Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms

MILLER, THOMAS A. Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am. J. Physiol. 245 (Gastrointest. Liver Physiol. 8): G601-G623, 1983. Recent evidence indicates that prostaglandins (PGs) possess potent gastric antiulcer properties independent of their known inhibitory effects on acid secretion. The mechanism underlying this cytoprotective property, as it has been called, has remained elusive. Although exogenously administered PGs can prevent disruption of the gastric mucosal barrier, enhance gastric mucosal blood flow, and stimulate mucus and bicarbonate secretion, as well as a number of cellular transport processes, evidence for and against each of these proposed mechanisms for cytoprotection has been demonstrated. Thus, it is doubtful whether any of these effects of PGs on gastric epithelium is the mechanism responsible for cytoprotection, if indeed a single, common mechanism exists. In addition, an association between alterations in endogenous PGs and gastric mucosal injury induced by a variety of damaging agents has also been observed, but the importance of this association in terms of mediating gastric damage needs further clarification. Finally, the phenomenon of adaptive cytoprotection in which mild irritants protect the gastric mucosa against the damaging effects of various necrotizing agents may also be PG mediated since it can be blocked by indomethacin, an inhibitor of PG synthesis, but a clear association between changes in endogenous PGs and adaptive cytoprotection remains to be demonstrated. Despite being inconclusive, these findings suggest that PGs may play a significant role in the pathogenesis of gastric ulceration and may serve an important function in maintaining normal gastric mucosal integrity.

cytoprotection; gastric epithelium; gastric ulceration

PROSTAGLANDINS (PGs) comprise a family of long chain, saturated, oxygenated fatty acids, first discovered in human seminal fluid in the early 1930s (82, 225). They have been found in a wide variety of mammalian species and have been detected in virtually every tissue studied. Approximately 20 different natural prostaglandins have been identified, differing from one another mostly by changes in the 5-carbon ring and the number of double bonds that make up the PG molecule. Of particular note are the relatively large quantities of PGs found in gastrointestinal mucosa. Prostaglandins of the E, F, and I types have been found in gastric mucosa, gastric juice, intestinal mucosa, and intestinal secretions (10, 176, 180, 182). Although the relative distribution of these PG subgroups varies among different species, the high concentration of PGs in the gastrointestinal wall throughout the gastrointestinal tract suggests that these agents may play an important role in gastrointestinal physiology.

This hypothesis is strengthened when it is realized that PGs exert their activity at the site where they are produced (182), and enzymes responsible for their biosynthesis and degradation have been identified in the epithelial wall of the stomach (9, 211) (Fig. 1), even though the exact cell of origin of these substances has yet to be defined. Further, PGs also influence a number of gastrointestinal functions (10, 176, 180, 182). Thus, PGs have been shown to both relax and constrict the lower esophageal sphincter, contract longitudinal smooth muscle, both contract and relax circular smooth muscle of the intestine, induce vomiting and diarrhea, and inhibit absorption of electrolytes and water from the small bowel. Of special importance has been the effect of PGs on gastric acid secretion (178, 179, 182). Numerous studies have clearly documented that PGs of the E, A, and I series in both natural and synthetic forms are potent inhibitors of basal and stimulated gastric acid secretion.
CELL MEMBRANE PHOSPHOLIPIDS

ARACHIDONIC ACID

5-Lipoxygenase

Leukotriene A

5-Hydroxyeicosatetraenoic acid (5-HPETE)

Prostaglandin

Cyclic Endoperoxides (PGG₂ and PGH₂)

Leukotriene B₄ (LTB₄)

12-Hydroxyeicosatetraenoic acid (12-HPETE)

Thromboxane A₂ (TXA₂)

Thromboxane B₂ (TXB₂)

Prostaedrin (PGI₂)

Prostaglandin (PGF₂α)

PGD₂

PGE₂

PGF₂α

FIG. 1. Products of arachidonic acid metabolism.

in rats, dogs, cats, frogs, and humans when administered parenterally, orally, or topically.

Due to the pronounced inhibition of gastric acid secretion elicited by PGs, the possibility that these substances might possess antiulcer activity was studied. It has been found that E-type prostaglandins and several of their methyl analogues are capable of preventing the formation of gastric ulcers in rats induced by pylorus ligation (126), restraint (222), spinal cord transection (197), glucocorticoid administration (186, 187), cold stress (103), ethanol, strong acids and bases (185), reserpine (126), serotonin (60), bile salts (141), and a wide variety of nonsteroidal anti-inflammatory compounds including indomethacin, aspirin, and flurbiprofen (134, 178, 232, 233). Other PG subgroups, including those of the A, B, C, D, F, and I types, when administered orally, subcutaneously, or intravenously, have also been noted to inhibit gastric ulcer formation in a variety of experimental animal models (153, 178, 182). Further, duodenal ulcers produced in rats following subcutaneous injection of secretagogues such as histamine, pentagastrin, carbachol, cysteamine, and propranolol could also be prevented by PGs (179). These antiulcer effects are not limited to a specific species and have been noted in guinea pigs, cats, rats, dogs, and frogs (153, 178, 182). In addition, drug-induced gastric injury in humans, assessed in terms of the amount of occult fecal blood loss, has also been prevented by PGs (37, 98, 242). Finally, a number of reports have underscored the ability of PGs to accelerate the healing of human peptic ulcers, both gastric and duodenal in origin, through endoscopic measurement of changes in ulcer size (69, 70, 79, 190, 224).

Although initial studies suggested that this antiulcer effect of PGs was related to their known, potent antisecretory properties, further experimental observations have suggested that other mechanisms must be involved. Evidence supporting this hypothesis is fourfold (153, 178, 182). First, virtually all PGs tested to date have demonstrated an ability to protect against ulceration. This finding is noteworthy since in other respects PGs differ dramatically. For example, PGs of the A, E, and I types tend to be vasodilators and lower the systemic arterial blood pressure. In contrast, PGs of the F type are vasoconstrictors and they raise blood pressure. Similarly, E-type PGs are potent bronchodilators, whereas those of the B and F types constrict the tracheobronchial tree. Nevertheless, all these PGs provide comparable protection against experimentally induced ulcerations in the rat. A second observation is that many PGs possessing antisecretory properties when given in nonantisecretory doses can still protect the gastrointestinal tract against lesions produced by various ulcerogenic agents. Robert and associates (185) have shown that gastric ulcerations in the rat induced by ethanol, strong acids and bases, hypertonic salt solution, or boiling water can be effectively prevented by PGs with known antisecretory actions in doses less than 1% of the threshold dose needed to inhibit gastric acid secretion. Similar observations have been noted by other investigators (153, 155, 178, 182, 217). Third, other antisecretory agents such as anti-cholinergics and histamine H₂-receptor blockers have been shown not to confer full protection against a variety of ulcerogenic interventions despite the fact that PGs were fully protective under similar experimental conditions (25, 153, 157, 181). Finally, the demonstration that intestinal ulcerations, induced by anti-inflammatory compounds such as indomethacin, can be effectively prevented in the nonacidic environment of the small intestine by a wide variety of PGs supports the conclusion that the mechanism of intestinal protection involves factors beyond simple inhibition of acid secretion (68, 177). This ability of PGs, independent of their known antisecretory properties, to protect the cells of gastrointestinal epithelium against a variety of potentially noxious agents, which otherwise have the capability of producing cellular damage and necrosis, has been termed “cytoprotection” (153, 181). Although historically cytoprotection was first described with reference to prevention of indomethacin-induced ulcerations in the rat ileum by PGs (177), in its pure sense it refers to the ability of PGs to prevent ulcerations throughout the gastrointestinal tract. As employed in this discussion, the term will be confined to the ability of PGs to prevent gastric mucosal ulceration.

The mechanism underlying gastric cytoprotection has not been defined. Despite this inability to elucidate a specific mechanism, several observations are pertinent to a discussion of this topic. First, compounds damaging the gastric mucosa, against which PGs are protective, do not appear to be related chemically. Thus, ulcerations induced by bile salts, ethanol, strong acids and bases, and nonsteroidal anti-inflammatory compounds, as well as a host of other damaging agents to the gastric epithelium, can be prevented from initiating such injury by PGs (153, 181, 182). The lesion elicited by these agents may vary in intensity and location within the stomach but generally consists of necrosis of the mucosal epithelium in the acid-secreting portion of the stomach and occasionally the antrum.

The type of PG offering protection is also not limited to any specific subgroup. PGs of practically every type (A, B, C, D, E, F₃, F₅, and I) possess cytoprotective properties (153, 181, 182). While it is true that some PGs
are more effective in preventing gastric injury than others, and require lower doses to do so, the only difference among these subgroups is a quantitative one. The route of administration, though, appears to play some role in the effectiveness of PGs in mediating their antiulcer properties. Oral or topical administration has been demonstrated to be three to five times more effective when compared with parenteral administration (182, 185). This may relate to a larger dose of PG exerting a topical action directly on the gastric epithelium when administered orally or topically, which does not occur as efficiently when PGs are administered parenterally due to their distribution throughout the entire body and partial degradation.

Finally, whatever the mode of action whereby PGs mediate their cytoprotective properties, such protection seems to occur instantaneously. In experiments by Robert and associates (185), PGs were shown to be cytoprotective for the stomach when administered orally as soon as 1 min prior to exposing the gastric epithelium to a known damaging agent.

EXOGENOUS PROSTAGLANDINS AND GASTRIC MUCOSAL INJURY

Despite attempts by a number of investigators to identify the sequence of events by which PGs mediate their antiulcer properties, the mechanism(s) underlying cytoprotection has yet to be defined. Using a variety of in vitro and in vivo experimental preparations in rats, guinea pigs, cats, dogs, amphibians, and subhuman primates, PGs (both natural and synthetic) have been observed to affect a number of biochemical and physiological processes that have been purported either alone or in combination to play a role in the cytoprotective action of these agents. An influence by PGs on some of these processes has even been observed in humans in the few human studies that have been performed. The following discussion summarizes the major theories and the experimental evidence supporting them that have been offered to explain the mechanism of cytoprotection (Table 1).

