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Perspective

Development and Therapeutic Role of Synthetic Prostaglandins in Peptic Ulcer Disease

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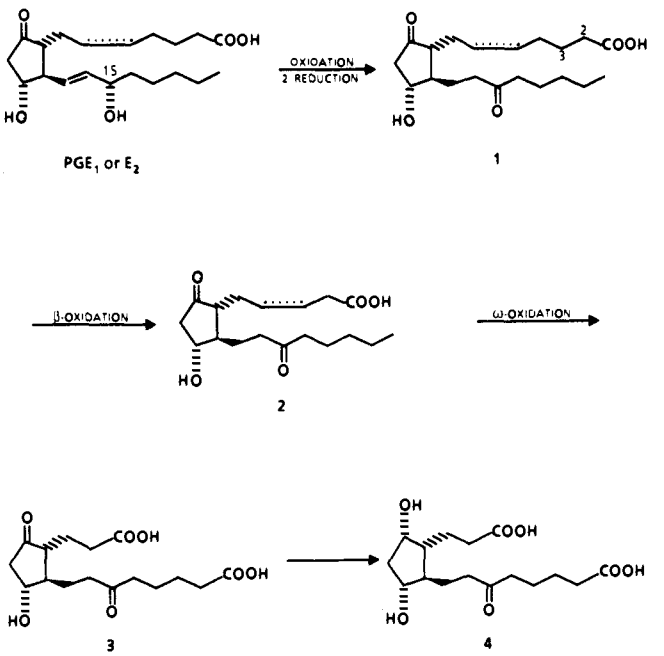
The mid 1960s were a time of great excitement in the prostaglandin field. These naturally occurring substances had been "rediscovered" following a quiescent period during and after World War II, and research into all aspects of this area was intense in academic and industrial laboratories. The potential use of prostaglandins as treatments and cures in a vast array of disease and therapeutic categories was awesome. They were anticipated to be useful in fertility control, labor induction, male infertility, asthma, arthritis, peptic ulcer disease, hypertension, platelet dysfunction, nasal congestion, and even periodontal disease. Indeed, prostaglandins were referred to as the "steroids" of the 1970s. History has not borne out the early enthusiasm. The primary prostaglandins and their synthetic analogues have failed to find utility in many important therapeutic areas such as arthritis and asthma, while for other indications the pathway from laboratory to market has been unduly long. The development of synthetic prostaglandins for peptic ulcer disease has been no exception. The progress toward market for antiulcer prostaglandins has been impeded by three major problems which will be discussed in detail in this Perspective as well as minor ones associated with each individual compound. It now appears, however, that this therapeutic area will provide significant rewards for perservering research efforts in the prostaglandin field. One synthetic analogue, misoprostol, is currently marketed in Mexico and Switzerland, approved in several other countries, and is under consideration for approval in most major markets. In addition, a second compound, enprostil, was recently approved in Mexico, and a number of other synthetic prostaglandins are in clincal study (Table I).

Disadvantages of Natural Prostaglandins

The discovery that naturally occurring prostaglandins of the E series inhibit gastric secretion was made in 1967 by Robert et al.[1] Subsequent research in a number of laboratories soon established three critical drawbacks of the natural prostaglandins which would have to be overcome if their potential as a treatment for peptic ulcer disease were to be realized. These problems were (1) rapid metabolism which was manifested as a lack of oral activity and a short duration of action when administered parenterally, (2) incidence of numerous side effects, and (3) chemical instability.

Scheme I. Metabolism of Natural Prostaglandins



The natural prostaglandins are subject to three major modes of enzymatic degradation (Scheme I) in animals and man. The most rapid of these processes is oxidation of the 15-hydroxy group to the corresponding ketone and subsequent reduction of the 13,14-double bond. The resulting metabolite 1 is virtually devoid of biological activity. The second process is β oxidation of the carboxylic acid chain (α chain), a reaction common to fatty acids in general. This reaction sequence involves dehydrogenation at carbons 2 and 3, followed by oxidation to give the 3-ketone and finally cleavage to produce the dinor metabolite **2** and acetic acid. A second sequence usually occurs to generate the tetranor metabolite. The third point of attack is the ω chain terminus. Oxidation occurs either at carbon 20 to give the corresponding alcohol and subsequently the acid **3** or at carbon 19 to produce the 19-hydroxy metabolite. The major urinary metabolite of natural prosta-

(1) Robert, A.; Nezamis, J. E.; Phillips, J. P. *Am. J. Dig. Dis.* **1967**, *12*, 1073.

