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PROSTAGLANDINS AND GASTRIC ULCERS:
From Seminal Vesicle to Misoprostol (Cytotec^{R})

Internal Medicine Grand Rounds

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July 13, 1989

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INTRODUCTION

Misoprostol (Cytotec, G.D. Searle & Company, Chicago, IL) is the first of a new class of orally-administered prostaglandin analog drugs to be marketed in the United States. Misoprostol was approved for the prevention of gastric mucosal ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDS) in high risk patients. This represents a potentially important development in the pharmacotherapy of peptic ulcer disease.

The purposes of this Grand Rounds are to review a) the biochemistry, physiology, and pharmacology of prostaglandins, especially those synthesized by the stomach, b) the potential role of prostaglandin deficiency in the pathophysiology of gastric ulcer disease, and c) the role of prostaglandin analogs in the prevention and therapy of gastric ulcer disease and in other conditions. As the mechanism of action of these new drugs differs from that of the histamine H_2-receptor antagonists (H_2-blockers), prostaglandin analogs will, whenever possible, be compared with the H_2-blockers [cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid) and famotidine (Pepcid)], currently the cornerstone of peptic ulcer therapy in this country.

WHAT ARE PROSTAGLANDINS (PGs)?

PGs are a family of 20-carbon, oxygenated, unsaturated fatty acids. Their actions were first described in 1930 when Kurzrok and Lieb, American gynecologists, reported that human seminal fluid contained a substance that would contract or relax the human uterus (1). This substance was soon detected in seminal vesicles and seminal fluid of sheep and humans by von Euler in Sweden and Goldblatt in England (2,3). These investigators observed that the extract contracted uterine and intestinal smooth muscle and lowered blood pressure. von Euler determined that the substance was lipid soluble and acidic; assuming that the compound was produced primarily in the prostate gland, von Euler called the substance prostaglandin.

It was not until around 1960 that the first PGs were isolated at the Karolinska Institute by Bergstrom, Samuelsson, and their associates, who also introduced the currently used nomenclature for PGs (4,5). In 1971, Vane presented evidence that the therapeutic effect of aspirin-like drugs resulted from inhibition of PG synthesis (6). As we shall see, there is also evidence that some of the toxicity of aspirin-like drugs is also mediated by reduced PG synthesis.

All naturally occurring PGs are "derivatives" of a hypothetical, parent compound, prostanoic acid (Figure 1), which contains a cyclopentane ring between carbons 8 and 12, a double bond between carbons 13 and 14, and a -OH group in the α-position on carbon 15. (The α position, shown as a broken line in Figure 1, refers to a group below the plane of the molecule).

PGs are named for two distinguishing features. First, substitution of -OH or =O groups on carbon 9 and 11 of the cyclopentane ring determines the family of PG. For example, the PGE family has an =O on carbon 9 and an α-OH on carbon 11, while the PGD family is a mirror image of the PGE family, with an α-OH on

carbon 9 and an =O on carbon 11. The PGF family has α-OH group on both carbons. The second distinguishing feature of PGs is the number of double bonds in the molecule, which determines its subscript. 1-series PGs, like prostanoic acid, have a single double bond at carbons 13-14 (e.g., PGE_1). 2-series PGs, the most plentiful, contain two double bonds, one between carbons 13-14 and another between carbons 5-6 (e.g. PGE_2). 3-series PGs have a third double bond between carbons 17 and 18 (e.g. PGE_3).

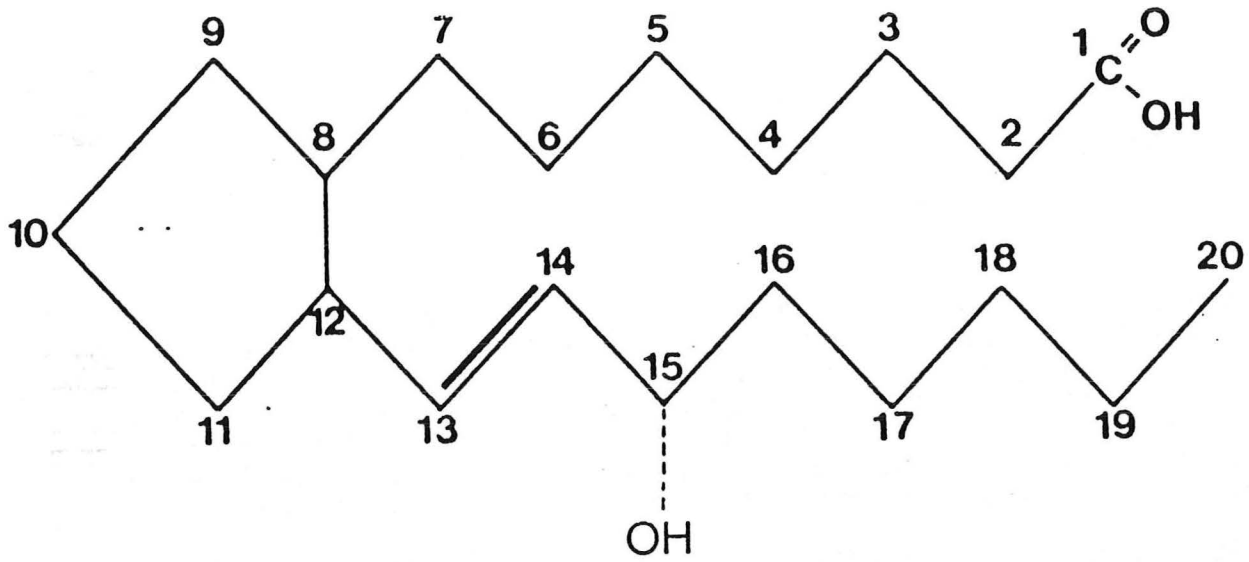


FIGURE 1. A HYPOTHETICAL COMPOUND, PROSTANOIC ACID, FROM WHICH ALL PGs CAN BE DERIVED AND NAMED.

PGs are synthesized, not from the hypothetical compound prostanoic acid (Figure 1), but instead from essential dietary fatty acids (7), as shown below (Figure 2). Linoleic acid, the major unsaturated essential fatty acid in Western diets, is found in oil from plant seeds, such as safflower oil, sunflower oil, corn oil, wheat germ oil, peanut oil, and linseed oil and it is present in many kinds of nuts. Linoleic acid has 18 carbons and 2 double bonds, the most distal double bond 6 carbons from the end of the molecule (hence its designation C18:2n-6). Linoleic acid is further desaturated and also elongated by adding 2 more carbons to produce eicosatetraenoic acid (C20:4n-6), or arachidonic acid, which is the precursor of 2-series PGs and thromboxane A_2 (TxA_2). Arachidonic acid can also be derived directly from the diet from beef, chicken, or pork. Linoleic acid can also be converted to 1-series PGs.

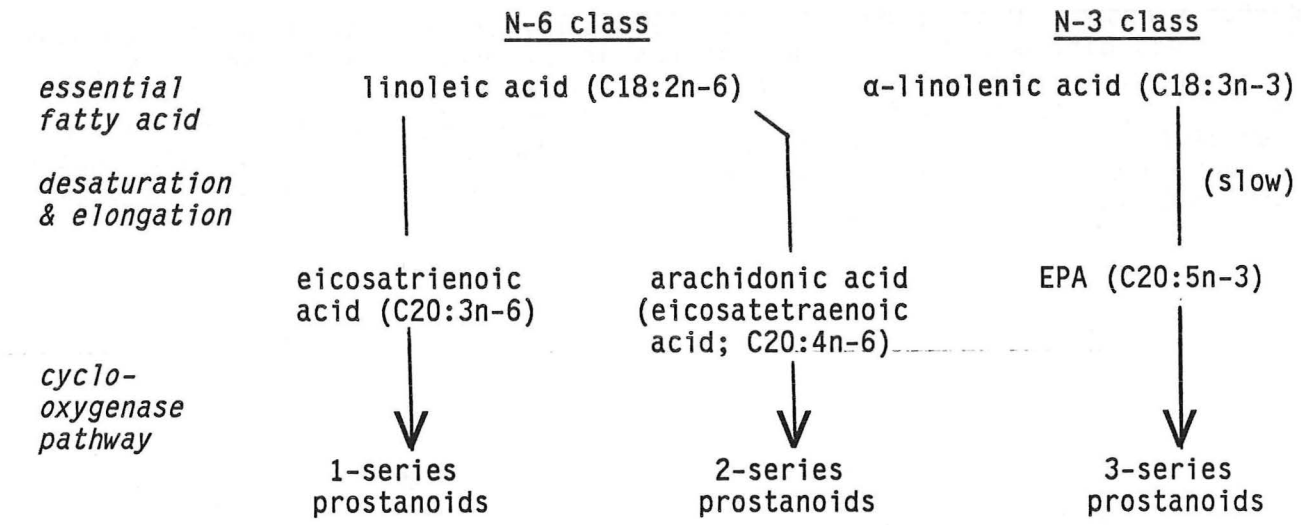


FIGURE 2. SYNTHESIS OF PROSTANOIDS FROM DIETARY FATTY ACIDS VIA THE CYCLOOXYGENASE PATHWAY

Alpha-linolenic acid (C18:3n-3) is present in soybean oil, wheat germ oil, nuts, and linseed and in humans can be converted (slowly) by desaturation and elongation to eicosapentaenoic acid (C20:5n-3), also called EPA. EPA, the immediate precursor of 3-series PGs, can be obtained directly from the diet from a wide variety of fish oils or from cod liver oil. As will be discussed later, increasing intake of these fish oils or of linolenic acid itself can alter the relative proportions of 2- and 3-series PGs produced in certain tissues.

PGs are not stored in cells to any significant degree, but instead are synthesized from precursor molecules (Figure 2) in response to mechanical or chemical stimuli. The precursor for 2-series PGs, arachidonic acid, is stored within cell membranes as a component of phospholipid molecules. In response to an appropriate stimulus or signal, the nature of which varies from cell to cell, arachidonic acid and other unsaturated fatty acids are released from phospholipids by the action of a membrane-bound enzyme, phospholipase A_2. Phospholipase A_2 is readily activated by slight perturbation of the cell membrane and also by immune complexes, thrombin, and collagen. Once released into the cytoplasm of the cell, arachidonic acid is rapidly metabolized through the cyclooxygenase enzyme pathway, the 5-lipoxygenase pathway, or both pathways (Figure 3). Corticosteroids inhibit phospholipase A_2 and thus reduce products of both pathways (8).