### Table 1. Proposed mechanisms for prostaglandin cytoprotection

<table>
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<tr>
<th>Mechanism</th>
<th>Ref. Discussing Mechanism</th>
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</tr>
<tr>
<td>Stimulation of mucus secretion</td>
<td>1, 2, 12, 17, 19, 52, 70, 80, 83, 97, 123, 140, 163, 165, 167, 174, 184, 189, 214, 221, 238, 243</td>
</tr>
<tr>
<td>Enhancement of gastric mucosal blood flow</td>
<td>8, 28, 34, 75, 76, 78, 84, 85, 96, 101, 102, 115, 116, 125, 138, 139, 143, 181, 182, 228, 234, 236</td>
</tr>
<tr>
<td>Stimulation of nonparietal cell alkaline secretion</td>
<td>1, 2, 6, 12-15, 17, 30, 31, 33, 50, 51, 61-84, 68, 70-74, 90, 95-97, 100, 104, 109, 123, 129, 144, 150, 154, 156, 158, 161, 165, 170-173, 175, 184, 188, 189, 191, 196, 205, 212, 214, 221, 231, 238, 239, 243</td>
</tr>
<tr>
<td>Stimulation of macromolecular synthesis</td>
<td>54, 57, 58, 99, 112, 136, 149</td>
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<tr>
<td>Stimulation of cellular transport processes</td>
<td>20, 26, 88, 89, 118-121, 135, 152, 196</td>
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<td>Chloride transport</td>
<td>20, 192</td>
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<td>Stimulation of cAMP</td>
<td>22, 26, 76, 140, 198-201, 206-209, 220, 240, 241</td>
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<td>Stabilization of tissue lysosomes</td>
<td>5, 60, 94, 226, 227</td>
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<td>Dissolution of gastric mucosal folds</td>
<td>124, 147, 148</td>
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<td>Maintenance of gastric mucosal sulfhydryl compounds</td>
<td>7, 21, 56, 117, 145, 163, 213</td>
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<tr>
<td>Stimulation of surface-active phospholipids</td>
<td>24, 93, 129, 203, 204, 229, 230</td>
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Prevention of Gastric Mucosal Barrier Disruption

The possibility that prostaglandins may prevent disruption of the gastric mucosal barrier and thereby protect the gastric epithelium from injury has been proposed by several investigators. The nature of this barrier, the existence of which was first postulated by Theorell in 1933 (215), is still poorly understood and ill defined anatomically. Nevertheless, it is quite well established through the elegant studies of Davenport (43, 45, 49) that a definite barrier exists physiologically, its fundamental function being to contain within the gastric lumen hydrochloric acid that is secreted by the mucosa of the stomach, thus preventing its autodigestion. The same property of this barrier that prevents hydrogen ion from diffusing back into the mucosa once it has been secreted also prevents the diffusion of sodium (which is normally maintained in the interstitial fluid surrounding the gastric mucosa at a concentration very nearly equal to its concentration in plasma) from the mucosa into the gastric lumen. If this barrier is disrupted, which may occur when any one of a variety of agents (i.e., aspirin, ethanol, urea, or bile salts) is topically applied to the gastric epithelium, a change in gastric mucosal permeability results, allowing hydrogen ions to diffuse back into the mucosa and sodium and potassium ions to diffuse from the mucosa into the gastric lumen (43-49). Paralleling these permeability changes is a decrease in the gastric transmucosal potential difference, suggesting that normal electrochemical gradients between the mucosa and the gastric lumen have also been disrupted (46, 49, 77). The ultimate outcome of this increased hydrogen ion backdiffusion and sodium and potassium efflux is direct damage to the gastric mucosa with rupture of mucosal capillaries, interstitial hemorrhage, and the formation of frank mucosal lesions with bleeding into the gastric lumen.

That PGs can prevent barrier disruption has been experimentally demonstrated. In a number of recent studies, several synthetic and natural PGs have been shown to either totally prevent or markedly attenuate the permeability alterations associated with barrier disruption. In both dogs (16, 33, 36, 41, 115, 150, 155, 210, 216, 217) and rats (18, 234), prostaglandins have been shown to prevent disruption of this physiological barrier. Studies by Miller and associates (150, 155, 217) demonstrated that 16,16-dimethyl PGE2 prevented barrier disruption in the canine stomach by both aspirin and alco
hol when administered intravenously and by alcohol when applied topically to gastric mucosa. Other investigators have reported similar protective effects of prostaglandins against barrier disruption induced by aspirin (18, 36, 41), indomethacin (36), alcohol (115, 210), and bile salts (33, 216, 234). Thus, the three standard barrier breakers (i.e., aspirin, ethanol, and bile salts) commonly used in studies of the gastric mucosal barrier have all been shown to be rendered ineffective in their ability to induce barrier disruption by various prostaglandins.

In addition to preventing barrier disruption, Bolton and Cohen (16) observed that prostaglandins were also capable of halting further barrier disruption even when administered after this process had already commenced. Further, prevention of gastric mucosal barrier disruption by prostaglandins is not limited to laboratory animals. Using healthy adult male volunteers, Cohen and Pollett (38) observed that the fall in gastric transmucosal potential difference induced by topical aspirin and indomethacin could be prevented with concomitant administration of PGE2. Muller and associates (160) observed a similar ability of 16,16-dimethyl PGE2 to prevent the drop in potential difference induced by aspirin and taurocholate in their studies involving healthy human subjects.

In addition to the alterations in transmucosal potential difference and mucosal permeability associated with barrier disruption, Davenport (48, 49) also observed that acid backdiffusion released histamine from mucosal stores into the gastric contents and gastric venous blood and suggested that this increased histamine release may play an important role in mediating tissue damage by acting on the parietal cells to enhance additional acid secretion, and thereby more backdiffusion of acid, and on the microcirculation to alter blood flow and permeability. To explore the possibility that PGs may mediate their cytoprotective actions through inhibition of histamine release, Aures and associates (4) studied the effects of ethanol in acid solution on ulcer formation and histamine release with and without PG pretreatment in the rat stomach. Increasing concentrations of ethanol instilled intragastrically resulted in increasing lesion formation and histamine release into the gastric contents. Pretreatment with 16,16-dimethyl PGE2 significantly reduced lesion formation and the associated histamine release. If histamine with tracer [14C]histamine was instilled intragastrically either with or after 50% ethanol, significant tissue uptake of histamine and increased acid secretion were observed without altering the protective effects of this PG analogue. It was concluded that the cytoprotective effects of PG in the rat stomach were independent of intramucosal histamine release. A similar reduction in histamine release in gastric mucosa damaged by bile and alcohol was observed by Soper and Tepperman (210) and Tepperman (216) in response to 16,16-dimethyl PGE2 in the dog stomach, but because this PG analogue also lessened the degree of barrier disruption induced by these damaging agents, it was not known whether the change in histamine release was the cause or effect of the change in barrier dysfunction.

In other studies, the possibility was further examined that PGs might cytoprotect by preventing absorption of a damaging agent by gastric epithelium and thereby prevent its resultant injurious effects (86). In rat stomachs exposed to 40 mM aspirin alone and following PG pretreatment, it was found that the mucosal salicylate concentration was the same in aspirin-damaged stomachs and those cytoprotected by 16,16-dimethyl PGE2. These findings suggested that PGs prevent gastric barrier disruption through other mechanisms.

In the majority of studies cited above, prevention of barrier disruption by prostaglandins was most effective when these agents were administered during a pretreatment period prior to exposing the gastric epithelium to the damaging agent being studied. Although the degree of barrier disruption was decreased even when prostaglandins were administered at the same time as a given damaging agent, the effectiveness of the protective abilities of PGs was generally less in this circumstance than if a pretreatment period had been rendered. Thus, it would appear that prostaglandins in some way make the gastric mucosal barrier more resistant to disruption and that this can best be accomplished if the animal has been pretreated with PG prior to exposing the stomach to a given damaging agent.

The mechanism underlying this resistance to barrier disruption is unknown. Part of the difficulty in identifying this mechanism is our current lack of knowledge concerning the morphological correlates of the gastric mucosal barrier itself. It has been proposed that alterations in the “tight junctions” between surface epithelial cells may occur during injury and account for the permeability changes observed during barrier disruption (46, 193). Although evidence supporting this hypothesis has been demonstrated in aspirin-damaged mucosa (67), it does not appear to be a universal finding with all damaging agents (55, 66). Forte and associates (66), for example, in an electron microscopic study of bile salt-induced gastric damage, were unable to demonstrate alterations in the tight junctions or basement membranes even though surface epithelial cells were badly injured by this damaging agent. Consequently, to obtain a better understanding of the nature of the gastric mucosal barrier and to determine how PGs enhance resistance to barrier disruption, careful morphological studies, using electron microscopic techniques, are necessary to elucidate the physical pathways through which gastric mucosal permeability is altered by damaging agents and how such alterations are prevented by PGs.

Despite the convincing nature of the aforementioned studies that PGs may mediate cytoprotection through prevention of barrier disruption, it must be emphasized that not all investigators have observed these effects on the barrier. Using an in vivo canine chambered stomach preparation, Cheung (29) was unable to demonstrate a protective effect of topical 16,16-dimethyl PGE2 against aspirin-induced disruption of the gastric barrier. Harmon and Lewis (90), using conscious dogs with previously prepared Heidenhain pouches, while observing some attenuation of barrier disruption by bile salts in response to intravenous 16,16-dimethyl PGE2, failed to observe the degree of protection against barrier disruption by this damaging agent that other investigators have previously noted. Similarly, Kenyon and associates (194)
were unable to reverse taurocholate-induced barrier disruption with 15(R)-methyl PGF<sub>2</sub> methyl ester in the canine stomach. Further, Muller and associates (159) were unable to demonstrate a protective effect of 16,16-dimethyl PGF<sub>2</sub> in humans when administered intragastrically to healthy volunteers against the decrease in transmucosal potential difference induced by 48% ethanol even though the doses used in this study were previously noted by the same investigators to prevent the aspirin- and sodium taurocholate-induced drop in gastric potential difference in the human stomach (160). Finally, in a canine aspirin-shock model, Larsen and associates (125) observed that SC-29,333, a PGE<sub>2</sub> synthetic analogue, prevented the formation of gastric mucosal ulceration even though the indices of barrier disruption observed in aspirin-treated mucosa alone and aspirin in combination with PG were not significantly different. Puurunen (166) also noted that ethanol-induced gastric ulceration in the rat was prevented by PGE<sub>2</sub> even though the effect of ethanol on the backdiffusion of H<sup>+</sup> was not prevented by PG.

