How do NSAIDs cause ulcer disease?

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Gastroduodenal ulceration and bleeding are the major limitations to the use of non-steroidal anti-inflammatory drugs (NSAIDs). The development of safer NSAIDs or of effective therapies for the prevention of the adverse effects of existing NSAIDs requires a better understanding of the pathogenesis of NSAID-induced ulcer disease. NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury. The presence of acid in the lumen of the stomach also contributes to the pathogenesis of NSAID-induced ulcers and bleeding, by impairing the restitution process, interfering with haemostasis and inactivating several growth factors that are important in mucosal defence and repair. In recent years, a fuller understanding of the pathogenesis of NSAID-induced ulcer disease has facilitated some new, very promising approaches to the development of stomach-sparing NSAIDs.

Key words: ulcer; non-steroidal anti-inflammatory drug; acid; neutrophils; cyclo-oxygenase; nitric oxide.

The ability of non-steroidal anti-inflammatory drugs (NSAIDs) to cause ulceration and bleeding in the upper gastrointestinal tract was first documented by the endoscopic study of Douthwaite and Lintott in 1938. In that study, the investigators demonstrated the ability of aspirin to damage the stomach. In the years that followed, more potent NSAIDs, such as indomethacin, phenylbutazone and the fenamates, were brought to market. Shortly thereafter, case reports of melena associated with the use of aspirin and the newer NSAIDs began to appear in the literature, and in the 1960s and 70s, case-control studies began to document the gastrointestinal toxicity of this class of drug. In recent years, the upper gastrointestinal tract damage caused by NSAIDs has been referred to as an ‘epidemic’ by a number of investigators. This is in part attributable to the widespread use of these drugs, particularly by patients with osteo-arthritis and rheumatoid arthritis. The world market for NSAIDs is approximately $8 billion. The cost of treating NSAID-related gastrointestinal adverse effects almost certainly exceeds this amount (the annual cost of treating NSAID gastropathy in rheumatoid arthritis patients in the USA, for example, having been reported to exceed $4 billion).

Developing anti-inflammatory drugs that do not produce ulceration or bleeding in the gastrointestinal tract, or developing prophylactic therapies that substantially...
reduce the toxicity of existing NSAIDs, depends upon clearly understanding the pathogenesis of NSAID-induced ulceration. In this chapter, the mechanisms by which NSAIDs damage the mucosa, interfere with repair and promote bleeding will be reviewed. In general, the properties of NSAIDs that contribute to ulcerogenesis can be divided into two categories: (1) topical irritancy, and (2) the suppression of prostaglandin synthase activity. In addition, the presence in the stomach and duodenum of acid and, in some cases, *Helicobacter pylori* (*H. pylori*), may contribute to the ability of NSAIDs to damage the mucosa.

**TOPICAL IRRITATION OF THE MUCOSA**

Studies in the 1960s by Davenport suggested that aspirin could directly damage the gastric epithelium. The breaking of the ‘barrier’ permitted the back-diffusion of acid into the mucosa, which eventually led to the rupture of mucosal blood vessels. These topical irritant properties were subsequently found to be predominantly associated with those NSAIDs with a carboxylic acid residue. The unionized forms of these drugs can enter epithelial cells in the stomach and duodenum. Once in the neutral intracellular environment, the drugs are converted to an ionized state and cannot diffuse out. This has been referred to as ‘ion trapping’. As the drug accumulates within the epithelial cell, the osmotic movement of water into the cell results in swelling of the epithelial cell, eventually to the point of lysis.

Another mechanism by which NSAIDs could damage the gastroduodenal epithelium is via the uncoupling of oxidative phosphorylation in the epithelial cells. Various NSAIDs have been shown to uncouple mitochondrial respiration, leading to a depletion of ATP and therefore a reduced ability to regulate normal cellular functions, such as the maintenance of intracellular pH. The ability of NSAIDs to uncouple oxidative phosphorylation also appears to be related to some extent to acidic moieties (such as carboxylic acid residues), since substitution at these sites interferes with the ability of these compounds to act as uncouplers.