Various PG and non-PG products of eicosatrienoic, eicosatetraenoic (arachidonic), or eicosapentaenoic acid (EPA) are called eicosanoids. The relative activities of the cyclooxygenase pathway and the 5-lipoxygenase pathway and thus the amount of eicosanoids produced vary considerably from cell to cell. For example, in platelets most arachidonic acid enters the cyclooxygenase pathway and is converted to thromboxane A_2 (TxA_2), while in neutrophils and macrophages a considerable amount of arachidonic acid enters the lipoxygenase pathway and is converted to leukotrienes (LTs) and other inflammatory mediators. Which particular cyclooxygenase or lipoxygenase product(s) are produced in a given tissue depends

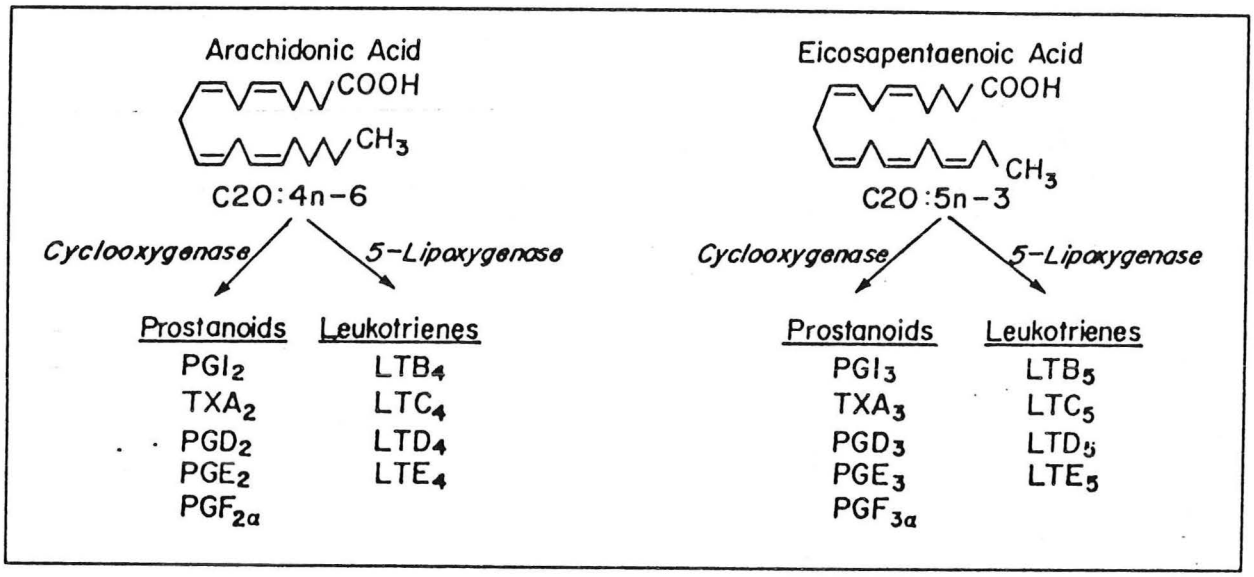


FIGURE 3. SPECTRUM OF EICOSANOIDS PRODUCED IN MAMMALIAN CELLS. LEFT. METABOLISM OF ARACHIDONIC ACID (C20:4; EICOSATETRAENOIC ACID) BY THE CYCLOOXYGENASE AND LIPOXYGENASE PATHWAY. RIGHT. METABOLISM OF EICOSAPENTAENOIC ACID (C20:5; EPA), A FISH OIL. (FROM REF. 90).

on the activity of enzymes in that tissue controlling synthesis of the various eicosanoids. While in platelets most arachidonic acid is converted to thromboxane A_2, a vasoconstrictor, in the vascular endothelium most arachidonic acid is converted to PGI_2 (prostacyclin), a vasodilator. Cyclooxygenase in platelets is more sensitive to blockade by low doses of aspirin than endothelial cyclooxygenase, partly explaining the usefulness of aspirin in unstable angina.

Various PG products of arachidonic acid may have very different biological functions (9-11). For example, PGE_2 (like PGI_2) is a vasodilator while $PGF_{2\alpha}$ contracts smooth muscle and is a vasoconstrictor. Some of PGE_2's effects are thought to be mediated by stimulation of adenylate cyclase, increasing intracellular cyclic AMP, while some of $PGF_{2\alpha}$'s effects are thought to be mediated by stimulation of guanyl cyclase, increasing intracellular cyclic GMP.

WHICH PGs ARE PRODUCED IN THE GASTRIC MUCOSA AND WHAT IS THEIR FUNCTION?

PGs are produced by nearly all cells within the body, including gastric mucosal cells (12-20). PG content of the gastric mucosa is much higher than the PG content of the submucosa and the muscle layer or the PG content of many other organs. Furthermore, enzymes responsible for generation and breakdown of PGs are present in the gastric mucosa (16). If a gastric mucosal homogenate is incubated with arachidonic acid, a large number of prostanoids are produced (12,17). [Prostanoids refer to cyclooxygenase products of arachidonic acid and include not only PGE_2, $PGF_{2\alpha}$, and PGD_2, but also PGI_2 and thromboxane A_2]. By radiolabelling the arachidonic acid with ^{14}C, it is possible to separate the various radioactive products by high-performance liquid chromatography (HPLC) and quantitate them, at least in relative terms (Figure 4).

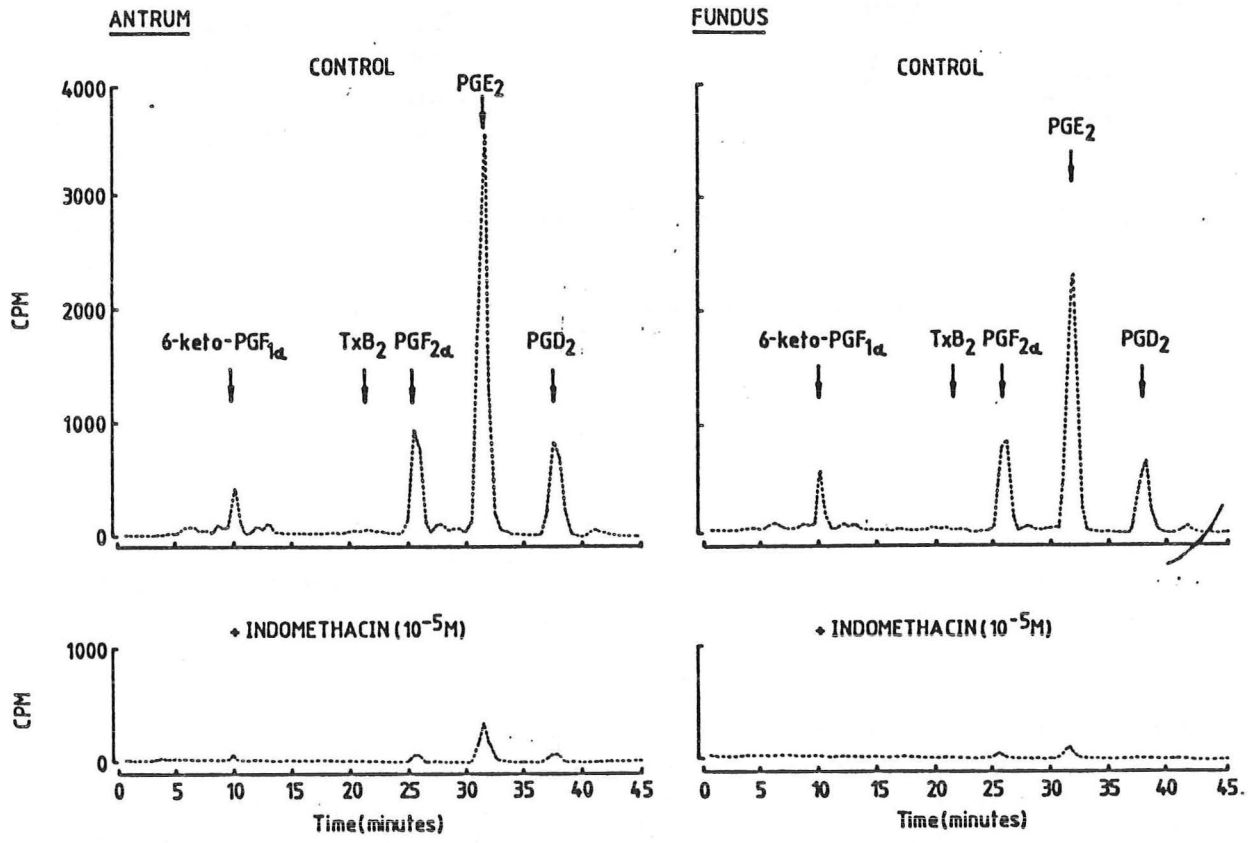


FIGURE 4. (TOP):HPLC PROFILE OF PG PRODUCTS SYNTHESIZED IN VITRO FROM [^{14}C]ARACHIDONIC ACID IN HUMAN ANTRUM (LEFT) AND FUNDUS (RIGHT). (BOTTOM):PROFILE OF PG PRODUCTS AFTER PREINCUBATION WITH INDOMETHACIN. (FROM REF. 17).

TABLE 1. SPECTRUM OF GASTRIC MUCOSAL PROSTANOIDS IN VARIOUS SPECIES

SPECIES	PGE_2	$PGF_{2\alpha}$	PGD_2	PGI_2 (6-keto PGF1α)	TxA_2 (TxB_2)
MAN	+++	+++	++	+	-
RAT	+			+++	
DOG	++	++	++	+++	+
RABBIT	+++	++	+	+++	-

Based upon the work of Dr. J. Stephen Redfern in our laboratory, the relative amounts of prostanoids produced in the gastric mucosa in different species is shown in Table 1. There is considerable interspecies variation in prostanoid products of arachidonic acid. In the human gastric mucosa, the major products are PGE_2 and $PGF_{2\alpha}$, while PGD_2 and PGI_2 are less prominent. (PGI_2 and also thromboxane A_2 are very unstable, being rapidly converted to 6-keto $PGF_{1\alpha}$ and thromboxane B_2 (TxB_2), respectively. Thus, when measuring PGI_2 and TxA_2, it is customary to measure their metabolites.)

TABLE 2. GASTRIC MUCOSAL CELLS AND THEIR PRODUCTS

CELL	PRODUCT(S)	REGION (SEE FIG.5)
Epithelial Cells		
Surface	Mucus, HCO_3^-	All Regions
Mucous Neck	Mucus, Pepsinogen	All Regions
Parietal	HCl, Intrinsic Factor	F,B
Chief	Pepsinogens	F,B
Endocrine Cells		
G	Gastrin	A,P
D	Somatostatin	All Regions
Cells in Lamina Propria		
Mast Cell	Histamine, Others	All Regions
Plasma Cells	IgA	All Regions
Lymphocytes	Many	All Regions
Macrophages	Many	All Regions
Endothelial cells	Many	All Regions

Because so many cells are present in the gastric mucosa (Table 2) and because these cells are in such proximity, it is often difficult to assign a particular function, such as PG synthesis, to a particular cell. The known products of the gastric mucosal cells and their regional distribution in the stomach are also given in Table 2.

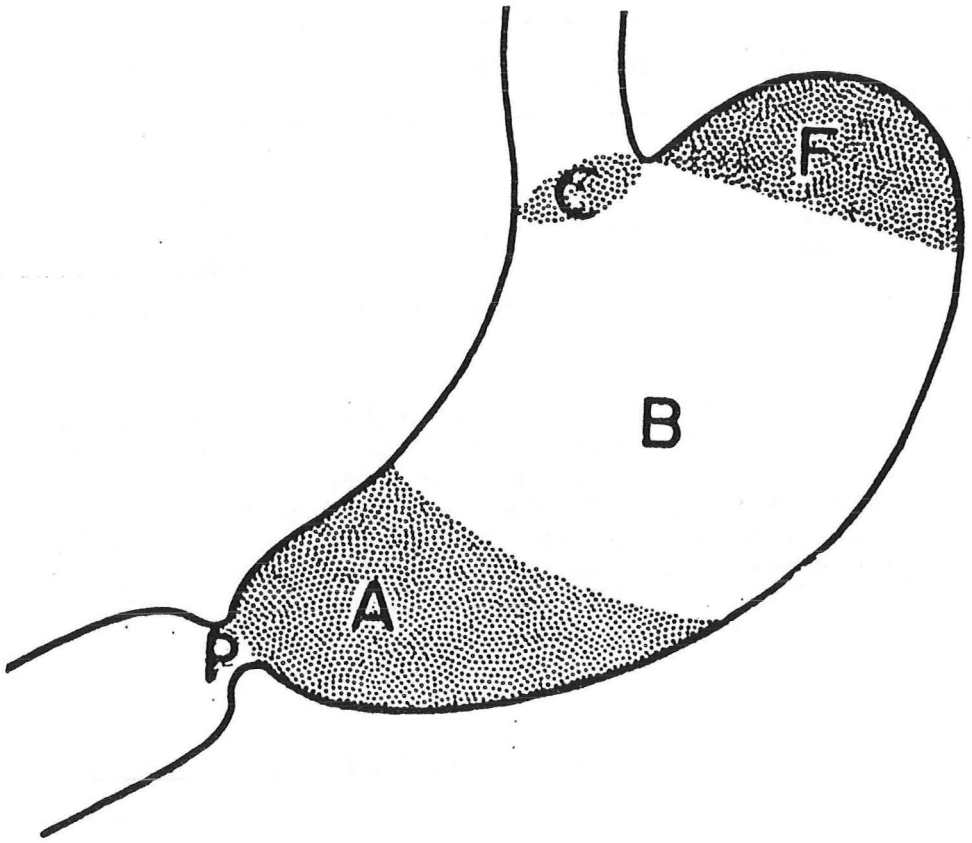


FIGURE 5. ANATOMIC REGIONS OF THE HUMAN STOMACH. C=CARDIA; F=FUNDUS; B=BODY; A=ANTRUM AND P=PYLORUS. (SEE TABLE 2 FOR CELL DISTRIBUTION).