It seems clear from these findings that further studies are needed to correlate the alleged protective effects of PGs against gastric mucosal barrier disruption and the underlying epithelial ultrastructure. If prevention of barrier disruption is an important mechanism underlying cytoprotection, it could certainly explain the rapidity by which PGs mediate their cytoprotective action, but how this is accomplished by PGs remains to be elucidated.

**Stimulation of Mucus Secretion**

The role of mucus in preventing gastric ulceration continues to be debated among physiologists. Although Heatley (91) proposed nearly three decades ago that mucus may play a role in mucosal protection, traditionally, mucus has been considered to be primarily a lubricant whose major function is to protect the underlying mucosal cells from mechanical injury. Recent advances in knowledge concerning bicarbonate secretion by gastric mucosa (see discussion below on nonparietal cell alkaline secretion) have rekindled an interest in the concept that continuous secretion of bicarbonate into the unstirred layer of water within the gastric gel mucus may provide an effective barrier to the movement of hydrogen ions from gastric lumen to epithelium (1, 2, 221). This unstirred mucus gel layer could confine the reaction between luminal acid and secreted bicarbonate in such a fashion that a pH gradient will occur with a low value on the luminal side of this gel to a pH approaching neutrality on the mucosal side. In this way, the damaging effects of an ulcerogen in acid medium could be greatly attenuated. That gastric gel mucus can indeed impede the diffusion of hydrogen ion, and thereby conceivably enhance its neutralization by secreted bicarbonate at the mucosa-mucus interface, has recently been reported (165, 238). In studies with pig gastric mucos, Williams and Turnberg (238) observed that the diffusion coefficient for hydrogen ions through a known thickness of mucus was four times smaller than the diffusion coefficient through an equivalent thickness of unstirred solution. Similar findings were also obtained by Pfeiffer (165).

In addition to their other effects on gastric epithelium, PGs stimulate the formation of gastric mucus. In dogs, rats, and humans, administration of a variety of prostaglandins has been shown to elicit a rapid secretion of gastric mucus as demonstrated by measurement of various components of this secretion (17, 97, 184, 189). In one study (70) involving patients with peptic ulceration, 15(R)-15-methyl PGF<sub>2</sub> methyl ester was shown to markedly increase the amount of mucus in mucin cells. LaMont and associates (123) observed that PGF<sub>2α</sub> added to aspirin-induced damage. In addition to these findings, a number of studies (52, 163, 167, 174) have shown that any one of a variety of nonsteroidal anti-inflammatory agents, including aspirin and indomethacin, which have been shown experimentally to inhibit prostaglandin synthesis (65, 128, 223), inhibit the activity of biosynthetic enzymes responsible for mucus production, reduce the incorporation of radiolabeled precursors into mucus glycoproteins, and alter the thickness of the mucus layer itself. Bile salts and ethanol have also been shown to inhibit mucus production (80, 142, 174). While not conclusive, all these observations support a possible role for mucus in gastric mucosal protection.

If mucus secretion plays a role in cytoprotection, several criteria must be met before such a role can be claimed. First, doses of PG rendering cytoprotection must be shown to elicit mucus release. In the few studies examining cytoprotection and mucus production, such a correlation has been demonstrated (12, 123, 184, 189). Second, since cytoprotection has been shown to occur within minutes following exposure of the gastric epithelium to a damaging agent, the time course of mucus release must be equally as rapid. Third, and most important, as emphasized by Grossman (83), the only obvious mechanism whereby the mucus gel might offer protection to the underlying mucosa is by establishing a steep gradient such that the concentration of the injurious agent is much lower on the epithelial side than on the luminal side of the gel. For this gradient to occur, the gel must be almost impermeable to the injurious agent or the agent itself must be rapidly disposed of at the cell
surface (83). In the case of hydrogen ions, both impaired diffusion through the mucus gel (165, 238) and neutralization at the mucus cell interface (1, 2, 221) have been demonstrated experimentally (see discussion on nonparietal cell alkaline secretion), making mucus secretion potentially very important in the cytoprotective process. With regard to specific damaging agents, though, it is not known whether the disposal rate of any injurious agent is sufficiently great to establish a large enough gradient across mucus to be protective. In view of the chemical diversity of damaging agents, it is unlikely that mucus would be capable of establishing such a gradient for all injurious substances.

Enhancement of Gastric Mucosal Blood Flow

Because many prostaglandins possess potent vasoactive properties, enhancement of gastric mucosal blood flow by these agents may play an important role in mediating cytoprotection. A number of PGs are known to exhibit potent vasodilatory actions and affect various vascular beds throughout the body, including those of the gastrointestinal tract (153, 181, 182). These vasoactive effects are especially evident during parenteral administration and often occur quickly after injection.

At least two mechanisms have been proposed to explain the means by which enhanced mucosal perfusion could protect the gastric epithelium against injury (84). These include 1) the maintenance of adequate oxygen availability and energy sources to ensure the efficiency of intracellular aerobic metabolism and 2) the promotion of the more rapid elimination and buffering of backdiffused hydrogen ions that have gained access to the lamina propria. Using a hemorrhagic shock model, Menguy and associates (146) noted a profound reduction in gastric mucosal adenine triphosphate levels in the rat following hemorrhage that coincided with the development of mucosal ulcerations. They proposed that the cellular necrosis resulted from a deficit in mucosal energy metabolism secondary to the hemorrhagic shock and concluded that the integrity of the gastric epithelium requires a constant and consistent supply of glucose and oxygen to prevent an anaerobic state. In other studies, Kivilaakso and colleagues (106) studied the pH of the lamina propria of both the rabbit and dog fundic mucosa bathed with acid solution during hemorrhagic shock using a microelectrode technique. In the rabbit gastric mucosa, which is a relatively permeable epithelium, the pH dropped quickly in this shocklike state and coincided with the development of severe lesion formation. In the canine fundic mucosa, which is a more impermeable epithelium, hemorrhage decreased the intramural pH more slowly. However, when this same ischemic mucosa was exposed to 5 μM taurocholate, the mucosal barrier was further disrupted, resulting in a rapid and profound decrease in intramural pH and the development of extensive mucosal lesion formation. It was concluded from these studies that a critical determinant of whether gastric ulceration will occur relates to an impaired capacity of the mucosa to remove or buffer the influx of hydrogen ion. Other studies have supported this conclusion (143).

Evidence that the antulcer effects of PGs are mediated by changes in gastric mucosal blood flow has been offered by several investigators. In the rat, using a [14C]amline clearance technique to measure gastric mucosal blood flow, Main and Whittle (138, 139) found that prostaglandins of the E and A series significantly increased resting mucosal blood flow when perfused locally or administered systemically. In other studies, Whittle and associates (236) found a 116% increase in nonstimulated gastric blood flow during PGI2 administration, also in the anesthetized rat. Similar findings were reported by Guth and Moler (85). These investigators, using an in vivo microscopy technique, observed that superfusion of the rat stomach with PGE2 produced a dose-related vasodilation in the submucosal arterioles. Such stimulatory effects on gastric blood flow are not limited to the rat stomach. Using a canine in vivo chambered stomach preparation, Cheung (28) observed that 16,16-dimethyl PGE2 significantly increased resting mucosal flow as measured by radioactive microspheres. PGI2 (78, 101, 102, 115, 228), SC-29333 (a PGE2 analogue) (96, 125), PGE2 (101), PGE2 (78, 101, 228), and arachidonic acid (78, 101) have also been shown to increase gastric blood flow in the canine stomach, and PGI2 was recently observed to enhance mucosal flow in the stomach of the miniature swine (75, 76). Taken together, these observations indicate that PGs of the E, A, and I series are gastric mucosal vasodilators and are capable of increasing mucosal blood flow when administered exogenously.

An association between gastric mucosal blood flow and the protective effects of PGs against gastric injury has also been noted. Whittle (234) studied the effects of taurocholate alone and in combination with indomethacin on gastric blood flow and erosion formation in the rat. When given alone, taurocholate increased mucosal blood flow and had only minimal ulcerogenic effects. When taurocholate was administered in combination with indomethacin, blood flow significantly decreased and the number of erosions correspondingly increased. If 15-S-methyl PGE2 was administered concomitantly with indomethacin and taurocholate, gastric mucosal blood flow was again increased and the number of erosions was markedly reduced (234). Similar findings have been observed in the dog stomach by Cloud and Ritchie (34), who noted that topically applied taurocholate increased gastric mucosal blood flow in a dose-related fashion. Parenteral indomethacin significantly blunted this effect on blood flow, resulting in mucosal ulceration, but concomitant intraarterial PGI2 infusion close to the stomach completely reversed the effect of indomethacin on gastric perfusion and provided total mucosal cytoprotection. In other studies in both anesthetized and conscious dogs, Konturek and Robert (115) noted that the permeability changes associated with barrier disruption induced by ethanol were prevented by PGI2 and that coincident with this protection was a marked increase in gastric mucosal blood flow. In both of these canine studies, it was concluded that the enhanced mucosal perfusion elicited by PGI2 was responsible for the cytoprotection against taurocholate and alcohol damage.

Although enhancement of gastric blood flow may play a role in mediating the cytoprotective effects of PGs against some forms of gastric ulceration, other experi-
mental observations suggest that additional mechanisms must be involved. PGE$_2$, a PG demonstrating cytoprotective activity under a variety of experimental conditions (153, 181, 182) and previously noted to enhance gastric mucosal blood flow in the rat (138, 139) as measured by aniline clearance, was shown to have no effect on gastric blood flow in the canine stomach (116) as measured by aminopyrine clearance. Similarly, 16,16-dimethyl PGE$_2$, shown by Cheung (28) to enhance blood flow in the dog stomach, as measured by both microscope and venous outflow techniques, was noted to have no effect on this flow by Larsen and associates (125) using a similar experimental preparation and the venous outflow method to measure gastric blood flow. These results indicate that PGs may not always have consistent effects on gastric blood flow, which may be related in part to the experimental animal being studied, the design of the experimental protocol, and the method employed to measure blood flow.