The theory that NSAIDs cause topical injury by virtue of their effects on mitochondrial respiration has been challenged, mainly based on the observation that gastric and duodenal ulcers are observed following the parenteral or rectal administration of NSAIDs. Erosions and ulcers can also be produced in experimental circumstances in which NSAIDs are administered parenterally. It is also difficult to comprehend how the uncoupling of oxidative phosphorylation would occur in gastrointestinal epithelial cells but not in the numerous other cells with which an NSAID would have contact subsequent to its absorption. On the other hand, the small intestine would be repeatedly exposed to NSAIDs that are excreted in bile and recycled enterohepatically, so it is conceivable that the uncoupling of oxidative phosphorylation is an important component of the pathogenesis of NSAID-induced enteropathy.

A third mechanism that could account for the topical irritant properties of NSAIDs is their ability to decrease the hydrophobicity of the mucus gel layer in the stomach. Lichtenberger and co-workers have proposed that this layer is a primary barrier to acid-induced damage in the stomach. They demonstrated that the surface of the stomach is hydrophobic and that this hydrophobicity can be reduced by various pharmacological agents. For example, NSAIDs were shown to associate with the surface-active phospholipids within the mucus gel layer, thereby reducing its hydrophobic properties. These investigators further demonstrated that the mucus gel layer in the stomach of rats and mice given NSAIDs was converted from a
non-wettable to a wettable state. This effect was found to persist for several weeks or months after the cessation of NSAID administration.\textsuperscript{12,14}

Attempts have been made to produce NSAIDs with reduced topical irritant effects. These include formulations in slow-release or enteric coated tablets, as well as the preparation of the drug as a pro-drug that requires hepatic metabolism in order to be active (e.g. sulindac). However, the incidence of gastroduodenal ulceration with prodrugs is comparable to that seen with standard NSAIDs.\textsuperscript{16–18} This is taken as evidence that the topical irritant properties of NSAIDs are not paramount in terms of their ability to induce frank ulceration in the stomach. However, one cannot completely exclude this possibility. Most NSAIDs are excreted in bile. Even with parenteral administration of the NSAID, therefore, a reflux of duodenal contents into the stomach would result in the topical exposure of the gastric mucosa to these drugs.

Efforts have recently been made to develop gastrointestinally safe NSAIDs on the basis of a reduced ability to interfere with the surface-active phospholipid layer in the gastrointestinal mucus. Lichtenberger et al proposed that pre-associating NSAIDs with zwitterionic phospholipids prior to their administration should reduce the ability of the NSAIDs to associate the phospholipids in the mucus gel, and should therefore reduce their ulcerogenicity.\textsuperscript{12} They demonstrated this to be the case by pre-associating aspirin and other NSAIDs with dipalmitoyl-phosphatidylcholine (DPPC) and demonstrating that the complex produced significantly less damage in the gastrointestinal tract than did the parent drug.\textsuperscript{14} Importantly, the pre-association of aspirin with DPPC did not interfere with the effectiveness of the aspirin to reduce fever or inflammation.\textsuperscript{19} Similar effects could be obtained with other NSAIDs.\textsuperscript{14,19}

**SUPPRESSION OF PROSTAGLANDIN SYNTHESIS**

Vane’s discovery in 1971 that NSAIDs inhibit prostaglandin synthesis\textsuperscript{20} led directly to the discovery of the ability of minute quantities of exogenous prostaglandins to protect the gastrointestinal tract from injury induced by topical irritants and NSAIDs.\textsuperscript{21} This in turn led to extensive research into the roles of prostaglandins in mucosal defence. There is substantial evidence that the ability of an NSAID to cause gastric damage correlates well with its ability to suppress gastric prostaglandin synthesis\textsuperscript{22–25}; agents that are weak inhibitors of gastric prostaglandin synthesis are less ulcerogenic.\textsuperscript{24,25} There is also a good correlation between the time- and dose-dependency of suppression of gastric prostaglandin synthesis by NSAIDs and their ability to cause gastric ulcers.\textsuperscript{22–24} Why does the suppression of gastric prostaglandin synthesis lead to mucosal injury? As mentioned above, it is now clear that prostaglandins play a central role in modulating mucosal defence. Endogenous prostaglandins are involved in the regulation of mucus and bicarbonate secretion by the gastric and duodenal epithelium, mucosal blood flow, epithelial cell proliferation, epithelial restitution and mucosal immunocyte function.\textsuperscript{26} This is not to say that prostaglandins are the only endogenous substances regulating these components of mucosal defence; indeed, nitric oxide appears to perform many of the same functions as the prostaglandins in this respect.\textsuperscript{26} Thus, the inhibition of prostaglandin synthesis alone may not result in the formation of gastric erosions or ulcers. For example, mice in which the gene for cyclo-oxygenase-1 was disrupted exhibited negligible levels of gastric prostaglandin synthesis yet did not spontaneously develop gastric erosions or ulcers.\textsuperscript{27} Of course, one would, in such a situation, anticipate that adaptation of the stomach to the chronic absence of prostaglandins would occur (i.e. there might be an enhanced production of other...
gastroprotective substances). On the other hand, the suppression of mucosal pro-
staglandin synthesis, while not necessarily resulting in ulcer formation, will reduce the
ability of the gastric mucosa to defend itself against luminal irritants. This has been
demonstrated very clearly in experimental animals. Doses of NSAIDs that substantially
reduced mucosal prostaglandin synthesis did not cause overt gastric injury but did
greatly increase the susceptibility of the gastric mucosa to damage induced by irritants
(e.g. bile salts).28