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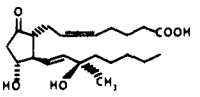
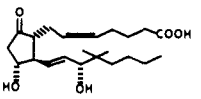
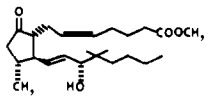
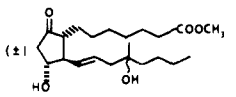
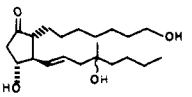
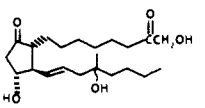
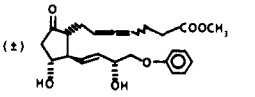
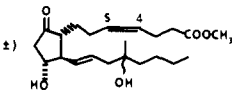
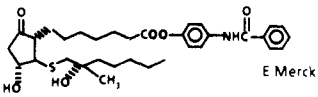
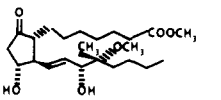
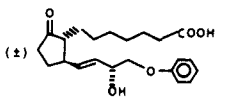
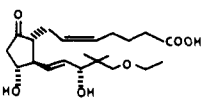
Table I. Synthetic Prostaglandins under Development for Peptic Ulcer Disease

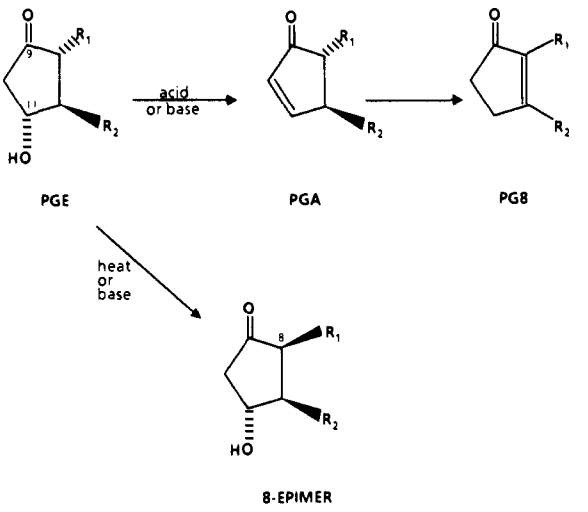
COMPOUND	STRUCTURE	COMPANY	APPROXIMATE CLINICAL STATUS
(15R)-15-Methyl PGE_2 Arbaprostil		Upjohn	PHASE III
16,16-Dimethyl PGE_2		Upjohn	PHASE II/III
Trimoprostil		Hoffman LaRoche	PHASE II
Misoprostol		Searle	PHASE III
Rioprostil		Miles, Ortho and Bayer AG	PHASE I
CL-115,574		Lederle	PHASE I
Enprostil		Syntex	PHASE III
Enisoprost		Searle	PHASE I
EMD-33,290 Tiptostanide		E Merck AG	PHASE I
MDL-646		Lepetit	PHASE I
M&B 28,767		May & Baker	PRECLINICAL
HOE-260		Hoechst	PRECLINICAL

glandins is 4, which is the product of all three of these oxidative processes plus the reduction of the carbonyl group at carbon 9.

The natural prostaglandins display a wide variety of side effects when administered systemically to animals and man. For example, in laboratory animals, effects such as rhinorrhea, trembling, retching, emesis, and diarrhea are routinely observed with PGE_1 and occur even at effective gastric antisecretory doses.[2] In man the symptoms associated with the administration of prostaglandins include erythema of the face, headache, abdominal cramps, hypotension, hyperthermia, and shivering.[3,4] Natural prostaglandins also have significant actions on the reproductive and cardiovascular systems. While desirable for certain indications such as estrus synchronization, cervical dilatation, hypertension, and platelet dysfunction, these activities must be considered as troublesome side effects when prostaglandins are given to treat peptic ulcer disease. In fact, potential side effect problems exist for any organ system in which prostaglandins play a biological role. An indication of the magnitude of this problem is the finding that PGE_1 produced cortical hyperostosis in infants.[5]