Of further interest, Harzilai and associates (8) have recently shown that ulceration in vivo in amphibian gastric mucosa can be prevented by 16,16-dimethyl PGE$_2$, indicating that cytoprotection did occur experimentally in a preparation devoid of arterial perfusion. Finally, PGE$_2$-$\Delta_2$, a vasoconstrictor, has been shown to possess equally potent antiulcer properties comparable with PGE$_2$, a vasodilator, under a variety of experimental conditions (181, 182). These observations support the conclusion that if a single mechanism is responsible for cytoprotection enhancement of gastric mucosal perfusion is not it.

**Stimulation of a Nonparietal Cell Alkaline Secretion**

One problem encountered by investigators studying the effects of PGs on gastric mucosal barrier disruption has been the difficulty in separating the alterations in mucosal permeability induced by PGs themselves from those elicited by known damaging agents. Although these permeability alterations have been noted on parenteral bleeding from canine Heidenhain pouches when directly ported (104, 161) that 16,16-dimethyl PGE$_2$, elicited of this agent have failed to reveal any damaging effects on this flow by Larsen and associates (125) using a similar experimental preparation and the venous outflow method to measure gastric blood flow. These results indicate that PGs may not always have consistent effects on gastric blood flow, which may be related in part to the experimental animal being studied, the design of the experimental protocol, and the method employed to measure blood flow.

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papillar cell alkaline secretion may play a role in me-
diating the cytoprotective properties of PGs. This hy-
thesis is based on several experimental findings. First,
in amphibian (63, 64, 73, 74), canine (100, 156), and
feline (205) stomachs, several PGs have been shown to
elicit the secretion of gastric bicarbonate in a dose-
related fashion. This stimulatory effect on bicarbonate
secretion has been demonstrated when PGs were admin-
istered both parenterally and on topical application to
gastric epithelium (73, 74, 100, 156, 205). In the dog, at
least, alkaline secretion is more pronounced when PGs
are administered topically than when they are injected
parenterally (100). Second, known gastric mucosal ulcer-
genesis, including ethanol (63), bile salts (171, 172), and a
variety of nonsteroidal anti-inflammatory agents (63, 71,
73, 74), inhibit gastric bicarbonate secretion both in vivo
and in vitro in various experimental animals. Further,
both taurocholate and aspirin have been observed to
inhibit bicarbonate secretion in the human stomach
(173). In several animal studies this inhibition has been
reversed by PGs (63, 71, 73, 74). Finally, acetazolamide,
an agent that blocks the production of gastric bicar-
bonate by inhibiting the enzyme carbonic anhydrase, has
been shown to abolish the ability of gastric mucosa to
resist concentrations of luminal acid greater than 25 mM
in the dog (231) and prevent the known cytoprotective
action of PGE2 in the rat (109).

To what extent stimulation of bicarbonate secretion
by PGs contributes to the cytoprotective action of these
agents is unknown. Since the magnitude of bicarbonate
production by the stomach approaches only 5–10% of
the capabilities of the gastric mucosa to secrete hydrogen
ion, the amount of bicarbonate produced by the stomach
stoichiometrically, even on stimulation with PGs, would
not be sufficient to neutralize the quantity of hydrogen
ion produced under physiological conditions and thus
would offer little protection if neutralization in the lu-
minal bulk solution was all that occurred (62, 63). How-
ever, if gastric bicarbonate was secreted into an unstirred
layer of mucus gel, as proposed by Allen (1) and Allen
and Garner (2), the buffering capabilities of bicarbonate
at the mucus-mucosal interface could be much more
efficient (1, 2, 63, 221).

As indicated in the section on mucus secretion, PGs
stimulate not only the production of gastric bicarbonate
but also elicit the copious secretion of mucus (12, 70, 97,
123, 184, 189, 243). The properties of this mucus have
been extensively studied by Allen (1) and Allen and
Garner (2), who have observed that it consists of a matrix
of glycoprotein molecules which form a gel that is joined
together by physical noncovalent interactions, making it
particularly suitable to support hydrogen and bicarbon-
ate ion gradients. Direct evidence that such a pH gradient
does occur across the gastric mucus gel has recently been
offered by Williams and Turnberg (239) in vitro in vivo
and fundic mucosa in vitro and human
fundic mucosa in vitro (6). Further, bile salts and aspirin
were shown to reduce this gradient across the rat gastric
mucosa layer, probably by inhibiting bicarbonate secre-
tion (188). Of equal interest is the recent observation
that diffusion of hydrogen ion across this mucus gel is markedly slowed (165, 238). Conceivably, such retard-
ation of hydrogen ion diffusion could be especially im-
portant in enhancing the efficiency of neutralization of
acid by bicarbonate and help maintain a neutral pH at
the luminal cell membrane even though the pH of the
luminal bulk solution may be less than 2.

In addition to the important role that the bicarbonate
component of nonparietal cell secretion may play in
mediating PG cytoprotection, Moody and associates
(158) have also proposed that the sodium-rich transudate
may itself provide important buffering and enhance
swelling away of H+ from the gastric epithelial surface
cells before damage can occur. In preliminary studies
from their laboratory (144), gastric ulcerations induced
by aspirin were prevented in the dog stomach by topical
16,16-dimethyl PGE2. If the outward flow of the sodium-
rich secretion induced by this PG was obviated by a
counterpressure technique, no protection against aspirin
damage was observed. Unfortunately, a decrease in mu-
cosal blood flow was also observed in the group of dogs
receiving counterpressure so that it is not known whether
the decrease in nonparietal cell secretion, gastric blood
flow, or both was responsible for the lack of cytoprotec-
tion in this experimental setting. Further, since the
bicarbonate composition of the nonparietal cell secretion
was not measured in their studies, it is entirely possible
that secreted bicarbonate was responsible for their find-
ings rather than any independent buffering properties of
the sodium-rich transudate.

Although the preceding information suggests that a
PG-induced mucus-bicarbonate barrier may play an im-
portant role in cytoprotection, further studies are needed
to clarify the significance of this role. Other experimental
observations indicate that bicarbonate may be of little to
no importance in mediating the antiulcer properties of
PGs. Despite the fact that the synthetic analogue 16,16-
dimethyl PGE2 has been observed by several investiga-
tors, using in vitro frog preparations, to enhance bicar-
bonate secretion, Schiessel and others (191) reported
that 16,16-dimethyl PGE2 was without effect on bicar-
bonate transport in bullfrog fundic mucosa, even though
studies from their laboratory have shown that the same
analogue is able to protect this particular mucosa against
ulceration (8). In vivo canine gastric mucosa, Swierz-
czek and Konturek (212) observed that 16,16-dimethyl
PGE2 decreased transmucosal potential difference (an
index of gastric damage) at the same time as it enhanced
gastric alkaline secretion when applied topically to gas-
tric mucosa. They observed that these effects were dose
dependent and that, in addition to lowering the potential
difference and enhancing alkaline output, the highest
doses of PG studied also caused the mucosa to become
cyanotic and edematous, suggesting PG-induced gastric
injury. Application of standard barrier breakers, such as
aspirin, ethanol, and taurocholate, to gastric mucosa also
produced a dose-dependent increase in bicarbonate out

put and a reduction in potential difference. Combining PG with ethanol did not reverse these effects. It was concluded from these studies that the increased alkaline secretion induced by 16,16-dimethyl PGE₂ and barrier breakers was not due to active transport of bicarbonate ion but was caused by passive diffusion of this ion into the gastric lumen as a result of the enhanced mucosal permeability from the damaged mucosa. Recent studies by Dayton and associates (50) in which it was shown that passive diffusion accounts for almost all bicarbonate output produced by ethanol-treated oxyntic mucosa in the dog are in agreement with these findings. In still other studies (175), inhibition of bicarbonate secretion by acetazolamide failed to alter the ability of exogenous PG to protect the gastric mucosa against ethanol-induced damage in the rat, suggesting that other mechanisms were involved besides bicarbonate secretion to confer such protection. Similarly, Cloud and Ritchie (33) have published evidence indicating that bile salt-induced damage in the canine stomach is prevented by intravenous 16,16-dimethyl PGE₂ independent of any effects on bicarbonate secretion. Further, in studies employing conscious, chair-adapted rhesus monkeys, Shea-Donohue and associates (196) observed that intravenous infusion of 15(S),15-methyl PGE₂ markedly increased nonparietal secretion from the stomach, 15(S),15-methyl PGF₂α only mildly increased this secretion, and prostacyclin had no effect on nonparietal secretion. Despite these differences, all three PGs have been shown to be cytoprotective under a variety of experimental conditions (153, 181, 182). A synthetic PGE₂ analogue, SC-29533, was also observed to have no effect on nonparietal cell secretion when topically applied to canine gastric mucosa (96, 125), even though this agent has exhibited superior cytoprotective effects against aspirin damage (51, 125) when compared with other PG analogues. Finally, unlike 16,16-dimethyl PGE₂ and 16,16-dimethyl PGF₂α, which stimulate the secretion of an alkaline fluid in isolated amphibian gastric mucosa, Garner and associates (73) found prostacyclin to be devoid of this effect.

Stimulation of Macromolecular Synthesis

Evidence that PGs may stimulate macromolecular (i.e., DNA, RNA, and protein) synthesis has been reported. Eaglstein and Weinstein (54) found that E-type PGs markedly stimulated DNA, RNA, and protein synthesis in human skin as measured by incorporation of radiolabeled precursors. Lupulescu (136) reported similar findings in the healing of experimental wounds. Little data are available on the effects of PGs on the synthesis of these substances in gastrointestinal tissues. Consequently, the relation between macromolecular synthesis and cytoprotection is unknown. This author is aware of only one study in which such a relationship has been convincingly demonstrated. In rat studies in which gastric ulcers were produced by intragastric administration of acidified aspirin, Konturek and associates (112) observed that DNA synthesis in mucosa damaged by this agent was suppressed by about 18% compared with saline control animals. These aspirin-induced ulcers were completely prevented, and the associated suppression of DNA synthesis was almost totally reversed by concomitant subcutaneous or intragastric treatment with known cytoprotective doses of PGE₂ or PGI₂.