In terms of the pathogenesis of ulcer disease, is there one component of mucosal
defence that is more important than others with respect to its impairment by
NSAIDs? This question has not yet been completely answered. The fact that gastric
ulcers can be induced by parenterally administered NSAIDs9–11, and that this damage
can be produced independently of the presence of luminal acid29,30, suggests that the
impairment of mucus and/or bicarbonate secretion may be of lesser significance. While
prostaglandins are extremely potent inhibitors of mast cell degranulation31, and mast
cells are capable of releasing a variety of mediators (e.g. leukotriene C4 and platelet-
activating factor) that can contribute to mucosal injury32,33, the effects of NSAIDs on
mast cells do not seem to be crucial to the pathogenesis of mucosal injury. This latter
conclusion is based on the observation that rats in which mucosal mast cells have been
depleted by chemical means, or mice that are genetically deficient of mast cells, exhibit
similar susceptibility to NSAID-induced gastric injury as do their respective controls.34

The rate of epithelial turnover has been shown to be reduced by NSAIDs and could
contribute to the pathogenesis of ulcer disease.35 However, it is unlikely that this
effect is the principal one that leads to the development of an ulcer.

The component of mucosal defence that appears to be most profoundly altered by
NSAIDs is the gastric microcirculatory response to injury. When the mucosa is
exposed to an irritant, or when superficial epithelial injury occurs, mucosal blood flow
substantially increases. This is probably a response aimed at removing any toxins or
bacterial products that enter the lamina propria, neutralizing back-diffusing acid and
contributing to the formation of a microenvironment at the surface of the mucosa that
is conducive to repair.36 As described in greater detail below NSAIDs can reduce
gastric mucosal blood flow and profoundly alter the behaviour of neutrophils flowing
through the gastric microcirculation.

EFFECTS ON THE MICROCIRCULATION

The ability of NSAIDs to reduce gastric mucosal blood flow has been recognized for
several decades.37–39 Prostaglandins of the E and I series are potent vasodilators that
are continuously produced by the vascular endothelium, so the inhibition of their
synthesis by an NSAID leads to a reduction in vascular tone. Several lines of evidence
have suggested that damage to the vascular endothelium is an early event following the
administration of NSAIDs to experimental animals.40,41 Endothelial injury is also an
early event in the pathogenesis of gastrointestinal damage associated with ischaemia–
reperfusion42, in which neutrophils have been demonstrated to play a critical role as
mediators of endothelial injury.43 This observation led us to examine the possible role
of the neutrophil in the pathogenesis of experimental NSAID gastropathy (Figure 1).

Our studies and those of others demonstrated that NSAID administration to rats
resulted in a rapid and significant increase in the number of neutrophils adhering to
the vascular endothelium in both gastric and mesenteric venules.25,44–46 This effect was
typically seen within 15–60 minutes after the administration of an NSAID, consistent
with the period of time required for the suppression of prostaglandin synthesis by these drugs. Subsequent studies demonstrated that this adherence was dependent on the expression of the \( \beta_2 \)-integrins (CD11/CD18) on the neutrophil and intercellular adhesion molecule-1 (ICAM-1) on the vascular endothelium. Such adherence could also be demonstrated to occur in vitro using isolated human neutrophils and endothelial cells from human umbilical vein. Furthermore, the upregulation of ICAM-1 on the vascular endothelium in the gastric microcirculation was shown to occur within 15–30 minutes of the administration of an NSAID to rats, and this could be prevented by the administration of exogenous prostaglandins.