With the exception of the mast cell located in the lamina propria of the stomach, which synthesizes PGD_2 (and also LTs), it is uncertain which cells in Table 2 are responsible for mucosal PG production. Studies using an enriched population of canine parietal cells incubated with arachidonic acid suggest that these cells can synthesize $PGF_{2\alpha}$ and PGE_2 (13), the major PGs in the gastric mucosa. However, it has recently been suggested that the majority of PGE_2 in the canine gastric mucosa is synthesized not by parietal cells or chief cells, but by macrophages and capillary endothelial cells that reside in the lamina propria between epithelial cells (14). Furthermore, PGE_2 synthesis by these cells seems to be triggered by accumulation of reactive oxygen metabolites (15). In the near future, it should be possible to clarify which cell (or cells) is responsible for PG production in the gastric mucosa and whether the target cell for PGs is another nearby cell (paracrine effect) or possibly even is the same cell ("autocrine" effect) (21). It should also be possible to clarify to what extent the gastric mucosa synthesizes LTs.

PGs have very short half-lives (a few minutes), being rapidly metabolized by enzymes such as 15-OH-PG-dehydrogenase and 13-14 reductase which are present in

gastric mucosa, liver, and lungs (22). For example, PGE_2 is metabolized by the former enzyme to 15-keto PGE_2 and then by the latter to 13,14-dihydro,15-keto PGE_2. Many of the synthetic analogs of PGs have methyl or other hydrocarbon substitutions on some of the carbons of the basic PG structure, usually on carbons 15 or 16 (Figure 1). Addition of these groups often markedly delays inactivation, thus prolonging the half-life of the analog to several hours without reducing the biological action of the PG.

As natural PGs are tissue-active compounds with very short half-lives once they enter the circulation, it has been difficult to determine their concentrations *in vivo*. Bunnett et al implanted very small hollow fibers in the canine gastric submucosa to allow sampling of µl quantities of extracellular fluid for determination of PGE_2 concentrations (23). They obtained basal values of approximately 14 nM (at a time when PGE_2 was undetectable in peripheral venous blood). PGE_2 in the fundus increased 2-fold with feeding (no changes were seen in the antrum) and decreased with indomethacin therapy. However, it is uncertain whether the presence of the hollow fibers, *per se*, served as an irritant to the mucosa, augmenting baseline synthesis of PGs.

Several experimental approaches have been utilized to unravel the physiologic role of the PGs present in the gastric mucosa. These include administration of a) the PG exogenously; b) an inhibitor of PG synthesis; or c) an antagonist of PG action. Each of these approaches has its advantages and drawbacks, as will be reviewed below.

Effect of Exogenous PGs on the Stomach

Gastric Secretion. When PGs or their analogs are administered to animals or humans, a wide variety of gastric effects are observed. The most obvious and first to be recognized is an inhibitory effect on gastric secretion (9,11,24-39). The most potent inhibitors of acid secretion belong to the PGE family, whereas PGAs and PGIs inhibit acid secretion as well. A wide variety of PGE_2 and PGE_1 analogs developed by pharmaceutical companies inhibit gastric acid secretion and on the same order of inhibition as H_2-blockers. For example, 70 µg (.07 mg) enprostil, a PGE_2 analog, inhibits acid secretion in man to approximately the same extent as does 150 mgm ranitidine (39). Thus, on a molar basis, PG analogs are very potent inhibitors of acid secretion.

Figure 6 shows a current model of gastric acid secretion by the parietal cell (40). The cell contains on its basolateral membrane a receptor for histamine (H_2-receptor), a gastrin receptor, and a muscarinic receptor for acetylcholine (M_2-receptor). Histamine is stored in mast cells in the lamina propria near parietal cells. Factors controlling release of histamine from mast cells in the stomach are poorly understood. Activation of the parietal cell by the histamine-H_2 receptor complex involves a GTP-regulatory protein (Gs) which stimulates adenylate cyclase, converting cytosolic ATP to cyclic AMP (c-AMP). Then, c-AMP phosphorylates a protein kinase which, by as yet unclear steps, activates the proton pump (hydrogen/potassium ATPase), actively exchanging hydrogen ions for potassium ions. This H^+/K^+ exchange process is facilitated and regulated by a KCl symporter which is activated by intracellular c-AMP. Gastrin, released into the circulation from endocrine cells (G cells) in the antrum and pylorus of the stomach, and acetylcholine, released from postganglionic neurons near parietal cells, activate the protein pump and KCl symporter not by increasing c-AMP

but by increasing intracellular calcium ions. This is accomplished either by increasing movement of calcium into the parietal cell from extracellular fluid, by releasing calcium from intracellular stores, or by both mechanisms. There is some evidence that, in addition to increasing c-AMP, histamine also increases intracellular calcium concentrations.

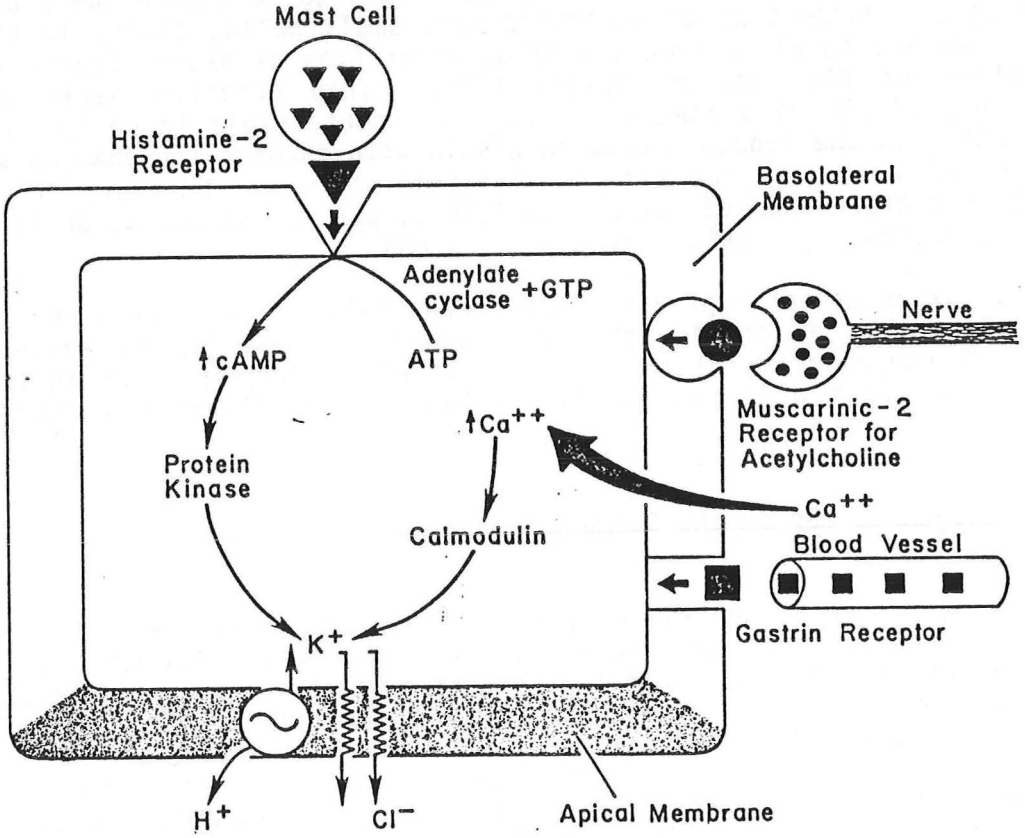
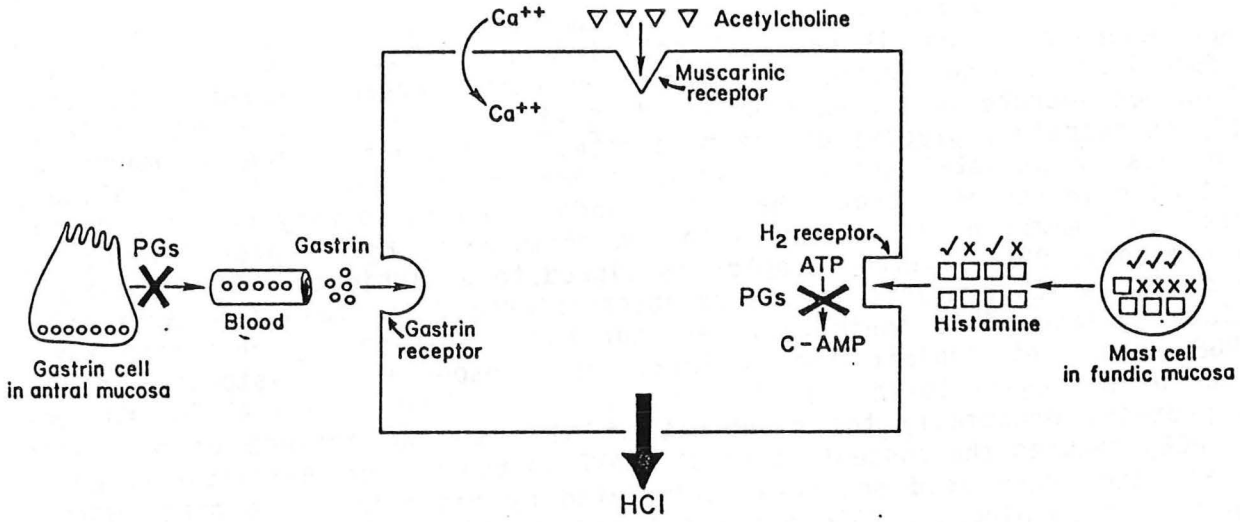


FIGURE 6. MODEL OF GASTRIC ACID SECRETION BY PARIETAL CELL (FROM REF. 40).

The mechanisms by which PGs inhibit acid secretion by parietal cells are summarized in Figure 7. Some PGs, usually in the E_2 family, suppress gastrin release from G cells and lower circulating gastrin concentrations, thereby reducing acid secretion (31,34,39,41). As an example, 100 µg 15,15 dimethyl PGE_2 reduced meal-stimulated serum gastrin concentrations significantly in a group of duodenal ulcer patients studied in our laboratory (Figure 8). However, some PGs and PG analogs (e.g., PGI_2, the PGE_1 analog misoprostol) reduce acid secretion without lowering circulating gastrin concentrations (32,42). This indicates that PGs must reduce acid secretion by a gastrin-independent mechanism. This must be the case since PGs also can inhibit acid secretion stimulated by exogenous gastrin (32,43).



SITES OF ACTIONS OF PROSTAGLANDINS (PGs) ON ACID SECRETION

FIGURE 7

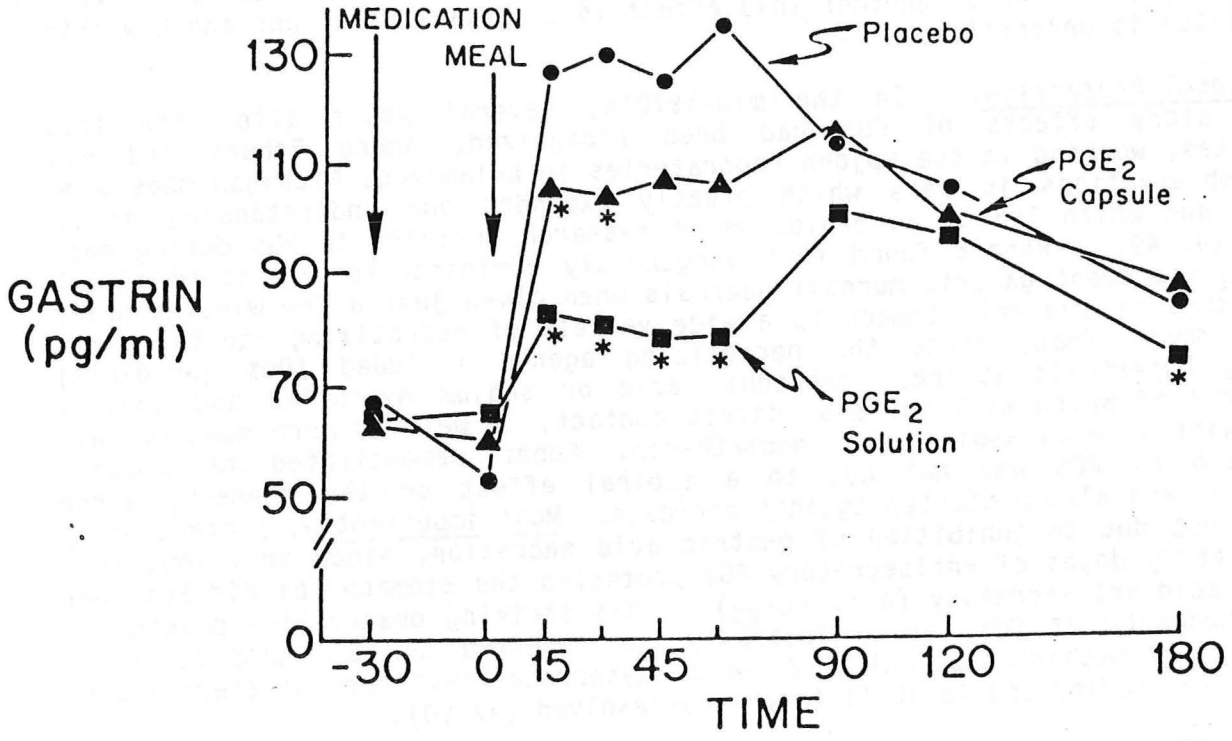


FIGURE 8. EFFECT OF 100 µg ARBAPROSTIL (PGE_2 ANALOG) GIVEN IN A CAPSULE OR IN SOLUTION ON MEAL-INDUCED SERUM GASTRIN RELEASE IN HUMANS (FROM REF. 31).