Although PGs may in some way prevent the inhibitory effects on DNA synthesis induced by damaging agents as demonstrated in the above study, it seems doubtful that stimulation of macromolecular synthesis would play a major role in maintaining cellular resistance against the acute, immediate damaging effects of various noxious agents when topically applied to gastric epithelium since PG-mediated cytoprotection can be demonstrated as early as 1 min following prostaglandin pretreatment (185), and synthesis of protein and other macromolecules would need to occur equally as rapidly if such a mechanism was responsible for cytoprotection. In studies with rat fundic mucosa, Johnson and Guthrie (99) were unable to demonstrate any ability of 16,16 dimethyl PGE₂ to stimulate DNA synthesis, even though parallel studies using the hormone gastrin elicited the synthesis of this macromolecule within 16 h (57, 99). The fact that it took gastrin, a known potent stimulant of DNA synthesis, this lengthy period of time to mediate such synthesis suggests that any stimulatory effects on macromolecular synthesis by PGs could not be initiated rapidly enough to account for their cytoprotective properties. In studies by Fang and associates (58), in which 16,16-dimethyl PGE₂ was noted to prevent indomethacin-induced intestinal necrosis in the rat, protection by this agent was observed to be totally independent of stimulation of DNA, RNA, or protein synthesis. In other studies involving rat gastric mucosa, Miller and associates (149) showed that the protective effect of 16,16-dimethyl PGE₂ against alcohol-induced gastric injury was totally independent of any stimulatory effects of this prostaglandin on DNA synthesis. Although stimulation of DNA, RNA, or protein synthesis by PGs could conceivably play a role in the healing of ulcers once they occurred, or prevent more chronic forms of gastric ulceration, it appears that cytoprotection against acute gastric injury is independent of any stimulatory effects on macromolecular synthesis.

Stimulation of Cellular Transport Processes

Sodium transport. Studies by Shanbour and associates (118, 119, 121, 195) have suggested that the permeability changes induced in gastric mucosa by damaging agents may actually be a late phenomenon. They have proposed that the initial action of ulcerogens on gastric epithelium is inhibition of active ion transport. Using the isolated nonstimulated dog gastric epithelium, these investigators found that active transport of sodium was inhibited by ethanol, aspirin, and bile salts, although no alteration in the passive transport of this ion (representing increased mucosal permeability) occurred until the mucosa had been exposed to these agents for a long period of time (118, 119, 121). In further studies using an in vivo chambered dog stomach, they observed that these damaging agents inhibited the active secretion of hydrochloric acid stimulated by histamine (118, 119, 195). Their findings were interpreted as indicating that the initial damaging effect of ethanol, aspirin, and bile salts was related to
inhibition of the active transport of sodium and that the gastric sodium pump is essential for the integrity of the gastric epithelium. According to Shanbour's hypothesis, the cascade of events leading to gastric mucosal damage would first include inhibition of active transport of sodium ion by damaging agents, leading to an intracellular accumulation of sodium, anions, and water. The resultant osmotic swelling of epithelial cells would then produce severe damage and altered permeability with consequent disruption of cells.

Chaudhury and Jacobson (26) used a similar isolated preparation of canine gastric mucosa to study the effects of indomethacin on epithelial sodium transport and confirmed the findings of Shanbour and colleagues (118, 119, 121, 195). They found that an early effect of indomethacin was inhibition of active transport of sodium. Only after prolonged contact with this agent or with high concentrations of indomethacin did the gastric mucosa exhibit increased permeability to sodium. Based on previous work by Bowen and colleagues (20), who showed that prostaglandin stimulates the active transport of sodium in gastric mucosa, Chaudhury and Jacobson (26) next studied the effects of 16,16-dimethyl PGE2 dibutyryl cAMP, and theophylline on the damaging effects induced by indomethacin. They found that these drugs completely reversed the action of indomethacin on gastric mucosal sodium transport (26). In addition, they also observed that 16,16-dimethyl PGE2 increased mucosal cyclic AMP content. They hypothesized that 16,16-dimethyl PGE2 stimulates the sodium pump by activating the enzyme adenyl cyclase and thereby increases intracellular cyclic AMP content. These findings in dog gastric mucosa parallel quite closely earlier findings in the isolated frog skin (88, 89) and toad bladder (135) in which it was shown that PGE2 stimulated sodium transport in both of these tissues, most likely by increasing the intracellular cyclic AMP level.

Although the observations of Chaudhury and Jacobson (26) have led to the contention that gastric mucosal cytoprotection may be mediated in part through stimulation of a gastric sodium pump, more recent work by Miller and associates (152) has challenged this hypothesis. Also using in vitro strips of mounted canine gastric mucosa, these investigators evaluated the effects of ethanol with and without 16,16 dimethyl PGE2 on sodium transport. Although 16,16-dimethyl PGE2 in the serosal bathing solution stimulated sodium transport, as previously demonstrated by Bowen and colleagues (20) and Chaudhury and Jacobson (26), it could not prevent the inhibitory effects of ethanol on such transport. This is particularly noteworthy since these same investigators were able to confirm the earlier findings of Chaudhury and Jacobson (26) that the inhibitory effects of indomethacin on sodium transport are prevented by PG in this in vitro preparation (152). It was concluded from these studies that stimulation of the gastric sodium pump may be important in mediating the protective effect of PGs against indomethacin induced damage, but it plays no role in protecting the gastric epithelium against alcohol-induced damage. Whether the inhibitory effects of other damaging agents, such as aspirin and bile salts, on sodium transport in canine mucosa can be prevented by PGs is not presently known. Further, the effect of PGs on sodium transport in gastric epithelia of other species and its possible relationship to cytoprotection remain to be studied. Finally, it is possible that changes in sodium transport cannot be interpreted in terms of damage or protection since ouabain has also been shown to inhibit sodium transport in vitro canine gastric mucosa, even though this agent is not known to be damaging to this epithelial tissue (120).

Chloride transport. Effects of PGs on chloride transport have also been reported. In in vitro studies using sacs of bullfrog fundic mucosa, Schiessel and associates (192) observed a high incidence of ulcersations when bicarbonate ion was absent from the nutrient bathing solution. Despite this absence, 16,16-dimethyl PGE2 prevented such ulceration to a significant degree except when chloride was removed from the bathing solution or 4-acetamido-4-isothiocyanostilbene-2,2′-disulfonic acid (SITS) was added to this solution to block anion transport. These studies were interpreted as indicating that PGE2 stimulated the exchange of cellular chloride for nutrient bicarbonate and thereby provided protection of the surface cell against the hostile environment of luminal acid. Although these studies suggest that chloride transport may play a role in cytoprotection in amphibian stomach, Bowen and associates (20) were unable to demonstrate any effect of PG on chloride transport in canine gastric mucosa. Further studies are clearly needed to investigate the possible relation between chloride transport and cytoprotection in other types of gastric epithelia and under other experimental conditions.

Stimulation of cyclic AMP

Several investigators have reported an increase in gastric mucosal cyclic AMP in response to prostaglandins coincident with their other effects on gastric epithelium. Chaudhury and Jacobson (26) observed that both dibutyryl cyclic AMP and theophylline mimicked the effect of 16,16-dimethyl PGE2 on the sodium pump in canine gastric mucosa and noted that this prostaglandin analogue increased tissue cyclic AMP levels in this epithelium coincident with its effect on sodium transport. Similarly, Terano and associates (220) observed that 16,16-dimethyl PGE2 stimulated cyclic AMP production in cultured rat gastric epithelial cells. Of additional interest, Gaskill and associates (76), in experiments with miniature swine, observed that prostaglandin-induced gastric mucosal blood flow was potentiated by theophylline, suggesting a role for cyclic AMP. Finally, recent studies in the human stomach have shown that incubation of mucosal homogenates with a variety of nonsteroidal anti-inflammatory agents inhibited adenylate cyclase activity, whereas concomitant incubation with PGE2, PGA2, 15(S),15-methyl PGE2, or 16,16 dimethyl PGE2 markedly stimulated the cyclic AMP enzyme system (198–201). Such findings have lent support to the hypothesis that prostaglandins may mediate their cytoprotective effects through direct stimulation of cyclic AMP.

Against a role for cyclic AMP in gastric cytoprotection are other studies using isolated canine parietal cells. PGE2, prosta-cyclin (PGI2), and two of its stable analogues, 6β-
PGI and the (5α)5,9-epoxy-16-phenoxyl-PGF analogue, were all shown to inhibit histamine-stimulated cAMP production over the same range of concentrations in which they reduced parietal cell aminopyrine accumulation, an index of parietal cell response to stimulation (206, 208). Similar inhibition of histamine-stimulated cAMP generation by PGF in canine parietal cells has been reported by Major and Scholes (140). These studies are of interest since inhibition, rather than stimulation, of cAMP formation has been linked to the antisecretory action of prostaglandins.

In contrast to these findings in which relatively low concentrations of prostaglandins were shown to inhibit histamine-stimulated cAMP, other studies have demonstrated that much higher concentrations of PGs stimulate cAMP production when incubated directly with gastric mucosal cells obtained from dog, rat, and mouse stomachs (22, 110, 206, 208, 241). In one study in which an attempt was made to define the cell type most affected by prostaglandin, PGE-induced stimulation of cAMP was noted to be more prominent in nonparietal cells than in parietal cells (241). Similar effects on cAMP by PGs in nonparietal cells have been observed by Sonnenberg and associates (209). These findings are of potential interest since many nonparietal cells originate from the surface epithelium where cytoprotection presumably takes place. Other studies in guinea pig gastric mucosa have also demonstrated that high concentrations of prostaglandin elevate cAMP levels in gastric tissue (240). Since the concentrations of prostaglandins used in the aforementioned studies were considerably higher than corresponding antisecretory doses, this ability to stimulate cAMP production may be pharmacological.

