAIDs also inhibit cyclooxygenase-2 to varying degrees, and the critical factor may be the ratio of isoenzyme inhibition.

McAdam et al.<sup>103</sup> recently reported that celecoxib, but not ibuprofen, suppressed the urinary excretion of prostacyclin in healthy subjects, whereas thromboxane activity related to cyclooxygenase-1 was suppressed only by ibuprofen. The authors speculated that long-term therapy with these agents might increase the rate of thrombotic events in patients who were at increased risk for cardiovascular disease, although no data were collected on such events.<sup>103</sup> On a positive note, the expression of cyclooxygenase-2 messenger RNA is enhanced in human colorectal adenomas and adenocarcinomas, and selective cyclooxygenase-2 inhibition may thereby reduce the risk of colorectal cancer.<sup>104</sup> The results of these studies indicate that although the highly selective cyclooxygenase-2 inhibitors offer considerable promise in the treatment of inflammatory arthritides, careful surveillance will be important to determine their ultimate benefit and safety profile.

#### NSAIDs Containing Nitric Oxide

Nitric oxide has a critical role in maintaining the integrity of the gastroduodenal mucosa, exerting many of the same effects as endogenous prostaglandins.<sup>105-107</sup> It has even been suggested that nitric oxide and prostaglandins may act synergistically to mediate mucosal protective effects,<sup>1</sup> and Salvemini et al.<sup>108</sup> have demonstrated that nitric oxide stimulates cyclooxygenase enzymes. Such redundancy in preserving normal physiologic function is not unique, and it constitutes the rationale for the development of formulations in which nitric oxide is released and compensates for the suppression of mucosal prostaglandins. Under these conditions, the desired effects of NSAIDs are maintained, including the inhibition of both cyclooxygenase isoenzymes, while toxicity is minimized (Fig. 4).<sup>109-111</sup> Nitric oxide-containing compounds have antiinflammatory and antipyretic activities that are similar to those of the parent compound and may have analgesic effects that are greater than those of the parent compound.<sup>110</sup>

In a recent seven-day clinical trial, a flurbiprofen-nitric oxide formulation was found to cause fewer gastric erosions than the parent drug, with the same inhibitory effects on gastric mucosal prostaglandin synthesis and serum thromboxane levels.<sup>112</sup> In addition, nitric oxide, like aspirin, inhibits platelet aggregation, but it does not suppress cyclooxygenase activity or cause gastric mucosal injury.<sup>113</sup> The use of nitric oxide-aspirin compounds as prophylaxis against



**Figure 4.** Postulated Mechanism by Which Nitric Oxide–Releasing NSAIDs Maintain the Ability to Protect the Gastroduodenal Mucosa while Suppressing the Level of Endogenous Mucosal Prostaglandins. Nitric oxide appears to stimulate some of the defensive properties of the mucosa that are affected by inhibition of the cyclooxygenase-1 isoenzyme. In addition, nitric oxide inhibits intercellular adhesion molecule 1, thereby decreasing neutrophil adherence, resulting in the prevention of NSAID-induced gastroduodenal mucosal injury. Adapted from Wallace.<sup>1</sup>

**TABLE 2.** CURRENT RECOMMENDATIONS FOR THE TREATMENT OF NSAID-RELATED DYSPEPSIA AND MUCOSAL INJURY.

CLINICAL SITUATION	RECOMMENDATION
Dyspepsia	Empirical treatment with H <sub>2</sub> -receptor antagonist (e.g., 400 mg of cimetidine, 150 mg of ranitidine or nizatidine, or 20 mg of famotidine, all twice daily) or proton-pump inhibitor (e.g., 20 mg of omeprazole, 30 mg of lansoprazole, 20 mg of rabeprazole, or 40 mg of pantoprazole daily before breakfast); individualize therapy
<i>Helicobacter pylori</i> infection	Treatment to eradicate infection only in patients with a history of peptic ulcer
Active gastroduodenal ulcer NSAID discontinued	Treatment with an H <sub>2</sub> -receptor antagonist (e.g., 800 mg of cimetidine, 150 mg of ranitidine or nizatidine, or 40 mg of famotidine daily before bedtime) or a proton-pump inhibitor (as above)
NSAID continued	Treatment with a proton-pump inhibitor (as above)
Prophylactic therapy	Concomitant treatment with misoprostol (≥200 μg three times a day), a proton-pump inhibitor (as above), or a cyclooxygenase-2–preferential or cyclooxygenase-2–selective NSAID

myocardial and cerebrovascular ischemia is also under investigation.

**Other Approaches**

Several other compounds are being developed, including NSAIDs associated with zwitterionic phospholipids, chiral NSAIDs, basic fibroblast growth factor, and trefoil peptides.<sup>94</sup> Although initial studies indicate that some of these compounds may help reduce the gastrointestinal toxicity of NSAIDs, their clinical use awaits further investigation.

**SUMMARY**

Recommendations for the prevention and management of gastroduodenal mucosal injury associated with NSAIDs are proposed in Table 2. Symptoms associated with the use of NSAIDs are common and can generally be treated empirically with an H<sub>2</sub>-receptor antagonist or a proton-pump inhibitor. Although additional studies are necessary, eradication of *H. pylori* should be reserved for patients with a history of ulcer disease. In general, if a gastroduodenal ulcer develops, the most prudent approach is to discontinue

the NSAID and substitute therapy with acetaminophen or a nonacetylated salicylate. If treatment with the NSAID must be continued, proton-pump inhibitors should be used, since they appear to heal ulcers at the same rate, whether or not NSAID therapy is continued. After the ulcer has healed and it has been determined that NSAID therapy must be continued, the most effective prophylaxis against recurrent ulcers is the concomitant administration of misoprostol (at least 200  $\mu\text{g}$  given three times a day) or a proton-pump inhibitor, or the use of an NSAID that preferentially or selectively inhibits cyclooxygenase-2. The ultimate choice of therapy in a particular patient depends on several things, including risk factors, the preferences of the patient and the physician, and cost. The development of cyclooxygenase-2-selective inhibitors and the formulation of other new, safer NSAIDs should broaden the range of options.

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