Of course, the fact that neutrophils adhere to the vascular endothelium following NSAID administration does not necessarily mean that these cells contribute to the endothelial injury of the mucosal tissue injury that can be induced by NSAIDs. To test this hypothesis, a number of studies were carried out. First, we demonstrated that depleting circulating neutrophils in the rat, either with an anti-neutrophil serum or with methotrexate, greatly reduced the severity of the gastric damage induced by indomethacin or naproxen. Importantly, the induction of neutropenia also prevented
the damage to the vascular endothelium induced by the NSAIDs.\textsuperscript{50} Second, we demonstrated that treating rabbits or rats with monoclonal antibodies that blocked NSAID-induced neutrophil adherence to the vascular endothelium also markedly reduced the extent of NSAID-induced gastric damage.\textsuperscript{41,46} Third, we found that administration of prostaglandins at doses previously shown to prevent gastric injury prevented NSAID-induced leukocyte adherence.\textsuperscript{44,45}

Further evidence for a link between neutrophil adherence and NSAID-induced gastric injury came from studies of arthritic rats.\textsuperscript{51} These animals, like humans with rheumatoid arthritis, exhibit an increased susceptibility to NSAID-induced gastric damage. Interestingly, these rats also exhibited an increased level of neutrophil adherence to the vascular endothelium. This appeared to be due to an increase in expression of ICAM-1 on the vascular endothelium of arthritic rats, since pre-treatment with an antibody against ICAM-1 reduced leukocyte adherence and the susceptibility to NSAID-induced gastric damage to levels seen in healthy controls.\textsuperscript{51}

These studies suggest that, in response to the suppression of prostaglandin synthesis by NSAIDs, there is a rapid upregulation of expression of ICAM-1 on the vascular endothelium and possibly an upregulation of \( \beta_2 \)-integrin expression on circulating neutrophils, resulting in an increased adherence of neutrophils to the endothelium. This begs the question of whether the enhanced adhesion molecule expression is purely a consequence of the reduction of prostaglandin synthesis, or whether there is another chemical signal produced in response to diminished prostaglandin synthesis that triggers the events leading to neutrophil adherence.

Santucci et al suggested that tumour necrosis factor-\( \alpha \) (TNF\( \alpha \)) might be the key signal for NSAID-induced neutrophil adherence within the gastric microcirculation.\textsuperscript{52} The release of TNF\( \alpha \) from macrophages and mast cells has been shown to be suppressed by prostaglandins\textsuperscript{31,53}, and TNF\( \alpha \) is a well-characterized stimulus for adhesion molecule expression.\textsuperscript{54} Santucci et al demonstrated that the levels of TNF\( \alpha \) in the plasma of rats significantly increased following the administration of indomethacin, this being accompanied by a parallel accumulation of neutrophils within the gastric microcirculation and the development of gastric injury.\textsuperscript{52} Furthermore, pre-treatment with a TNF\( \alpha \) synthesis inhibitor, pentoxifylline, dose-dependently reduced neutrophil accumulation in the gastric microcirculation and gastric damage.\textsuperscript{52} These results have been confirmed and extended by Appleyard et al using a number of structurally unrelated inhibitors of TNF\( \alpha \) synthesis and an anti-TNF\( \alpha \) antibody.\textsuperscript{55}

Another group of mediators that might contribute to the increase in neutrophil adherence following NSAID administration is the leukotrienes. Like prostaglandins, leukotrienes are derived from arachidonic acid. They have been shown to be capable of altering the susceptibility of the gastric mucosa to injury\textsuperscript{44,56–58}, at least in part through stimulatory effects on neutrophil adherence to the vascular endothelium.\textsuperscript{44} Inhibitors of leukotriene synthesis and leukotriene receptor antagonists have been shown to exert some protective effects in experimental models of NSAID-induced gastric damage.\textsuperscript{56–58} There is also evidence of an elevated leukotriene \( \text{B}_4 \) production following NSAID administration to laboratory animals\textsuperscript{44} and man\textsuperscript{59}, and inhibitors of leukotriene synthesis and a leukotriene \( \text{B}_4 \) receptor antagonist have been shown to prevent NSAID-induced neutrophil adherence to the vascular endothelium both in vivo\textsuperscript{44} and in vitro.\textsuperscript{48}