Further studies are needed to clarify the role of cAMP in cytoprotection. Since many prostaglandins possess cytoprotective properties in concentrations considerably lower than their corresponding antisecretory doses, it must be demonstrated that doses known to confer cytoprotection stimulate cAMP production. With our current knowledge, stimulation of gastric mucosal cAMP, which has generally been observed with only very high concentrations of prostaglandins, is unlikely to be a major mediator of cytoprotection, unless, as Soll and Whittle (207) have emphasized, such stimulation is produced in only a small population of the mucosal cells or is associated with enhanced cAMP turnover without increased cAMP content.

Stabilization of Tissue Lysosomes

Experimentally induced gastric ulcers by such damaging agents as aspirin, bile, and ethanol are associated with changes in lysosomal stability (94, 226, 227). Alterations in mucosal levels of lysosomal enzymes and their relative latency have been observed following topical application of such ulcerogens to gastric epithelium. Similar changes have been reported with gastric erosions induced by endotoxic shock (227). Such findings suggest that these tissue organelles may play a role in the pathogenesis of gastric mucosal damage. The precise steps in which lysosomes participate in ulcerogenesis are not entirely known but have recently been reviewed in considerable detail (227). Interestingly, serotonin-induced gastric ulcers in the rat were noted to be associated with the breakdown of lysosomal membranes (60). Treatment with PGE1 prevented such ulcer formation by this damaging agent and stabilized the lysosomal membranes (60). These findings suggested that stabilization of tissue lysosomes may be involved in the mechanism of cytoprotection. In contrast, studies using isolated lysosomal fractions failed to demonstrate a protective effect of PGF against the release of acid phosphates from lysosomes by 5, 10, and 20 mM aspirin (5). If stabilization of lysosomal membranes plays a role in prostaglandin-mediated cytoprotection, our current knowledge is too meager to identify the magnitude of this role.

Dissolution of Gastric Mucosal Folds

Previous studies in rat gastric mucosa have shown that gastric mucosal injury by agents such as absolute ethanol or 0.6 M HCl produce bandlike lesions along the longitudinal axis of the acid secreting portion of the stomach (185). Mersereau and Hinchee (148) have recently postulated that the shape of these lesions was due to their formation on the crest of the linear mucosal folds, which are prominent in the fasted rat stomach. They have also demonstrated that, on focal measurements of gastric mucosal potential difference, it was significantly lower at the crest of a mucosal fold than in the trough at the base of the fold. These findings suggested that the vulnerability of this area for lesion formation may be related to a local perfusion or permeability defect. Since these bandlike lesions can be abolished by a variety of prostaglandins (185), these investigators wondered whether the abolition of mucosal folding would also abolish such lesion formation and thus could explain a possible mechanism whereby prostaglandins mediated their antulcer effects.

To explore this possibility, fasted rats were anesthetized, their abdomens were opened, and the stomach was photographed to record the presence or absence of mucosal folds seen from the external surface (147). 16,16-Dimethyl PGE2 or placebo was then injected intraperitoneally, and 30 min later the stomachs were gavaged with 0.6 M HCl and fixed in formalin 30 min after that. In untreated animals, fixation was carried out subsequent to prostaglandin or placebo treatment. It was observed that in prostaglandin-treated animals mucosal folding was abolished and ulcer formation was virtually nonexistent. In contrast, animals receiving placebo had marked mucosal folding with the formation of significant ulceration. It was concluded that the prostaglandin-mediated cytoprotection was due to the abolition of mucosal folding (147). In other studies by Lancaster and associates (124), also using the rat stomach, dissolution of mucosal folds was accomplished by gastric distension with insufflation of air. In animals with and without dissolution of mucosal folds by distension, gastric mucosal necrosis was still observed following administration of absolute alcohol or 0.6 M HCl, and 16,16-dimethyl PGE2 was able to prevent such ulceration whether or not the stomach was distended. From these studies, it was concluded that dissolution of mucosal folds was not a
factor in prostaglandin-mediated cytoprotection. In view of these discordant results, it is obvious that further studies are needed to define the role of mucosal folds in gastric ulcer formation and the extent to which their dissolution contributes to cytoprotection.

Maintenance of Gastric Mucosal Sulfhydryl Compounds

The gastric epithelium contains high concentrations of nonprotein sulfhydryl compounds, the major component being reduced glutathione (21). Recent studies in the rat stomach by Szabo and associates (213) have shown that ethanol-induced gastric damage is preceded by and associated with a significant decrease in mucosal levels of nonprotein sulfhydryls that is dose related. If animals were pretreated with PGF₂α or one of several sulfhydryl-containing drugs, such as cysteamine (which is known to increase gastric mucosal nonprotein sulfhydryl levels (7)) prior to exposing the mucosa to ethanol, the formation of gastric erosions was markedly reduced. In contrast, pretreatment with agents that inhibit gastric mucosal sulfhydryl production, such as N ethylmaleimide, failed to protect the mucosa against ethanol damage. Of further interest, the protective effect of PGF₂α was also prevented by N-ethylmaleimide. These results suggested that nonprotein sulfhydryls may be important in maintaining gastric mucosal integrity and that prostaglandin cytoprotection may be mediated through endogenous sulfhydryl compounds.

If nonprotein sulfhydryls play a role in cytoprotection, the mechanism through which this occurs remains unknown. Of interest, these compounds have been reported to bind various metabolites and electrophilic radicals that may be damaging to normal cells (117, 145). Conceivably, a damaging agent such as ethanol could result in an accumulation of such substances. Nonprotein sulfhydryls, through binding these substances, could then decrease their concentration and reduce significantly their potentially deleterious effects. An alternative possibility is the influence that nonprotein sulfhydryl compounds may have on the structure and formation of gastric mucus. Various derivatives of sulfhydryl compounds containing the amino acid cysteine have been reported to alter the composition of mucus (168). If mucus plays a role in cytoprotection, endogenous nonprotein sulfhydryls may influence its efficacy in this regard.

Against a direct role of nonprotein sulfhydryls in mediating cytoprotection are the findings of Eberle and associates (56). In studies using the rat stomach, these investigators noted that stimulation of endogenous gastric mucosal glutathione by CoCl₂ failed to prevent alcohol-induced gastric injury by 100% ethanol. In contrast, depletion of this endogenous thiol by diethyl maleate or cyclohexane-1-one prevented alcohol damage in a dose-related fashion. Further, pretreatment with indomethacin partially blocked the protective effect of diethyl maleate. These findings suggested that an inverse relation between glutathione and cytoprotection may exist and that endogenous depletion of this substance in gastric mucosa may mediate cytoprotection through stimulation of prostaglandin formation.

Further studies are clearly needed to elucidate the role of sulfhydryl compounds in mediating prostaglandin cytoprotection. Not only will the effect of other damaging agents on gastric sulfhydryl compounds need to be studied but also the effect of inhibitors of sulfhydryl production on cytoprotection mediated by other PGs will need to be examined.

Stimulation of Surface-Active Phospholipids

Surfactants, the amphoterically-active phospholipids secreted by the alveolar cells of the lung, have long been known to play an important role in pulmonary physiology because of their ability to reduce surface tension at the air-liquid interface in the lung (23, 50, 81, 105, 107, 137, 164). In addition, it has been reported that surfactants have the capability of increasing the hydrophobicity of inert and biological membranes (92). Previously thought to be exclusively found in the lung, several research groups have now identified surfactant compounds in both the gastric juice and on the mucosal lining throughout the gastrointestinal tract (24, 93, 203, 204, 229, 230). Further, the gastric epithelium (particularly the oxyntic portion) has been found to have a highly hydrophobic surface with biophysical properties similar to a nonwetable substance such as polyethylene (93).

In view of these findings and the further observation that treatment of surfaces with cationic surfactants is capable of providing the underlying material with a hydrophobic coating that can protect that material against hydrochloric acid and other noxious water-soluble agents (133), Lichtenberger and associates (129) investigated the possible role of extrinsic and intrinsic surface-active phospholipids in preventing gastric mucosal damage. Using anesthetized, pylorus ligated rats, either saline or a surfactant mixture (similar to the concentration of pulmonary surfactant) was administered to the gastric lumen via an esophageal cannula. Thirty minutes later, an ulcerogenic dose of acid, 0.6 M HCl, was administered intragastrically. At the time of death, it was noted that the acid-induced gastric necrosis was markedly reduced in animals receiving the surface-active phospholipids and was independent of changes in intragastric pH or the volume of gastric aspirates. Also, intragastric bleeding was reduced by 60% in surfactant-treated animals.

In a further series of experiments (129), the role that prostaglandins may play in mediating the protective effects of surface active phospholipids was studied. In one group of studies, experiments were carried out in similar fashion to those outlined above, except that indomethacin, in a nonulcerogenic dose, was administered prior to commencing studies. Although indomethacin markedly aggravated the acid-induced bleeding in animals not receiving surfactant pretreatment, the phospholipid-induced reduction in gastrointestinal bleeding (60–70%) was not affected by this drug. In other studies (129), the concentration of surface-active phospholipids in gastric mucosa of control rate and those treated with a cytotoxic dose of 16,16-dimethyl PGF₂α was assessed. Compared with control animals, PG treatment increased the gastric mucosal concentration of major intrinsic surfactants by two- to sixfold. Taken together,
these findings suggested that PG synthesis was not required for extrinsic phospholipid-induced gastric protection but that PG induced cytoprotection may be mediated in part by a localized increase in phospholipid concentration, which in turn would enhance the hydrophobicity of the gastric mucosal lining.

Although the aforementioned studies offer another interesting means by which PGs could mediate their cytoprotective effects, additional studies are clearly needed to determine the role of surface-active phospholipids in this process. Specifically, the relation between ulcerogenesis by other damaging agents (i.e., aspirin, bile salts, and ethanol) and alterations in tissue phospholipids must be determined, and the ability of PGs to influence such alterations coincident with preventing ulceration must be assessed.