Recent in vitro studies by Chen et al using parietal cells isolated from the canine gastric mucosa have clarified the mechanism by which PGE_2 and one of its analogs, enprostil, inhibit parietal cell function (44). [The term "parietal cell function" is used, rather than acid secretion, because isolated parietal cells do not secrete acid when stimulated in vitro. Instead, biochemical indices (O_2 consumption, glucose utilization rate, aminopyrine uptake) or morphologic changes in parietal cells are used to monitor parietal cell activation.] Chen et al have recently shown that PGE_2 binds to an inhibitory receptor on the parietal cell membrane in proximity to the stimulatory H_2-receptor (Figure 7). The inhibitory, PGE_2-related receptor is linked to an inhibitory GTP-regulatory protein, Gi, which prevents the H_2-receptor-related Gs protein from activating adenylate cyclase. This inhibitory receptor can be blocked by pertussin toxin and PGE_2 does not inhibit the parietal cell response to histamine in the presence of pertussis toxin. Pertussis toxin ADP-ribosylates a 41,000 Kd membrane protein, presumably the α-subunit of Gi. In the absence of pertussis toxin, PGE_2 reduces the concentration of c-AMP in the histamine-stimulated parietal cell and hence acid secretion stimulated by histamine. In other words, though not an H_2-blocker, PGE_2 has a net effect which resembles antagonism of the H_2-receptor. Since gastrin and acetylcholine do not act via Gs, activation of Gi by PGE_2 does not inhibit parietal cell function stimulated by gastrin or acetylcholine in vitro (44). Nevertheless, PGE_2 analogs (like H_2-blockers) inhibit gastrin-mediated, cholinergically-mediated, and, in fact, all forms of stimulated acid secretion in vivo (40), possibly because c-AMP potentiates all forms of acid secretion, even those activated primarily by the calcium pathway. Thus, PGE_2 analogs (like H_2-blockers) reduce gastric acid hypersecretion even in patients with marked hypergastrinemia due to a gastrinoma (Zollinger-Ellison syndrome) (45).

PGs also inhibit gastric acid secretion in animals when administered directly into the brain (46). Whether this effect is a physiological one and how this is mediated is uncertain.

Mucosal Protection. In the mid-1970's, several years after the acid antisecretory effects of PGs had been recognized, Andre Robert and his associates, working in the Upjohn Laboratories in Kalamazoo, Michigan made some novel observations in rats which greatly expanded our understanding of PG actions and which led to an explosion of research activity in PGs during past decade (47-49). Robert found that exogenously administered PGs could almost completely prevent gastric mucosal necrosis when given just a few minutes prior to exposure of the rat stomach to a wide variety of necrotizing agents. This was no small feat, since the necrotizing agents included 100% (absolute) ethanol, hypertonic saline, hypertonic acid or sodium hydroxide and boiling water, all of which kill cells on direct contact, as well as more mundane gastric toxins such as aspirin and indomethacin. Robert demonstrated that mucosal protection by PGs was not due to a topical effect on the stomach, since parenteral PGs also protected against necrosis. Most importantly, protection by PGs was not due to inhibition of gastric acid secretion, since very low, non-antisecretory doses of antisecretory PGs protected the stomach, as did PGs that are not acid-antisecretory (e.g. $PGF_{2\beta}$). This striking observation pointed to second property of PGs, which initially was referred to as "cytoprotection" (47,50). The mechanism by which PGs were "cytoprotective" was not clarified by these early studies and is still largely unresolved (47-50).

Once these observations were reported and then confirmed by laboratories throughout the world, additional observations were made. Lacey and Ito soon

showed that, although gross evidence of mucosal injury was prevented by pretreatment with PGs, there was still histologic evidence of damage, at least to the surface cells (51). Glandular cells and blood vessels more deeply situated in the mucosa were protected by PGs, even at the histologic level. Because of persistent surface cell damage despite PG-pretreatment, the term "cytoprotection" is a bit of a misnomer and has now been largely replaced by "mucosal protection".

When PGs are administered exogenously, a wide variety effects on the gastric mucosa are observed, many of which could contribute to the mucosal protection phenomenon described above (9,11,52). Some of these actions are listed in Table 3.

TABLE 3. PROPOSED MECHANISMS OF GASTRIC PROTECTION BY PROSTAGLANDINS

Stimulation of bicarbonate secretion
Stimulation of mucus secretion
Enhancement of gastric mucosal blood flow
Prevention of gastric mucosal barrier disruption
Stimulation of cellular ionic transport processes
Stimulation of cyclic AMP production
Increase in surface-active phospholipids
Maintenance of gastric mucosal sulfhydryl compounds
Stabilization of tissue lysosomes
Stabilization of cell membranes

There is no clear evidence as yet that any of these mechanisms, alone or in combination, can explain the mucosal protective effects of PGs in rats. Of interest, neither PGE_2 or 16,16 dimethyl PGE_2 are protective against alcohol damage in mice (53). Furthermore, there is little evidence that low, non-antisecretory doses of PGs or PG analogs are protective in humans, although more work is needed in this area. Thus, the concept of cytoprotection may not apply to all species.

Effects of Inhibitors of PG Synthesis on the Stomach

Although studies using exogenously administered PGs and PG-analogs (described above) are of considerable interest, results usually cannot be interpreted in physiological terms since the concentration of PG achieved *in vivo* is probably much higher than the actual concentration of PG present under physiologic or even pathologic conditions. Thus, studies with exogenous PGs are, for the most part, pharmacologic, not physiologic.

The most popular physiologic tool for evaluating effects of endogenous PGs has been to administer a PG-synthesis inhibitor, most commonly indomethacin or aspirin. While a great deal of useful information has been obtained by this approach, conclusions need to be interpreted cautiously for the following reasons:

1. By blocking cyclooxygenase, NSAIDs reduce the synthesis of all PGs and also of thromboxanes more or less equally, making it difficult to separate PG effects from thromboxane effects and also to differentiate the effect of a specific PG product from that of another product (e.g., $PGF_{2\alpha}$ vs. PGE_2). As already mentioned, $PGF_{2\alpha}$ and PGE_2 often having strikingly different effects on target cells.

2. By blocking cyclooxygenase, NSAIDs may encourage precursor arachidonic acid molecules to be shunted down the lipoxygenase pathway, with accelerated formation of LTs (see Fig. 3). Thus, an observed effect of an NSAID may be due to increased LTs, decreased PGs, or both.

3. Indomethacin, aspirin, and other NSAIDs not only block cyclooxygenase, thus reducing PG synthesis, but have other actions which could affect the gastric mucosa (54). For example, aspirin is converted to salicylate which has toxic effects which are independent of cyclooxygenase inhibition, as reviewed recently by Kauffman (55). Thus, an effect of an NSAID may be totally unrelated to alterations in eicosanoid metabolism.

These reservations should be taken into consideration when reviewing studies using PG-synthesis inhibitors to evaluate effects of endogenous PGs on the stomach.

Acid Secretion. Several observations suggest that endogenously synthesized PGs may suppress acid secretion by parietal cells. First, indomethacin increases to a modest degree basal and histamine-stimulated acid secretion (56,57) and parietal cell function *in vitro* (58). The dose of indomethacin used in man was sufficient to reduce gastric mucosal prostaglandin content by 60-70% (17). Whether the increase in acid secretion was due to some other effect of indomethacin, such as enhanced LT formation, is uncertain (59). Salicylate therapy has also been reported to increase acid secretion (60), although not all studies have found this (61).

Mucosal Protection. It is well-established in animals and man that inhibitors of PG synthesis by aspirin or NSAIDs is associated with gastric mucosal damage (9,11,62-65). However, what is not so clear is the relationship between PG synthesis inhibition and mucosal damage. The following observations can be cited:

1. Some NSAIDs reduce PG content without damaging the mucosa, suggesting that other factors are required for mucosal damage (66,67).

2. There is not a high correlation between extent of mucosal damage and inhibition of PG content in individual subjects or animals (17,66).

3. In some human studies with aspirin, gastric mucosal damage may occur in the fundus and body of the stomach without a significant fall in gastric mucosal PGs (64).

4. Epidemiologic studies show a strong association not only between ingestion of aspirin and chronic peptic ulcer, but also between ingestion of acetaminophen and ulcers (68). As acetaminophen does not inhibit cyclooxygenase, the association may be more with analgesic intake per se than with cyclooxygenase inhibition.

5. In normal volunteers, early acute injury by aspirin or indomethacin disappears with continued NSAID ingestion, even though PG synthesis remains depressed (69,70). This phenomenon has been referred to as gastric adaptation (69).

Therefore, while reduction in PG synthesis may contribute to the gastric mucosal damage by NSAIDs, it is by no means clear that this is the only, or even the major, mechanism by which these agents damage the stomach.

Effects of PG Antagonists on the Stomach

At present, receptors for PGs have not yet been fully characterized and PG-receptor antagonists are unavailable for evaluating the physiologic role of PGs. However, in the past 4 years, a few investigators, including Dr. Redfern in our laboratory, have used selective antibodies against individual PGs to deduce the physiologic effects of various endogenously synthesized PGs on the stomach. This work has been summarized recently (71) and will be presented only briefly.

If PGs such as PGE_2, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$, or PGD_2 are conjugated in vitro to a carrier protein, such as thyroglobulin, the PG component becomes antigenic when injected subcutaneously. Thus, to produce specific antibodies to these PGs (for example, for subsequent use in radioimmunoassay) an animal, usually a rabbit, is injected with the PG-thyroglobulin conjugate in Freund's adjuvant, with subsequent booster immunizations. It had been known for some time that rabbits being immunized against PGs by this method often die a few months after beginning immunization. In 1985, Olsen et al reported that some of these rabbits died of perforated gastric or duodenal ulcers (72). Over the past few years, our laboratory has been studying the incidence, time course, and pathophysiology of gastrointestinal ulceration induced by antibodies to PGs in rabbits (and also in dogs) and our findings can be summarized as follows:

1. Active immunization with either PGE_2-thyroglobulin, $PGF_{2\alpha}$-thyroglobulin or PGD_2-thyroglobulin leads, within 4 weeks or so, to production of high-titer antibodies to the PG, antibodies which are highly specific (i.e., they have low cross-reactivity with other PGs). Thus, antibodies can be used as fairly specific probes for the effects of a particular PG (73).

2. Once animals produce antibodies to PGs, gastric ulcers and later on small intestinal ulcers develop, with an ultimate incidence in rabbits of around 85% for gastric ulcers and 60% for enteric ulcers (Figure 9). Furthermore, in around 20-25% of rabbits, the ulcers are complicated by perforation and death.