Evidence for a role for neutrophils in the pathogenesis of gastric ulceration in humans has recently been provided.\textsuperscript{60} Patients taking NSAID therapy who had significant numbers of neutrophils within the gastric mucosa were approximately six times more likely to develop an ulcer over the course of 24 weeks than were patients who
did not have significant numbers of neutrophils in their gastric mucosa. It is also noteworthy that, in a clinical trial examining the potential benefit of famotidine for the prevention of NSAID-related gastroduodenal ulcers, Taha et al observed that an increased peripheral white cell count was a significant risk factor for ulcer development. They suggested that this observation was consistent with the hypothesis that NSAID-induced gastropathy was mediated, at least partially, by neutrophils.

How would the adherence of neutrophils to the vascular endothelium contribute to the formation of gastroduodenal ulcers? First, the adherence of neutrophils to the vascular endothelium is accompanied by an activation of these cells, leading to the release of proteases (e.g. elastase and collagenase) and oxygen-derived free radicals (e.g. superoxide anions). These substances may mediate much of the endothelial and epithelial injury caused by NSAIDs. This is supported by observations that the severity of NSAID-induced mucosal injury can be markedly diminished by compounds that scavenge oxygen-derived free radicals and by inhibitors of neutrophil-derived proteases. Second, neutrophil adherence to the endothelium, and the subsequent recruitment of other elements of blood (e.g. platelets), could produce an obstruction of the capillaries, thereby reducing gastric mucosal blood flow. In this respect, it should be noted that the well-characterized ability of NSAIDs to reduce gastric blood flow has been shown to occur subsequent to the appearance of ‘white thrombi’ in the gastric microcirculation.

**INHIBITION OF RESTITUTION**

Damage to the gastric epithelium probably occurs on a daily basis but does not usually lead to deeper mucosal injury because of the ability of rapid (i.e. within minutes) repair to occur via the process of restitution. This process involves the rapid migration of healthy cells from the gastric pits to re-establish an intact epithelial barrier. The cells move along the denuded basement membrane, which acts as a template and has been shown to be crucial to the restitution process. The basement membrane can be damaged by acid, leading to an inhibition of restitution and the progression of necrosis to deeper layers of the mucosa. This does not, however, occur in normal circumstances because of the formation over sites of injury (i.e. exposed basement membrane) of a microenvironment in which the pH is maintained at near neutral, even in the presence of a significant acid load in the lumen. A ‘mucoid cap’ consisting of mucus, cellular debris and plasma proteins (particularly fibrin) forms within seconds of gastric epithelial injury, trapping the plasma that leaks from the underlying microcirculation. It is this plasma which accounts for the near-neutral pH within the protective mucoid cap, since even a very brief cessation of mucosal blood flow results in a rapid decrease in the pH within the mucoid cap, which in turn results in the formation of haemorrhagic erosions.

As discussed above, NSAIDs can decrease mucosal blood flow. Thus, NSAIDs can cause gastric injury by interfering with the appropriate function of the mucoid cap and therefore the process of restitution. Indeed, we observed that, following the systemic administration of an NSAID to an animal in which superficial epithelial injury had been induced, the pH within the mucoid cap that had formed over the sites of epithelial damage began to decline in parallel with the inhibition of prostaglandin synthesis. Within minutes thereafter, the formation of haemorrhagic erosions was clearly evident. This effect could be prevented through the luminal delivery of exogenous prostaglandins, as could the formation of haemorrhagic erosions.
REPAIR OF ULCERS