**ENDOGENOUS PROSTAGLANDINS AND GASTRIC MUCOSAL INJURY**

In addition to the ability of prostaglandins to prevent gastric mucosal damage when administered exogenously, recent evidence also suggests that endogenous prostaglandins may play a role in the prevention of gastric injury. Evidence supporting this latter hypothesis has been derived from three kinds of experimental observations.

**Phenomenon of Adaptive Cytoprotection**

In studies using the in vivo rat stomach, Chaudhury and Robert (27) and Robert and associates (183) administered a variety of "mild" irritants orally to fasted rats. These included 10–25% ethanol, 0.35 N HCl, 0.075 N NaOH, 5 mM taurocholate, and 4% NaCl solution. Control rats received only water. Fifteen minutes later, one of several necrotizing agents was then administered orally. These agents included such substances as absolute alcohol, 0.6 N HCl, 0.2 N NaOH, 80 mM acidified taurocholate, and 25% NaCl. When administered to control animals, each of these necrotizing agents produced massive damage of the gastric epithelium in the acid-secreting portion of the stomach as demonstrated by gross visual inspection and histological examination. In contrast, virtually total protection was observed in animals receiving pretreatment with mild irritants on subsequent exposure of the gastric mucosa to these necrotizing agents. Not only was this protection observed when a stomach pretreated with a given mild irritant was subsequently exposed to the more concentrated form of this agent (i.e., pretreatment with 20% ethanol and subsequent exposure to 80 mM taurocholate), but protection by mild irritants against the damaging effects of chemically dissimilar necrotizing agents was also observed (27). Thus, protection against the damaging effects of acidified 80 mM taurocholate was noted on pretreatment with 5 mM taurocholate, 20–25% ethanol, and 0.35 N HCl. Of further interest, it was noted that a certain dose of a given mild irritant was necessary before protection against a given necrotizing agent could be conferred. The lower the dose of mild irritant, the less effective it was in preventing damage on subsequent exposure to necrotizing agents. Ten percent ethanol or 0.75 mM taurocholate, for example, was not as efficient in preventing subsequent damage against 80 mM acidified taurocholate as was 25% ethanol or 5 mM taurocholate (27).

The mechanism by which mild irritants exerted their beneficial effects was not immediately apparent to these investigators. To explore the possibility that mild irritants may somehow mediate their effects by stimulating the formation of endogenous gastric PGs, studies were repeated in animals that had been pretreated 1 h earlier with indomethacin [an inhibitor of PG synthesis (223)]. Interestingly, indomethacin prevented the protective effects of mild irritants. It was concluded that mild irritants stimulate the formation of endogenous PGs by the stomach and that these PGs are responsible for the protection of gastric epithelium when subsequently exposed to necrotizing agents. This ability of mild irritants to confer such protection was termed "adaptive cytoprotection" (27, 183).

Other studies corroborate these findings and support these conclusions. In experiments by Deregnaucourt and Code (53), also using the rat stomach, an increased resistance of the gastric mucosa to barrier disruption with the second of two challenges of the known barrier breakers taurocholic acid and alcohol was observed. Thus, an initial exposure of the gastric epithelium to either 10 mM taurocholic acid or 20% ethanol significantly reduced the net fluxes of H⁺, Na⁺, and K⁺ and the changes in transmucosal potential difference induced by a second exposure 30 min later. These findings suggested that the mucosa had become more resistant to the barrier-breaking effects of these agents. Similar findings were recently observed by Miller and Henagan (151) in the canine stomach. Using a chambered stomach preparation, the effects of sequential 30-min exposures of the gastric mucosa to 20% ethanol in acid solution on barrier disruption and ulcer formation were assessed. The first exposure to 20% ethanol significantly reduced the net fluxes of H⁺, Na⁺, and K⁺ induced by a second and third exposure of the gastric epithelium to this damaging agent, with only minimal ulceration being observed. If indomethacin was given intravenously during these sequential challenges to 20% ethanol, this increase in barrier resistance was not observed, and significant ulceration of the gastric epithelium occurred even though indomethacin by itself had no adverse effect on barrier function and failed to induce any ulceration. In other studies in dogs with Heidenhain pouches, Levi and Carter (127) observed that the increase in hydrogen ion backdiffusion induced by topical bile salt instillation into the pouch was potentiated by parenteral indomethacin and that the rapid return of this ion flux to basal conditions seen with exposure of the mucosa to taurocholate alone was prevented. If the PG analogue 15(S),15-methyl PGE₂ was administered intravenously prior to giving the indomethacin and exposing the gastric epithelium to taurocholate, the indomethacin-mediated effects were reversed. In still another series of experiments, Scicluna and colleagues (194) confirmed the findings of Robert and associates (183) that low-dose alcohol prevented the necrotizing effects in gastric mucosa when subsequently
exposed to absolute alcohol. If animals had undergone previous abdominal vagotomy, the protective effect of low-dose alcohol against absolute alcohol was no longer observed. Based on the previous observation that stimulation of the vagus nerves enhances tissue formation and release of endogenous gastric PGs (11, 35, 202), these findings were interpreted as indicating that low-dose alcohol stimulated endogenous PG release, which subsequently prevented ulceration of the gastric epithelium on exposure to absolute alcohol, and that this PG release was mediated through the vagus nerve (194). Finally, rats subjected to chronic minimal restraint (metal ring placed subcutaneously in the back of neck) after 10 days were noted to be more resistant to alcohol-induced gastric injury when compared with sham-operated control animals (39). Since this protective effect was prevented by indomethacin, it was concluded that this phenomenon was a form of adaptive cytoprotection.

Taken together, these studies support the hypothesis that mild irritants may mediate their protective effects through PG release. Direct evidence for this, however, is uncertain. In the one published study (110) in which tissue levels of PGs were measured in response to mild irritants and necrotizing agents, mucosal generation of PGF$_2\alpha$ or PGI$_2$ in rat gastric epithelium exposed to 100% ethanol or 25% saline was not significantly different from that exposed to 20% ethanol prior to 100% ethanol and 5% saline prior to 25% saline, even though gross ulceration was significantly less pronounced in the mild irritant group when compared with mucosa exposed to absolute alcohol or 25% saline alone. That tissue PGs may play some role in protection is suggested by the depressed ability of mucosa to generate PGF$_2\alpha$ and PGI$_2$ in animals receiving indomethacin prior to exposing the stomach to the mild irritant-necrotizing agent combination. Further, both 20% ethanol and 5% saline alone were shown to stimulate mucosal generation of PGs to a significantly greater degree than mucosa exposed to normal saline alone. Other investigators have also observed that hypertonic saline stimulates PG synthesis and release both in the in vivo (3, 42) and in vitro (108) rat stomach. In addition, in the chronic minimal-restraint studies (39) referred to above, animals subjected to such restraint and found to be more resistant to alcohol-induced gastric injury when compared with control animals were also noted to have a greater capability to synthesize PGF$_2\alpha$ in fundic mucosa than corresponding controls. It is obvious that further studies are needed to clarify the relationship of PGs to adaptive cytoprotection and to determine the extent to which this phenomenon exists in other species since recent studies in the dog have failed to demonstrate evidence for it against bile salt-induced gastric injury (132).

Relation Between Endogenous Prostaglandin Metabolism and Gastric Mucosal Injury

In studies using the rat, Whittle et al. (237) measured the production of prostacyclin (PGI$_2$) employing a rapid, sensitive, and specific bioassay system as an index of cyclooxygenase activity in the gastric mucosa. Since cyclooxygenase is the enzyme responsible for the synthesis of prostaglandins from arachidonic acid, they hypothesized that, if gastric ulceration was related to a decrease in PG synthesis, this should be reflected as a decrease in PGI$_2$ production. After oral administration of aspirin, indomethacin, naproxen, and flurbiprofen to rats, they noted a dose-dependent inhibition of gastric mucosal PGI$_2$ activity that was reduced by all these agents to less than 20% of control. In addition, it was further observed that this reduction in PGI$_2$ activity was associated with the formation of gastric mucosal erosions. In a companion study (235), the temporal relation between cyclooxygenase inhibition and gastric mucosal ulceration was assessed after oral administration of indomethacin to rats. Three hours after indomethacin administration, obvious evidence of gastric injury on visual inspection of the mucosa was noted that was significantly less pronounced at 24 h and was macroscopically apparent at 48 h. Accompanying these lesions at 3 h was a 95% reduction in PGI$_2$ activity. At 24 h when the lesions were much less pronounced, the PGI$_2$ activity was only inhibited by 50–60%; by 48 h when lesions were absent, PGI$_2$ activity had returned to normal. It was concluded from these studies that the close relation between gastric injury and prostaglandin production supported the hypothesis that the gastric erosions were related to a deficiency in PG synthesis.

Although a close relation between prostaglandin production and gastric injury is convincingly demonstrated in the aforementioned experiments, the importance of alterations in tissue PGs in mediating mucosal damage remains uncertain. Studies performed on pigs (168) in which indomethacin was administered orally as a single bolus also elicited the development of gastric damage in parallel with a reduction in mucosal prostaglandin production. However, other indices of mucosal damage (i.e., a reduction in transmucosal potential difference in conjunction with an efflux of Na$^+$, K$^+$, and Cl$^-$ into the gastric lumen and a loss of luminal H$^+$) in this study preceded the changes in tissue PGs, suggesting that a reduction in tissue PGs and resultant ulcer formation may not be that tightly coupled. A similar dissociation between barrier disruption and reduction in tissue PGs has been observed by Ligumsky and associates (131) in the canine stomach injured with aspirin. These investigators also noted that salicylic acid and aspirin, while equally damaging to the gastric mucosal barrier, had different effects on endogenous prostaglandin production. Aspirin damage was associated with a marked reduction in canine gastric mucosal 6-oxo-PGF$_1\alpha$, the major metabolite of prostacyclin, PGE$_2$, and PGF$_2\alpha$, in a dose-related fashion, while salicylic acid-mediated damage had no effect on these tissue PGs despite the large dose range studied. Whittle and colleagues (237) were likewise unable to demonstrate a reduction in tissue prostacyclin generation in rat gastric mucosa damaged by salicylate. In studies in cats, Konturek and associates (114) observed that antral ulcers induced by a combination of aspirin and parenteral histamine or pentagastrin or intragastric hydrochloric acid significantly inhibited endogenous production of PGE$_2$, but the degree of this inhibition was not significantly greater than that observed in animals receiving aspirin alone in which ulcer-
gosa, Tepperman and Soper (218) have identified the presence of binding sites for PGE in what appear to be specific microsomal fractions of this epithelial tissue (219). Their studies fulfill the criteria that have generally been accepted for the establishment of true receptors, i.e., specificity with regard to ligand binding, saturability, reversibility, and high affinity (169). To this reviewer’s knowledge, the report of these investigators is the first demonstration detailing the binding of a PG to a preparation of gastric mucosal secretory tissue. Since identification of specific receptor sites in a given tissue suggests that the receptor-ligand interaction influences cellular processes within that tissue, these findings in porcine stomach lend credence to the hypothesis that PGs may play an important role in gastric epithelium under physiological conditions.