3. Immunization against an inactive (non-protective) prostaglandin, such as 13,14 dihydro-15-keto PGE_2 (DHK-PGE_2), a metabolite of PGE_2 synthesized in the gastric mucosa, leads to specific, high-titer antibodies to DHK-PGE_2. As antibodies to DHK-PGE_2 can bind complement (74), while DHK-PGE_2-immunized rabbits do not develop ulcers, it is unlikely that ulcers in PGE_2-immunized rabbits result from nonspecific formation of PG antigen-antibody complexes within the mucosa. Of

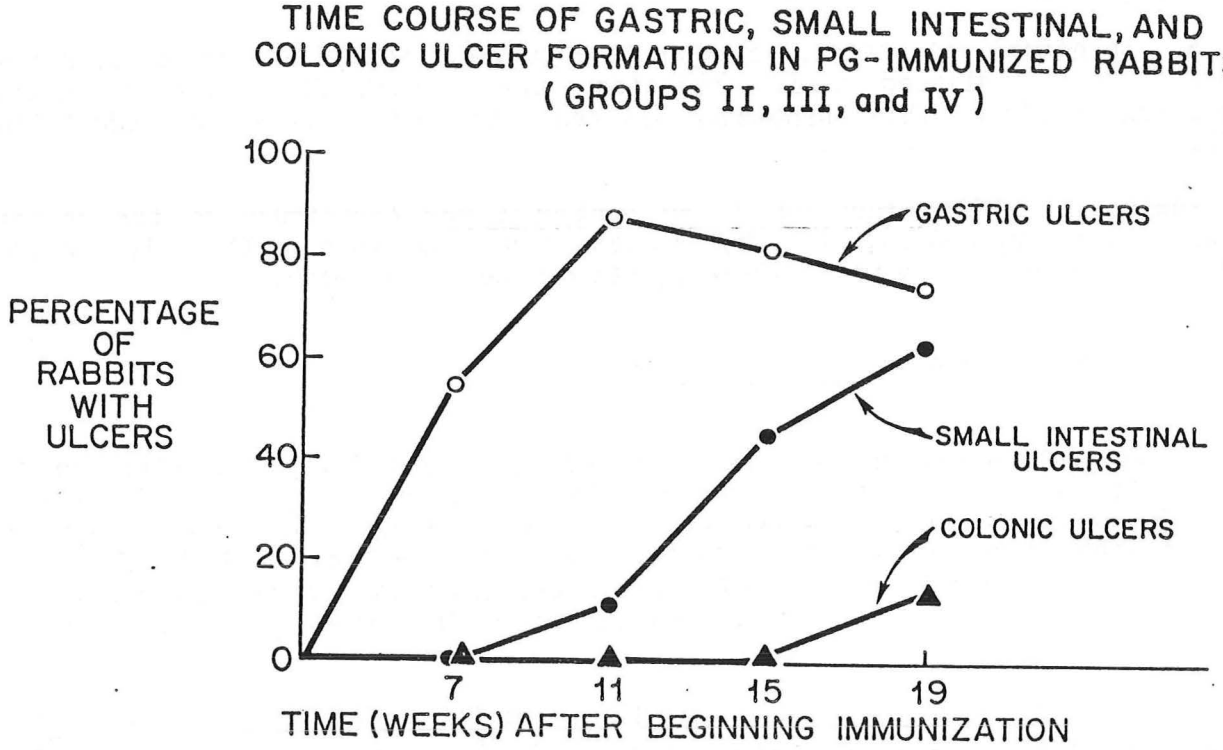


FIGURE 9

interest, immunization with 6-keto $PGF_{1\alpha}$, an inactivate metabolite of PGI_2, always leads to ulcers. However, antibodies to 6-keto $PGF_{1\alpha}$ highly cross-react with PGI_2 (prostacyclin). This was proven by demonstrating that antibodies to 6-keto $PGF_{1\alpha}$ antagonize the inhibitory effect of PGI_2 on ADP-induced platelet aggregation in vitro (74).

4. Ulcer formation can directly be attributed to PG antibodies per se, since passive immunization of recipient rabbits with plasma containing a high titer of antibodies to either PGE_2 or 6-keto $PGF_{1\alpha}$ produces gastric ulcers within 9 days (73,74).

5. In dogs, gastric erosions and ulcer formation in response to immunization with PGE_2 are not associated with increases in basal or maximal acid secretion (75).

The mechanism by which antibodies to PG lead to ulcers is uncertain and the focus of continued investigation in our laboratory. Antibodies to PGs do not affect rates of endogenous synthesis or catabolism of PGs (76). Presumably, antibodies result in a PG-deficiency state by preventing PGs that are synthesized

from reaching their sites of action. One finding that is quite provocative is that neutralization of a single endogenous PG (PGE_2, $PGF_{2\alpha}$, PGD_2, or PGI_2) leads to ulcers, even though the free concentrations of the other PGs should be unaltered, assuming the high degree of antibody specificity *in vitro* applies *in vivo*. This suggests that each PG may have an unique action that protects against ulcers.

It is remarkable that, with the exception of the gastrointestinal effects observed, rabbits immunized against PGE_2 and other prostanoids remained quite healthy despite the formation of high-titer antibodies to PGs. In contrast, dogs immunized with PGE_2 developed, in addition to gastrointestinal mucosal damage, a crippling bone disease with osteosclerosis, confirming an important role of PGE in bone metabolism (77-79).

Before leaving the topic of PG antibodies, one may speculate that some patients with idiopathic peptic ulcer disease could be producing antibodies to PGs spontaneously. However, we were unable to find any such patients out of 45 screened (80). Thus, if spontaneously occurring PG antibodies cause ulcer disease in man, this must be uncommon.

CAN PROSTAGLANDIN SYNTHESIS BE ALTERED BY THE DIET?

If endogenous PGs are important in protecting the gastric mucosa against damage and, perhaps also in suppressing acid secretion, then dietary alterations that increase PG synthesis may be useful in the prevention or treatment of acid-peptic diseases. Recently, Grant et al added either 13.5 g or 27.0 g linoleic acid (C18:2n-6) to a normal Western diet of 9 normal men for 2-3 weeks. As shown in Table 4 below, the gastric juice concentration of PGE_2 and its major metabolite, DHK-PGE_2, increased on this diet. Linoleic acid had a small inhibitory effect on acid secretion (81). Although this study did not have a placebo control group (instead, each subject served as his own control), the results suggest that gastric PG synthesis can be enhanced by providing an ample supply of arachidonic acid precursor in the diet. Whether linoleic acid therapy protected the gastric mucosa from damage as a result of enhanced PG secretion was not studied.

TABLE 4. EFFECT OF LINOLEIC ACID ON GASTRIC PGs IN HUMANS (FROM REF. 81)

GASTRIC JUICE OUTPUT (ng/h)	BEFORE LINOLEIC ACID (MEAN ± SEM)	AFTER LINOLEIC ACID (MEAN ± SEM)
PGE_2	498 ± 110	1254 ± 465*
DHK-PGE_2	165 ± 18	1168 ± 645*

(* $P < 0.05$)

Hollander et al have reported that intragastric (but not intrajejunal) administration of arachidonic acid to rats marked increases gastric juice PG concentration and, at the same time, protected against gastric mucosal damage by alcohol (82). Protection by arachidonic acid was abolished by indomethacin pretreatment. Therefore, in rats dietary alterations are capable of enhancing gastric PG synthesis and, as a result, of protecting the mucosa against injury.

It has also been suggested that oral ingestion of mild gastric irritants, such as mildly hypertonic solutions or dilute ethanol (15-25%), can enhance gastric mucosal PG production and thereby protect the mucosa against damage by stronger irritants (e.g., markedly hypertonic solutions, absolute ethanol, etc). This phenomenon has been referred to by Robert as "adaptive cytoprotection" or, adaptive protection (83). While adaptive protection has been demonstrated repeatedly, including in our own laboratory (84; Figure 10), the evidence that protection is mediated by an enhanced PG synthesis is controversial. Most but not all studies have, like Robert, shown that adaptive protection in rats can be prevented by indomethacin, an inhibitor of PG synthesis (Figure 10). However, unlike Robert many investigators have been unable to demonstrate that PG synthesis is enhanced by mild irritants (85-87). Thus, whether adaptive protection is

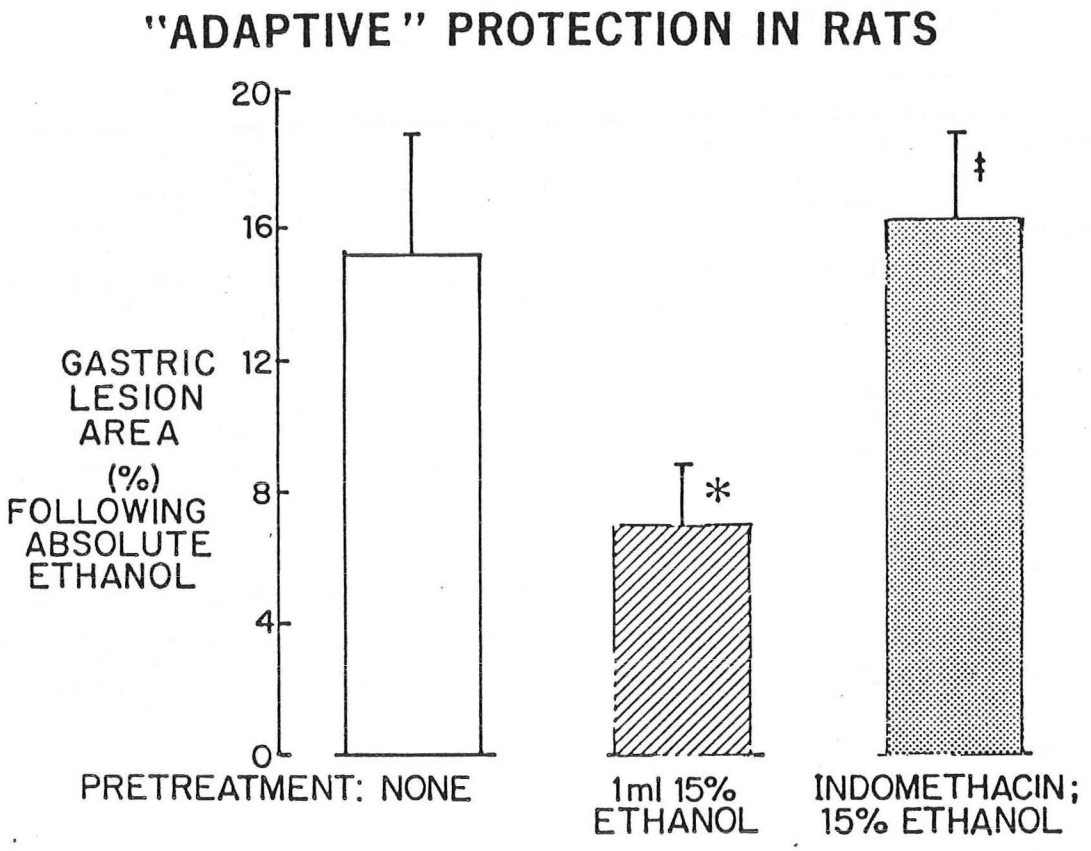


FIGURE 10. (DATA FROM REF. 84).

mediated by enhanced endogenous PG synthesis or some other mechanism is unknown, as is its clinical relevance. Nevertheless, a number of investigations have proposed that certain drugs that protect the gastric mucosa against damage do so by acting as a mild gastric irritant, possibly via enhanced PG synthesis. This mechanism has been proposed for sucralfate (88), but it is based on very little experimental data. Another compound that heals ulcers, carbenoxolone, is known to inhibit prostaglandin catabolism *in vitro* (89), although it is uncertain that this occurs *in vivo* after oral administration of this compound.

Dietary alterations that reduce PG synthesis might, theoretically, lower mucosal protection and predispose to mucosal injury. One dietary factor that has received recent attention is fish oils. Fish oils, unlike vegetable oils, are rich in omega-3 (n-3) fatty acids (90), such as eicosapentaenoic acid (EPA) (C20:5) and docosahexaenoic acid (DHA) (C22:6). While the function of DHA is largely unknown, DHA can be converted to EPA. When EPA and DHA are prominent in the diet, they have a number of actions that may affect PG metabolism. First, they inhibit the synthesis of arachidonic acid from dietary linoleic acid (Figure 2). Second, they compete with arachidonic acid for the 2-position in membrane phospholipids, reducing available arachidonic acid for conversion into 2-series PG products. Third, omega-3 fatty acids compete with available omega-6 fatty acids for cyclooxygenase and are converted into 3-series prostanoids (PGE_3, $PGF_{3\alpha}$, PGI_3, TxB_3, etc); they also compete for lipoxygenase and are converted to 5-series LTs (LTB_5, LTC_5, LTD_5, etc.). Addition of fish oil or linolenic acid (EPA precursor) to the diet of rats has been reported to reduce 2-series PG content in a number of tissues, including kidney and lung (91,92).