In addition to causing ulcer formation, NSAIDs can delay the healing of pre-existing ulcers and promote their bleeding.\textsuperscript{72,73} The effects on ulcer healing are probably related, once again, to the ability of NSAIDs to suppress prostaglandin synthesis. In normal gastric mucosa, prostaglandin synthesis occurs mainly via the cyclo-oxygenase-1 isoform. However, at a site of ulceration, and particularly around the ulcer margin, cyclo-oxygenase-2 appears to be the primary contributor to prostaglandin synthesis. Studies in mice and rats initially demonstrated the marked upregulation of cyclo-oxygenase-2 in ulcerated gastric tissue\textsuperscript{74,75}, and this has recently been confirmed in humans.\textsuperscript{76} Moreover, the treatment of rats or mice with selective inhibitors of cyclo-oxygenase-2 results in a significant delay of ulcer healing.\textsuperscript{74,75} These observations, and reports of selective cyclo-oxygenase-2 inhibitors exacerbating intestinal inflammation and ulceration\textsuperscript{77}, suggest that caution should be exercised in regarding the new cyclo-oxygenase-2 inhibitors as gastrointestinally safe.\textsuperscript{78,79}

The ability of NSAIDs to promote the bleeding of pre-existing ulcers is most probably related to their inhibitory effects on platelet aggregation.\textsuperscript{80,81} The inhibition of platelet aggregation by NSAIDs occurs as a consequence of the inhibition of thromboxane synthesis. It should be noted that, unlike other NSAIDs, aspirin produces an irreversible inhibition of thromboxane synthesis in the platelet. Thus, even the low doses of aspirin used for the prophylaxis of myocardial infarction and stroke can significantly increase the risk of gastrointestinal bleeding.\textsuperscript{82–84}

ROLE OF ACID

The observation that NSAID-induced ulcers can develop in achlorhydric individuals\textsuperscript{29,30} has contributed to a widely held belief that acid is not involved in the pathogenesis of these lesions. Further reinforcing this hypothesis are several studies demonstrating that treatment with histamine H\textsubscript{2}-receptor antagonists did not reduce the incidence of NSAID-induced ulceration.\textsuperscript{85–87} However, many of these types of studies have demonstrated that \textit{H}\textsubscript{2}-antagonists and proton pump inhibitors can prevent NSAID-induced gastric lesions, but not the formation of the clinically more significant ulcers, as well as ulcer complications. Recently, however, Taha et al reported that a high dose of famotidine (40 mg twice daily) was effective in preventing NSAID-induced ulcers\textsuperscript{61}, and Hawkey et al\textsuperscript{88} demonstrated that omeprazole could significantly reduce the incidence of NSAID-induced ulceration. These studies suggested that a profound suppression of acid secretion, as is produced by omeprazole or by a high dose of famotidine, was necessary in order to have a significant impact on the incidence of NSAID-induced ulcers.

Acid may contribute to NSAID-induced ulcer formation in several ways. First, acid can exacerbate damage to the gastric mucosa induced by other agents. For example, acid can convert regions of ethanol-induced vascular congestion in the mucosa to actively bleeding erosions.\textsuperscript{56} Second, acid will contribute to ulcer formation by interfering with haemostasis. Platelet aggregation, for example, is inhibited at a pH of less than 4.\textsuperscript{89} Third, as outlined above, acid can convert superficial injury to deeper mucosal necrosis by interfering with the process of restitution. Fourth, acid can inactivate several growth factors (e.g. fibroblast growth factor) that are important for the maintenance of mucosal integrity and for the repair of superficial injury, since these growth factors are acid-labile.\textsuperscript{90}
It is important to note that NSAIDs can increase gastric acid secretion, although it is not clear whether such effects have any impact on ulcer formation or healing. Prostaglandins exert inhibitory effects on parietal cells, so the inhibition of their synthesis by NSAIDs can result in an increase in gastric acid secretion.

**SUMMARY**

A great deal has been learned about the pathogenesis of NSAID-induced gastric injury over the past two decades. As a result, several new NSAIDs, which will have greatly reduced gastrointestinal toxicity relative to current drugs, are in the process of being introduced to the marketplace. For example, selective inhibitors of cyclo-oxygenase-2, which will spare the major form of cyclo-oxygenase in the gastrointestinal tract, produce substantially less injury to the stomach than do the current NSAIDs that inhibit both cyclo-oxygenase-1 and -2. Whether or not these agents prove to be as effective for the treatment of the full range of inflammatory conditions currently treated with NSAIDs remains to be seen, and some experimental studies suggest that this may not be the case. Nitric oxide-releasing NSAIDs represent another approach to reducing the adverse effects of this class of drug. The design of these new NSAIDs would not have been possible had it not been for an increased understanding of the pathogenesis of NSAID-induced ulceration.

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**REFERENCES**