HISTOLOGY OF CYTOPROTECTION

The large majority of published information on cytoprotection reviewed in the foregoing discussion has assessed protection in terms of the absence or reduction in macroscopically visible necrotic lesions under various experimental conditions. Thus, if a known damaging agent, such as absolute ethanol, induced the formation of necrotic lesions macroscopically and pretreatment with a given PG prevented such lesion formation, the PG being tested is said to be cytoprotective. The major problem in assessing cytoprotection in this fashion is that what might be perceived as damage or protection macroscopically may not correspond to what is actually observed microscopically.

Although only a few studies have been published detailing the histology of cytoprotection, it is noteworthy that a disparity has indeed been observed between what one could call protection on purely macroscopic grounds and what is actually seen at the microscopic level. In studies on the ultrastructure of the rat gastric mucosa treated with 16,16-dimethyl PGE, and subsequently challenged with ethanol, Lacy and Ito (122) noted on light microscopy using semithin sections of tissue that, while PG was able to reduce the longitudinal red streaks and apparent necrotic lesions associated with alcohol-induced gastric injury when mucosa was visualized with the naked eye, areas of mucosa presumed to be normal macroscopically with PG treatment showed extensive cytological disruption that was often indistinguishable from untreated mucosa. Although the depth of damage was reduced by about 20% and necrotic lesion formation virtually eliminated when PG pretreatment was rendered to animals prior to alcohol exposure, these investigators observed that all rats receiving absolute alcohol, with or without PG pretreatment, had about 78% of their superficial gastric surface epithelium damaged. A similar disparity between macroscopic evidence of gastric damage and what was observed microscopically in rat gastric mucosa exposed to absolute ethanol and pretreated with PG was also reported by Guth and associates (87) using the same PG analogue. Although the magnitude of this disparity was less than that found by Lacy and Ito (122), 58% of the gastric surface epithelium in animals receiving PG pretreatment prior to alcohol exposure was noted.
to be damaged on microscopic evaluation, even though macroscopically these stomachs were felt to be entirely normal. In animals not receiving PG pretreatment in which severe ulcerations were judged to be present macroscopically, 87% of the mucosa was noted to be damaged microscopically. With respect to actual ulcer formation, however, no necrotic lesions were observed in PG-pretreated mucosa when evaluated microscopically in contrast to 14% of the epithelial lining possessing histological evidence of necrosis in animals receiving alcohol without PG pretreatment. In still other studies, Okabe and associates (162) examined the effects of 16,16-dimethyl PGE; on indomethacin-induced gastric damage in rats and compared macroscopic evidence of damage with findings histologically. Macroscopically, this PG analogue was noted to inhibit the development of indomethacin-induced gastric lesions in a dose-dependent fashion. Scanning electron microscopy of these stomachs generally confirmed the macroscopic interpretation and revealed nearly complete protection of surface epithelial cells, although some damage was still observed microscopically in stomachs felt to be normal macroscopically. In contrast, animals exposed to indomethacin without PG pretreatment demonstrated a close correlation between macroscopic evidence of damage and what was observed microscopically.

Taken together, the results of these few available studies on the histology of cytoprotection emphasize the importance of judging the presence or absence of cytoprotection on histological grounds. Although one may get a rough idea as to whether a given PG possesses cytoprotective properties under a specific set of experimental circumstances by macroscopic assessment of the gastric mucosa, in future studies, proof that cytoprotection has indeed occurred will require evidence that cells have actually been protected from injury at the microscopic level.

SUMMARY AND FUTURE RESEARCH EFFORTS

It seems certain from this review that PGs do indeed possess the ability to prevent gastric mucosal ulceration independent of their known inhibitory effects on gastric acid secretion. One problem in assessing the extent to which cytoprotection occurs under various experimental circumstances and the alleged magnitude of this protection from the studies discussed in this review relates to the fact that the large majority of published information on cytoprotection has assessed protection in terms of the absence or reduction in macroscopically visible necrotic lesions. As noted in the section on histology, a disparity has been observed between what one sees grossly with the naked eye and what is seen microscopically when evaluating the presence or absence of cytoprotection. Thus, it cannot be emphasized too strongly that, in future studies evaluating the absence or presence of cytoprotection, careful morphological assessment of gastric epithelium using both light and electron microscopic techniques will be necessary before PGs can be claimed to be cytoprotective under the given set of experimental conditions being studied. What are the morphological correlates of cytoprotection? Are tight junctions and other paracellular pathways involved? What role do surface epithelial cells play? Questions of this nature will need to be addressed in future studies concerned with the cytoprotective properties of PGs.

Despite the efforts of a large number of investigators to define the sequence of events responsible for cytoprotection, the mechanism underlying this property of PGs is still elusive. One of the problems of unraveling this mechanism is that our current understanding of the pathogenesis of gastric ulceration is also ill defined. Common components of such injury include an increase in mucosal permeability to hydrogen ion, and under some circumstances gastric mucosal ischemia. That PGs are able to influence all of these components of injury is clear from the foregoing review. Thus, prevention of gastric mucosal barrier disruption with a resultant decrease in the permeability to hydrogen ion, stimulation of sodium and chloride transport and thereby obviating inhibition of metabolic cellular processes known to occur during gastric damage, stimulation of bicarbonate secretion to adequately buffer diffusing hydrogen ion, and enhancement of gastric mucosal blood flow to prevent tissue ischemia have all been shown to occur with a large number of PGs. What has not been shown is that all PGs mediate these same effects. Since evidence for and against each of the proposed mechanisms for cytoprotection reviewed above can be demonstrated experimentally, it is doubtful that any of these effects of PGs on gastric epithelium is the single mechanism responsible for cytoprotection. Perhaps one type of PG mediates its protective effects through one mechanism while another PG mediates its antulcer activity through an entirely different mechanism (Fig. 2). It will remain for future research to identify the mechanism of cytoprotection, if indeed a single common mechanism exists.

Finally, the relation between endogenous PGs and gastric mucosal injury needs further clarification. Although an association between gastric damage and tissue PGs has been convincingly demonstrated in a number of studies in which a variety of nonsteroidal anti-inflammatory agents have been employed to produce such damage, other studies have failed to confirm such a relationship. Since it is quite well established that the nonsteroidal anti-inflammatory agents block the synthesis of PGs from arachidonic acid through inhibition of the cyclooxygenase enzyme system (Fig. 1), it is not surprising that ulceration by these agents could be associated with depressed levels of PGs in gastric epithelium. Whether ethanol and bile salts, and possibly other damaging agents, have similar inhibitory effects on PG biosynthesis remains to be established. Similarly, the whole phenomenon of adaptive cytoprotection is assumed to be mediated through prostaglandin release even though direct evidence for this hypothesis is meager and at best uncertain. Because mild irritants protect gastric epithelium against the damaging effects of more noxious agents, and such protection can be obviated by indomethacin (a known inhibitor of PG biosynthesis), it has been assumed that the mechanism underlying this phe-
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DIRECT CYTOPROTECTION

Exogenous PG + Damaging Agent

Damaging Agent Alone
(i.e., Aspirin, Ethanol, Bile Salts)

Gastric Mucosal Injury and Necrosis

FIG. 2. Schematic representation of two proposed forms of cytoprotection. Exogenous administration of prostaglandin (PG) mediates direct cytoprotection. Endogenous formation of PG by mild irritants mediates adaptive cytoprotection.

REFERENCES


ADDENDUM

Shortly after this review went to press, an article was published by A. Robert, J. E. Nezamis, C. Lancaster, J. P. Davis, S. O. Field, and A. J. Haunches [Mild irritants prevent gastric necrosis through "adaptive cytoprotection" mediated by prostaglandins. Am. J. Physiol. 245 (Gastrointest. Liver Physiol. 5): G113–G121, 1983] providing further support for the hypothesis that adaptive cytoprotection may be mediated by endogenous prostaglandins. In studies using the rat, these investigators demonstrated that the mild irritant NaOH (in concentrations ranging from 0.005 to 0.1 M) when administered orally, increased mucosal levels of PGE2 and PGF2α, dose-related fashion.

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nomenon is PG mediated (Fig. 2). Future studies will need to address this hypothesis directly by continuing to measure tissue PGs to see whether indeed mild irritants cause their release from gastric mucosa.

Despite the gaps in our knowledge concerning gastric cytoprotection by PGs, the extent to which such protection can be demonstrated histologically, and the possible mechanisms through which this property of PGs is mediated, much has been learned in the past decade about ulcerogenesis of the stomach by studying these fatty acids. Regardless of the role that PGs will ultimately be shown to play in the pathogenesis of gastric injury, it is the opinion of this reviewer that continued intensive research in this area of gastric physiology will pay rich dividends. By elucidating the mechanism(s) whereby prostaglandins mediate their cytoprotective properties and characterizing the role of endogenous prostaglandins in the pathogenesis of gastric ulceration, our knowledge and understanding of the processes of injury and repair...


46. EBERLE, D., A. ROBERT, AND N. KAPLOWITZ. Gluthionc (GSH) and gastric cytoprotection: an inverse relationship (Abstract).
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