The net effect of all of the above biochemical alterations on gastric mucosal vulnerability to injury would be difficult to predict, since the magnitude of the reduction of 2-series PGs in the gastric mucosa is uncertain and the biological effects of 3-series PGs and 5-series LTs in the stomach are largely unknown. Our laboratory and others have been studying the effect of fish oils on the gastric mucosa (84,93). In rats, supplementation of the diet with 10% menhaden fish oil for a month reduced synthesis of 6-keto $PGF_{1\alpha}$ (the major prostanoid in the rat) by approximately 50% compared to animals fed corn oil, an omega-6 fatty acid (84) (Figure 11, left). This alone should enhance mucosal vulnerability to damage in fish oil fed rats. Furthermore, we recently found (94) that the 3-series prostaglandin $PGF_{3\alpha}$ is much less protective against alcohol-induced injury in rats than its 2-series analog, $PGF_{2\alpha}$ (Figure 12). If this were a general property of 3-series PGs, fish oil feeding might predispose the gastric mucosa to damage by ethanol by shifting synthesis of PGs into 3-series rather than 2-series compounds. In fact, just the opposite appears to be the case. Fish oil feeding protects the rat gastric mucosa against damage by ethanol (Figure 11, right) and perhaps also the human duodenal mucosa (95). Since fish oil does not protect against gastric mucosal injury by aspirin (96), we speculate that EPA is converted via the cyclooxygenase pathway to a prostanoid (other than $PGF_{3\alpha}$) which is more protective than its corresponding 2-series prostanoid.

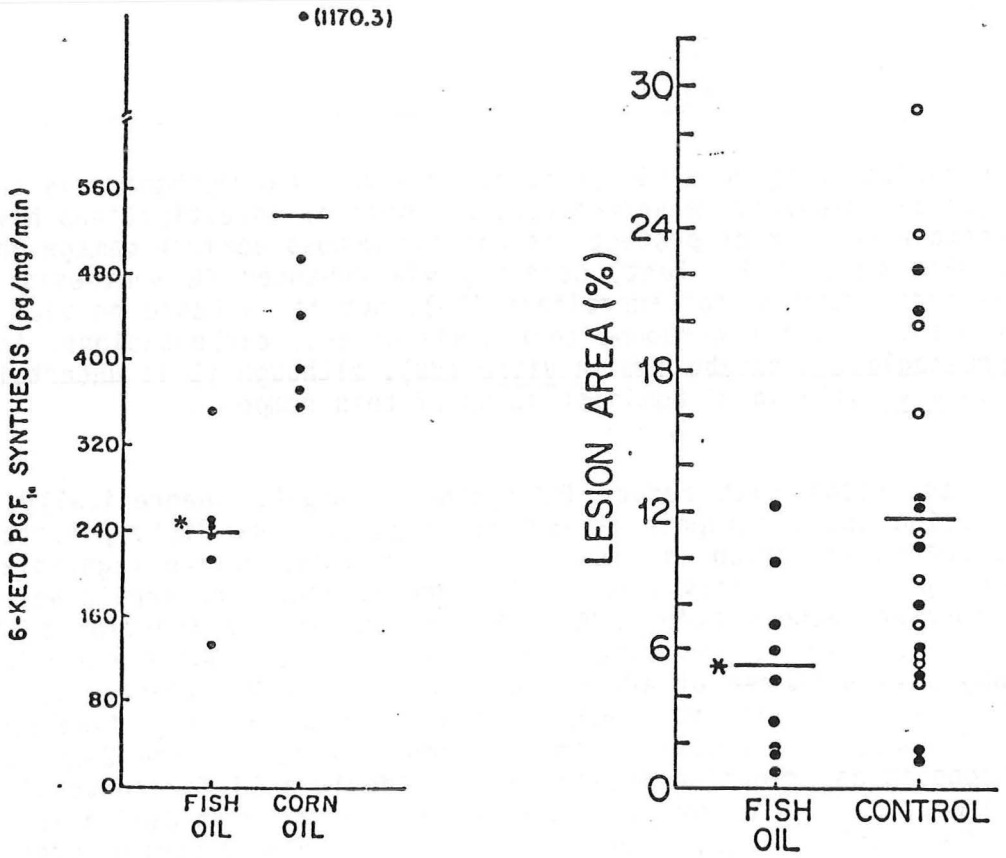


FIGURE 11. EFFECT OF 10% FISH OIL ON GASTRIC MUCOSAL PG SYNTHESIS (LEFT) AND ALCOHOL-INDUCED GASTRIC MUCOSAL LESION AREA (RIGHT) IN RATS (FROM REF. 84).

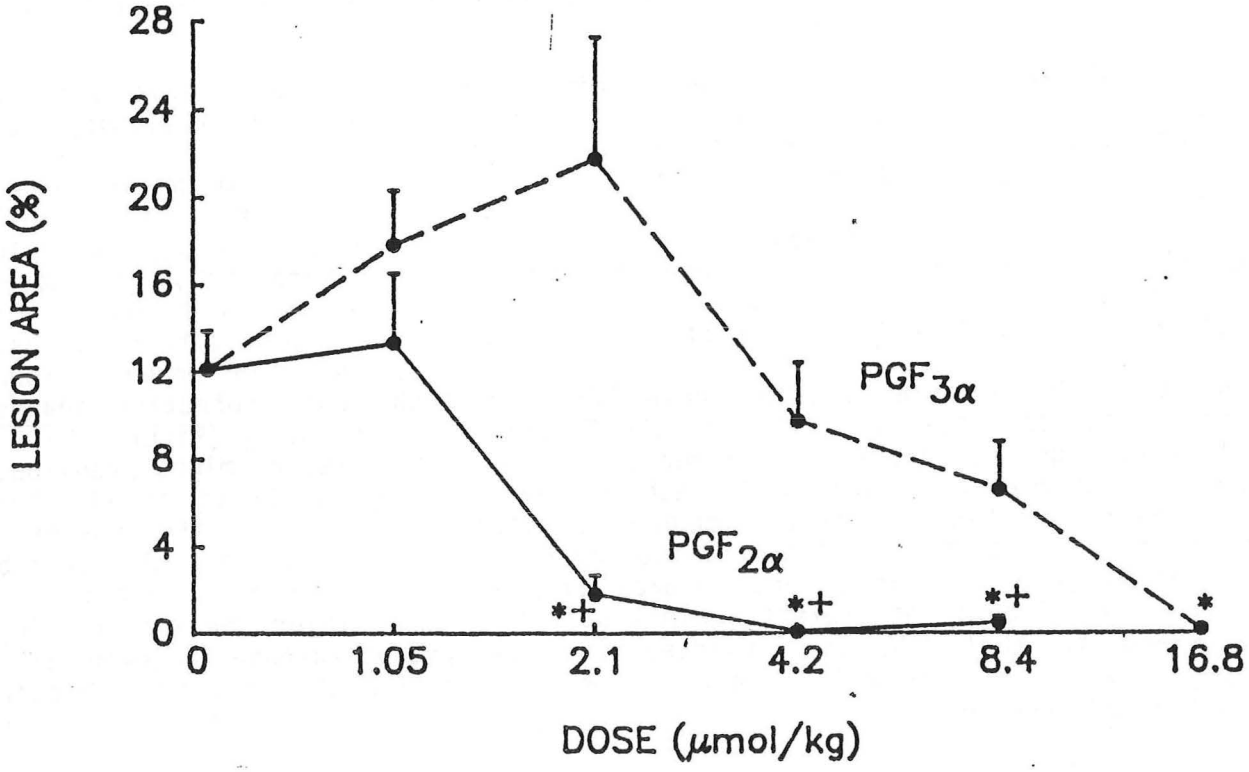


FIGURE 12. EFFECT OF VARIOUS SUBCUTANEOUS DOSES OF $PGF_{2\alpha}$ OR $PGF_{3\alpha}$ ON ALCOHOL-INDUCED GASTRIC MUCOSAL DAMAGE IN RATS (FROM REF. 94).

IS DEFICIENT GASTRIC MUCOSAL PG SYNTHESIS RESPONSIBLE FOR GASTRIC ULCER DISEASE IN HUMANS?

There are several reasons to propose that a gastric mucosal deficiency of PGs may predispose to gastric ulceration in humans.

1. NSAIDs, which reduce PG synthesis by blocking cyclooxygenase, cause gastric ulcers (GU) in humans. Between 10-25% arthritics taking NSAIDs chronically have GUs at endoscopy (97-100). The relative risk is increased 3-16 fold (100). These ulcers range from asymptomatic or painful ulcers to ulcers complicated by bleeding or perforation (101-109).

2. As described above, antibodies to PGs lead to GUs in animals, sometimes complicated by perforation or penetration (71).

3. Most (95% or more) GU patients secrete normal amounts, or even reduced amounts, of hydrochloric acid and pepsin. This implies that ulceration occurs as a result of an impaired mucosal defense rather than as a result of increased aggressive factors (acid-pepsin). As PGs are among the major defenders against mucosal damage, PG deficiency could contribute to some cases of GU (110,111).

Several studies have attempted to compare gastric mucosal PG synthesis or content in patients with GU and in non-GU controls, searching for a primary PG-deficiency state that may precede gastric ulceration. The studies are limited by the following factors: (a) relatively small numbers of GU patients; (b) not separating active from inactive GU patients; (c) not vigorously excluding use of aspirin and NSAIDs in GU patients; (d) including patients with dyspeptic symptoms undergoing endoscopy as controls rather than normal individuals; (e) inadequate control for sex and age; and (f) methodologic problems in measuring mucosal PG synthesis. Moreover, studies of this nature evaluate PG synthesis after GU has developed, not before. Therefore, it is difficult to determine whether abnormalities are causal or a secondary effect of the ulceration process itself.

Studies comparing gastric mucosal PGs in gastric ulcer patients and controls are summarized in Table 5. (The role of gastroduodenal PGs in duodenal ulcer disease is beyond the scope of this discussion; interested readers should consult references 111, 114, and 117-125.)

TABLE 5. GASTRIC MUCOSAL PGs IN PATIENTS WITH GASTRIC ULCER (GU)

REF	COUNTRY(YR)	GU PATIENTS	CONTROLS	FINDINGS IN GU PATIENTS
112	Germany '77	18	8 Patients	↑ antral PGE and F content in active GU; ↑ F in inactive GU
113	S.Africa '82	28	7 Normals	↓ PGE_2 in fundic (body) and antral mucosa
114	Poland '84	12	25 Normals	↓ PGE_2 and 6-keto $PGF_{1\alpha}$ in fundic (body) mucosa
115	Japan '86	24	16 Normals	↓ antral and fundic mucosal PGE_2 and 6-keto $PGF_{1\alpha}$ content;
116	UK '86	27	43 Patients	No change in fundic mucosal PGE_2 or TxB_2 synthesis
117	UK '87	10	29 Patients	↓ PGE_2 synthetic capacity and degradative capacity

A number of comments, besides those listed above, can be made about the studies summarized in Table 5.

1. Three studies used patients undergoing endoscopy as controls. Although these patients did not have gastric ulcers, their use as controls is questionable since some may have had gastric disease (e.g., gastritis). Not all studies included histologic assessment of the mucosa to exclude gastritis in controls (112).

2. Of the six studies, four found a significant decrease in PGs, one found no significant change, and only one found an increase (this study by Schlegel was in 1977 and did not use histology). All three studies that used normal controls, rather than patient controls, found decreased PG synthesis in GU patients.

3. The effect of inflammation (gastritis) on PG levels was confusing. Many patients with GU have gastritis (126). Schlegel found that not only did his GU patients have an increased PG content, but so did patients with gastritis (112). However, gastritis was not defined and histologic studies were not performed (112). Hawkey found that PG levels were higher if the mucosa was inflamed, whether GU was present or not (116). On the other hand, Crampton found that the reduced PGE_2 synthetic capacity in GU patients was unrelated to gastritis; in fact, gastritis tended to increase this synthetic capacity (117). Furthermore, Wright found that the reduced PGE_2 content of antral mucosa in GU patients was associated with histologic chronic atrophic gastritis (113).

4. One study (113) suggested that low PGE_2 levels in GU patients were predictive of poor GU healing. Additional studies are needed to confirm this.

5. PG levels were higher at the ulcer edge than in the rest of the gastric mucosa in two studies (113,115) but not in another (116).

6. No studies, as yet, have been carried out in the United States. Our laboratory is currently carrying out an NIH-funded controlled study in which PG content and synthesis is being measured in the gastric body, antrum, duodenal bulb, and post-bulbar duodenum in a large number of patients with active GU, healed GU, active DU, healed DU, and healthy controls. In addition, histology will be carried out, as well as an assessment of Campylobacter pylori-associated gastritis.

I believe that the current experimental data favor the hypothesis that PG deficiency may be present in individuals who develop gastric ulceration, even in the absence of NSAID ingestion. However, this hypothesis will require rigorous experimental confirmation before it can be fully accepted.

Risk Factors for Gastric Ulcer. Role of Prostaglandins

Unlike duodenal ulcer, male gender is not a risk factor for GU (i.e., women and men are affected equally). However, there are a number of demographic and behavioral risk factors for human gastric ulcer disease (126). It is possible that some of the risk factors, listed in Table 6, may predispose to GU by affecting PG synthesis or catabolism.

TABLE 6. RISK FACTORS FOR GASTRIC ULCER

Intake of aspirin or NSAIDs
Age
Smoking
Family history of GU
Stress

NSAIDs. Chronic ingestion of NSAIDs is probably the strongest risk factor for GU (68,100). Even in individuals taking "low dose" aspirin for prevention of myocardial infarction (1 g/day), the incidence of GU is increased 5- to 6-fold (127). For example, only 5 of 2257 placebo-treated patients were hospitalized for ulcer problems over a 3-year period compared to 27 of 2267 aspirin-treated patients. In arthritis patients taking various NSAIDs (e.g. ibuprofen, piroxicam, naproxen, others), 10-25% have gastric ulcers at any point in time. NSAID-induced gastric ulcers are associated with a higher incidence of bleeding and perforation (101-109), as reviewed by Dr. Peterson in February at Grand Rounds.

NSAIDs can also cause acute gastric mucosal injury. Thus, after one or a few doses of aspirin or an NSAID, the gastric mucosa endoscopically appears red and edematous and contains a variable number of petechial, submucosal hemorrhages and superficial erosions. [An erosion is defined as a shallow break in the mucosa that, histologically, does not extend through the muscularis mucosa. An ulcer extends through the muscularis mucosa into the submucosa or muscularis propria and thus has depth visible through the endoscope.] The antrum and fundus tend to be involved equally in acute NSAID damage, which some refer to as NSAID-gastropathy. Patients with acute gastric mucosal injury of this nature are often asymptomatic but may have dyspeptic symptoms (pain, nausea, vomiting, heartburn). An occasional patient given NSAIDs will acutely develop bleeding, with occult blood in the stool, melena, or hematemesis. The relationship between this acute gastric mucosal damage by NSAIDs or aspirin, which usually resolves even though the NSAID is continued (gastric adaptation; see ref. 69), and the subsequent development of chronic gastric ulcers is uncertain. It is uncertain what percentage of all GUs are associated with chronic NSAID use; at the Dallas VA Medical Center it is more than 50%. As discussed earlier, PGs are thought to play a major role in the pathogenesis of NSAID-induced ulcers.

Age. Gastric ulcer is rare before age 40 and the peak incidence is between ages 55-65 (126). One may wonder whether PG synthesis declines with aging. This topic has not been studied adequately. Although studies have reported no correlation between age and mucosal PGs in groups of controls of various ages (Table 5), these studies are by no means definitive. In rats, gastric mucosal damage by aspirin and various NSAIDs is less pronounced in juvenile rats than in

adults, but whether this is due to an exaggerated suppression of PG synthesis by NSAIDs was not studied (128). A recent study in rats suggests that this is not the case (129).

Smoking. Cigarette smoking is a risk factor both for GU and for DU, by an uncertain mechanism. Smoking also delays ulcer healing and predisposes to ulcer recurrences (126,130). In 1985, McCready et al reported that smoking 3 cigarettes reduced, by almost 50%, output of PGE_2 into gastric juice during intravenous pentagastrin infusion while inhibiting gastric fluid output by around 30% (131). More recently, Quimby et al demonstrated that smoking 4 cigarettes decreased fundic and antral mucosal PGE_2 and 6-keto $PGF_{1\alpha}$ synthesis by approximately 25-40% (132). Thus, smoking could predispose to GU, at least in part, by suppressing PG synthesis. The combination of smoking and aspirin use, common in ulcer patients (133), would seem to be especially hazardous. The mechanism by which smoking reduces PG synthesis is uncertain, as is the effect of smoking on PG catabolism. Recently, Sato reported that cigarette smoking decreases gastric mucosal blood flow in humans and leads to mucosal hypoxemia, effects that could be mediated by reduced PG synthesis; these changes were prevented by misoprostol (200 µg) but not by cimetidine (134).

Genetic Factors. First-degree relatives of patients with GU have a 3-fold increased of GU, but not DU (126). Twin siblings of GU patients have high risk of GU, but not DU. However, concordance for GU in identical twins is not 100%, indicating the need for an interaction between environmental and genetic factors. How genetic predisposition to GU is mediated physiologically or biochemically is unknown; a role of PGs is possible but only speculative at present.

Stress. Major trauma, burns, sepsis and severe medical illness are associated with acute gastric and duodenal mucosal erosions and ulcers (135). These "stress ulcers" usually present clinically as occult or gross GI bleeding. The pathogenesis of these lesions is multifactorial and not completely understood. Therefore, the possible role of PGs is uncertain.

A recent abstract reported that gastric mucosal PGE_2 (but not 6-keto $PGF_{1\alpha}$) synthesis was reduced by around 40% in rats subjected to cold restraint stress for 2 or 4 hours, during which time acute "stress ulcers" occurred (136). Of interest, chronic mild restraint for 10 days actually increased fundic PGE_2 and 6-keto $PGF_{1\alpha}$ synthesis and protected rats against gastric mucosal damage by ethanol (137,138).

While emotional stress is increased in patients with GU, as well as in DU patients (133), the relationship between emotional stress and PG synthesis in humans has not been reported as yet.

ARE PG ANALOG DRUGS EFFECTIVE IN HUMAN GASTRIC ULCER DISEASE?

First, I will discuss the role of PGs analogs in healing gastric ulcers. Then, I will review the use of these agents in the prophylaxis of GU. The chemical structures of several of these compounds are shown below (Figure 13).

PROSTAGLANDINS UNDER CLINICAL INVESTIGATION FOR GASTROINTESTINAL DISEASES

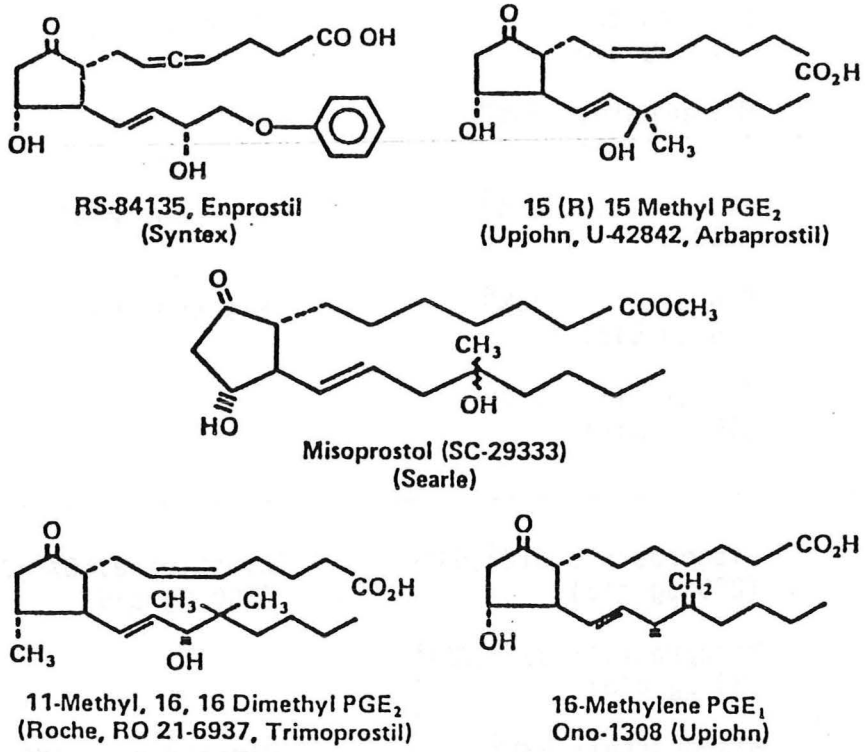


FIGURE 13.

Therapy of Active GU

There are 3 placebo-controlled studies evaluating the effect of PG analogs on GU healing (Table 7), two with misoprostol (a PGE_1 analog) and one with enprostil (a PGE_2 analog). In all 3 studies, the PG analog was more effective in healing GU than was placebo. Doses of PG analogs that facilitated GU healing significantly were all acid antisecretory.

As shown in Table 7, 3 additional studies compared PG analogs with H_2-blockers. In all 3 studies, there was no significant differences in GU healing rates between the highest dose of PG analog tested and the H_2-blocker, although healing rates were numerically a bit lower with the PG analogs. As these PG analog drugs also produce side effects (diarrhea and uterine cramps), they are not approved by the Food and Drug Administration (FDA) for use in therapy of active GU (see below).

TABLE 7. EFFECT OF PG ANALOGS ON GU HEALING

REFERENCE	PG ANALOG:HEALING RATE	COMPARATOR:HEALING RATE
139	Misoprostol: 62%[8] (100 µg qid)	Placebo: 45%[8]
	Misoprostol: 50%[8] (25 µg qid)	
140	Misoprostol: 67%[8] (200 µg qid)	Placebo: 26%[8]
141	Enprostil: 70%[6] (70 µg bid)	Placebo: 50%[6]
	Enprostil: 82%[6] (35 µg bid)	
142	Misoprostol: 51%[4];64%[8] (200 µg qid)	Cimetidine:58%[4];70%[8] (300 mg qid)
	Misoprostol: 39%[4];38%[8] (50 µg qid)	
143	Misoprostol: 58%[4] (200 µg qid)	Cimetidine: 60%[4] (300 mg qid)
	Misoprostol: 41%[4] (50 µg qid)	
144	Enprostil: 58%[4];80%[6];86%[8] (35 µg bid)	Ranitidine:66%[4];84%[6];89%[8] (150 mg bid)

4, 6, 8 = healing rate at 4, 6, or 8 weeks

In summary, PG analogs appear to be almost as good as H_2-blockers in healing GU (and also DU), but the doses required for healing are associated with more side effects. H_2-blockers remain the treatment of choice for GU healing. There are anecdotal reports that PG analogs can heal gastric ulcers resistent to H_2-blockers (145), but controlled studies are lacking.

Prevention of GU

In the United States, there are only about 3.5 new cases of GU per year for each 10,000 adults (146). Needless to say, cost-effective prevention of new GU cases would require identification of a group of individuals at especially high risk for this disease. While certain individuals at increased risk could be

chosen for preventive therapy, such as first-degree relatives of GU patients or cigarette smokers, the relative risk of GU in such individuals may not be sufficiently high to obligate the cost and potential side effects of prophylactic therapy.

There are two populations of individuals being considered for prophylactic therapy because of the high frequency of GU in these patients and because of the potential for serious ulcer complications. These include ICU patients (those with major trauma, serious burns, sepsis, or serious medical illnesses) and outpatients receiving NSAIDs chronically.

In the acute ICU setting, gastric and duodenal mucosal lesions (erosions/ulcers) occur early in the course of the underlying illness, usually within a few to several days (135). These acute mucosal lesions can be prevented by conventional anti-ulcer therapy, including intravenous H_2-blockers or oral or nasogastric administration of antacids or sucralfate (Carafate). The role of PGs in the pathogenesis of this injury is unclear, as is the potential protective role of exogenous PG analogs for these patients.

The major role for the new, synthetic PG analogs appears to be in the prevention of chronic gastric ulcers associated with NSAID therapy, since the incidence of GU in these patients is high and since ulceration may be associated with complications (bleeding, perforation) in a substantial proportion of patients. Unlike acute mucosal injury in ICU patients, there is very little evidence that H_2-blockers, antacid, or sucralfate are effective in preventing chronic GU in NSAID users, as reviewed recently by McCarthy (147). There is increasing, but still incomplete evidence, that PG analogs such as misoprostol (Cytotec, G.D. Searle) will fulfill this preventive role.

As reviewed earlier, aspirin and NSAIDs can produce acute gastric and duodenal mucosal injury and, later on, chronic gastric ulcers. In general, aspirin causes more acute mucosal injury than other NSAIDs (148,149). Buffered aspirin is about as damaging acutely as unbuffered aspirin, while enteric-coated aspirin appears less damaging (97,149). The high incidence of chronic gastric ulcers in aspirin-users appear to be unaffected by buffering the aspirin, while enteric-coated aspirin less commonly leads to chronic GU (97). Whether non-aspirin NSAIDs vary in their propensity to produce acute injury or chronic ulcers is not clear; some studies suggest the various agents differ and others suggest they are all equally ulcerogenic. Unfortunately, there appears to be no relationship between frequency or severity of acute injury with an NSAID and the incidence of chronic ulcers.

Initial studies of PG analogs evaluated a protective effect against acute NSAID damage, assessed endoscopically. The clinical relevance of such studies is uncertain because most subjects given NSAIDs develop some acute damage, while symptoms are rare and do not correlate with mucosal damage. Nevertheless, studies with misoprostol (150-153), arbaprostil (154), and enprostil (155-157) have shown significant protection against acute gastric and duodenal mucosal damage induced by ibuprofen (152), tolmetin (150) and aspirin (151,153-157). In one such acute study by Jiranek et al, in which 3.9 g of aspirin was given to normal subjects daily for a week (3.9 g/day), ulcers were present in a substantial proportion of placebo-treated subjects and in a much lower proportion of misoprostol-treated subjects (Table 8).

TABLE 8. PROTECTIVE EFFECT OF MISOPROSTOL ON ASPIRIN-INDUCED GASTRIC ULCER (GU) AND DUODENAL ULCER (DU) IN HEALTHY VOLUNTEERS (FROM REFERENCE 153)

	MISOPROSTOL DOSE q.i.d.			
	0 (Placebo)	50 µg	100 µg	200 µg
INCIDENCE OF GU (DAY 7)	43%	0%	3%	0%
INCIDENCE OF DU (DAY 7)	14%	3%	0%	0%

Whether such acute protection represents a major clinical advance is unclear. Symptoms were similar or even increased (152), in PG-treated patients. Moreover, in various acute studies, H_2-blockers protect against injury by aspirin, although this protection may not extend to other NSAIDs (147). Whether PG analogs are superior to H_2-blockers in preventing acute NSAID injury is unclear, but this is quite possible. Of interest, misoprostol has been reported to be more protective than cimetidine against acute, alcohol-induced gastric mucosal damage in non-human primates and in humans (158,159).

More recently, investigators have tried to prevent GU in chronic NSAID users. As mentioned already, there is little evidence that currently available agents (H_2-blockers, sucralfate or antacid) are effective in preventing ulcers in this setting (147).

An important multicenter study on this topic was reported recently by Graham, Agrawal and Roth (99). They endoscoped more than 500 osteoarthritis patients who (a) were receiving chronically one of three NSAIDs: ibuprofen, piroxicam, or naproxen; (b) were not receiving any "anti-ulcer" drugs other than antacids, and (c) had abdominal pain. Women of childbearing potential were excluded due to the known uterotonic effects of misoprostol. Twenty-five percent of the patients screened had a gastric ulcer and were excluded from the prevention study. These patients were randomized to receive therapy for up to 8 weeks with either misoprostol (100 or 200 µg qid) or placebo; healing results have not yet been published, but based on healing studies already reviewed (Table 7), it is likely that misoprostol will be shown to be effective.

The remaining 420 patients without gastric ulcers were randomly assigned to a one of three regimens (Table 9). Patients were then re-endoscoped 1, 2, and 3

TABLE 9. EFFECT OF MISOPROSTOL ON GASTRIC ULCER (GU) IN ARTHRITIS PATIENTS CHRONICALLY RECEIVING ONE OF THREE NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs). (FROM REF. 99).

	PLACEBO (N=138)	MISOPROSTOL (100 µg qid) (N=143)	MISOPROSTOL (200 µg qid) (N=139)
CUM. FREQ. OF GU ON NSAID[a]	22%	6%	1%
CUM. FREQ. OF DIARRHEA	13%	25%	39%

a ibuprofen, piroxicam, or naproxen

months later, looking for ulcers, which were defined by the authors as "... circumscribed breaks in the gastric mucosa of 0.3 cm or greater". Subjects were allowed up to 4 aluminum hydroxide antacid tablets per day for dyspepsia. Aldominal pain and side effects were also assessed.

After one month the frequency of GU was 17/138, 3/143, and 1/139 with placebo, 100 µg misoprostol qid and 200 µg misoprostil qid. By the end of the 3-month study, 30 placebo-treated patients had ulcers (21.7%), compared to 8 (5.6%) and 2 (1.4%) of low- and high-dose misoprostol-treated patients (Table 9). These differences were highly significant ($P<0.001$), although a dose-response with misoprostol was not clearly demonstrated.

Despite the impressive protection against GU by misoprostol, placebo-treated patients in the study did not necessarily fare worse than misoprostol-treated patients. For example, by the end of the 3-month study 57% of placebo-treated patients no longer had abdominal pain, compared to around 70% of misoprostol-treated patients, an insignificant difference. Moreover, as shown in Table 9, diarrhea was considerably less frequent in placebo-treated subjects. The frequency of ulcer perforation and bleeding was not reported, but presumably was quite low in all groups.

This important study was a major reason for FDA approval of misoprostol "for prevention of NSAID-induced gastric ulcers in patients at high risk of complications from a gastric ulcer, eg, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer." While these recommendations may seem logical, they do not necessarily derive from studies such as Graham's. As with other new drugs, the eventual role of misoprostol will gradually be defined in the next few years (post-marketing). Since it is now available by prescription, I will try to make some recommendations for use of this drug at present.

WHEN SHOULD MISOPROSTOL (CYTOTEC) BE USED?

Gastric Ulcer. Misoprostol should not be used to heal active GU. Instead, an H_2-blocker should be used, along with prn antacid. If a patient is receiving misoprostol as a prophylactic agent and yet develops a gastric ulcer on NSAIDs, misoprostol should be stopped (as should the NSAID, if possible) and the patient treated with an H_2-blocker for 6-12 weeks until complete ulcer healing has occurred.

In my opinion, misoprostol should be used as a GU prophylactic agent in certain patients receiving NSAIDs chronically. These are patients with a documented history of GU in the past. If such a patient had bled from a GU in the past or has had a perforated ulcer and absolutely must receive an NSAID, the use of misoprostol is logical. A dose of 100 µg misoprostol qid should be chosen initially, to reduce the risk of diarrhea. If this dose is well-tolerated, the physician may choose to increase the dose after a few weeks to 200 µg qid. (These dosage recommendations are at slight variance with FDA quidelines, in which the higher dose is recommended initially and the lower dose used if the higher cannot be tolerated). If possible, misoprostol can be started several days to a week or two prior to beginning NSAIDs. However, there is no evidence that the drug prevents ulcer complications. Alternatives to NSAID therapy (e.g., gold or pulse, low-dose methotrexate for rheumatoid arthritis) should seriously be considered.

Misoprostol (Cytotec) is available as 200 µg tablets. These tablets are scored so that they can be divided in half. It is likely that 100 µg tablets will be available soon. Misoprostol is not yet available as a liquid solution or for parenteral administration.

Misoprostol is extensively and rapidly absorbed from the GI tract and rapidly de-esterified at carbon 1 to its free acid, which is the active compound. The side chains of misoprostol acid are oxidized and the =O of the cyclopentane ring is reduced to -OH, giving rise to PGF-analog metabolites which are excreted mainly in the urine. However, no misoprostol dosage adjustment is recommended for patients with impaired renal function (160).

Food delays absorption of misoprostol but does not reduce ultimate availability, whereas total availability is reduced by concomitant antacid use. Drug-drug interactions of clinical significance between misoprostol and other drugs have not yet been reported. This includes drugs metabolized by the cytochrome P450 enzyme system in the liver (mixed function oxidase) and NSAIDs themselves. Furthermore, there is no evidence that misoprostol interferes with the analgesic or anti-inflammatory properties of NSAIDs.

The major concern about misoprostol is its use in women of childbearing potential. This drug can cause vaginal bleeding, uterine cramps, hypermenorrhea, and dysmenorrhea, although the incidence of each is less than 1%. The drug has abortifacient properties and its use in pregnant women is dangerous.

The per patient cost of a 30-day supply of misoprostol (Cytotec) in Dallas ranges from $64.80 to $73.08. Thus, a year of prophylactic therapy costs around $840. This is comparable to the cost of a year's worth of ranitidine (Zantac) in a dose of 150 mg twice daily.

In my opinion, the routine use of misoprostol in other patients on NSAIDs, including the elderly with no previous history of GU, is not yet justified, although preliminary cost analysis studies such that they could be of benefit (161).

Duodenal Ulcer. Misoprostol is almost as effective as H_2-blockers in healing DU (7), but are not yet approved for this indication. Therapy of choice for active DU includes an H_2-receptor antagonists or Carafate (1 gm a.c. and h.s.) for 4-8 weeks.

Misoprostol is less effective than ranitidine in preventing relapses of DU (162). There is little evidence that misoprostol can prevent DU in patients receiving chronic NSAID therapy (99). Fortunately, NSAID-related DU is considerably less common than GU, so that misoprostol still markedly reduces overall ulcer incidence (GU plus DU) in chronic NSAID users. In contrast to misoprostol, H_2-blockers such as ranitidine can prevent DU on chronic NSAID therapy (147,163). Thus, for the patient with a history of documented DU in the past, either uncomplicated or complicated, it seems prudent to treat them with prophylactic H_2-blockers in full doses (e.g., 150 mgm ranitidine bid). There may be an occasional patient with both prior GU and DU in whom prophylaxis with both misoprostol and H_2-blockers while on NSAIDs is warranted, although there are no studies as yet on this combination in patients on NSAIDS chronically. Combination therapy should be considered rarely due to its high cost.

Small Intestinal Inflammation. While not easily recognized clinically, NSAIDs can induce distal small intestinal ulceration and/or inflammation in both humans and animals (164-166). Using ^{111}indium-labeled leukocytes, Bjarnason et al reported that two-thirds of chronic NSAID users have small intestinal inflammation, especially in the ileum (166). The mechanism for this lesion is uncertain, although one hypothesis is: NSAID → ↓ intestinal PG synthesis → ↑ intestinal permeability to luminal antigens → penetration of antigens into the intestinal wall → inflammation in wall of intestine. In support of this theoretical sequence, when various probe molecules that are absorbed by different mechanisms are perfused through the gut, NSAIDs selectly increase permeability of molecules such as ^{51}chromium-EDTA that are absorbed passively through paracellular pathways. Furthermore, misoprostol prevents this NSAID-induced increase in small intestinal permeability to ^{51}Cr-EDTA (167). The clinical relevance of these observations remains to be clarified.

Non-GI Uses. It is likely that misoprostol and other PG analogs will have application in other areas as well. As an example, NSAIDs are known to impair renal function and this process is thought to be partly mediated by a decrease in renal PG synthesis (168). It is possible that misoprostol may protect against this decrement in renal function. Studies of this renal protective effect are anxiously awaited.

Acknowledgement. I wish to thank Mrs. Vicky Robertson for her outstanding assistance in preparing this protocol and to the Medical Media crew at the Dallas VA for their photographic assistance.

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