Natural and synthetic prostaglandins of the E type are inherently unstable compounds. Their instability is primarily due to the lability of the β-hydroxy ketone system in the cyclopentane ring. Under acidic or alkaline conditions, there is a strong driving force for elimination of the 11-hydroxy group as water to give the more stable α,β-unsaturated ketone system of PGA (Scheme II). The

Scheme II. Degradation Products of E Prostaglandins



A form can also isomerize to the PGB derivative under the same conditions. In general, esters or other carboxylic acid derivatives are more stable than the corresponding free acids, which are sufficiently acidic to catalyze their own dehydration. E-type prostaglandins also suffer from susceptibility to inversion of the α chain under alkaline or thermal conditions to give the 8-epimer. These stability problems are more serious than they may appear and have been a major stumbling block in the development of many of the synthetic prostaglandins.

Development of Synthetic Analogues

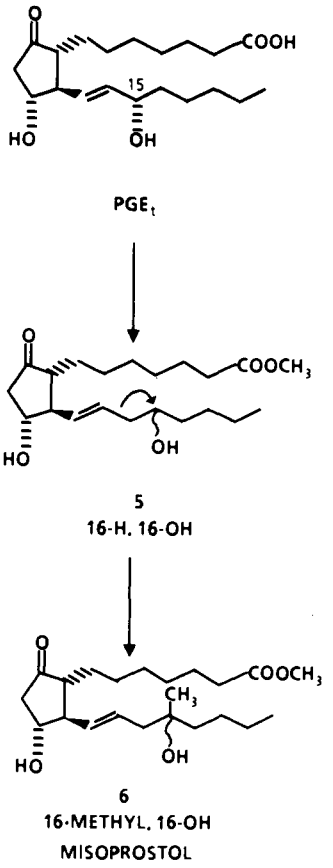
Consideration of one or more of these three disadvantages of natural prostaglandins have played a role in the development of most, if not all, of the synthetic prostaglandins for peptic ulcer therapy (Table I). The first major advance in this area was the substitution of methyl groups

(2) Dajani, E. Z.; Driskill, D. R.; Bianchi, R. G.; Collins, P. W.; Pappo, R. *Prostaglandins* **1975**, *10*, 733.
(3) Bergström, S.; Carlson, L. A.; Ekelund, L.-G.; Oro, L. *Acta. Physiol. Scand.* **1965**, *64*, 332.
(4) Dingfelder, J. R.; Brenner, W. E. *Acta. Obstet. Gynecol. Scand.* **1978**, *57*, 35.
(5) Ueda, K.; Saito, A.; Nakano, H.; Aoshima, M.; Yokota, M.; Muraoka, R.; Iwaya, T. *J. Pediatrics* **1980**, *97*, 834.

at carbon 15 or 16 of PGE_2 to block the metabolic oxidation of the 15-hydroxy group. The resulting derivatives, (15*S*)-15-methyl- and 16,16-dimethyl-PGE_2 were orally active, potent, and relatively long acting inhibitors of gastric secretion.[6,7] These two compounds created much excitement when first described in 1973. Further investigation, however, revealed that both analogues displayed a number of undesirable side effects which would limit their clinical utility. In phase I clinical studies, they caused nausea, vomiting, diarrhea, pyrexia, and oxytocic effects.[8] Efforts to minimize side effects of 15-methyl-PGE_2 switched developmental emphasis from the natural stereoisomer to its unnatural isomer, (15*R*)-15-methyl-PGE_2 (arbaprostil). Arbaprostil does not inhibit gastric secretion when given intravenously or intrajejunally but is active orally.[9] The reason for this interesting profile is that arbaprostil is intrinsically inactive, but the tertiary allylic alcohol at carbon 15 epimerizes in acidic media such as gastric juice to provide a source of the active 15*S* isomer. In contrast, arbaprostil is inactive by the other routes of administration because epimerization does not occur at the higher pH's of blood and intestine.

In clinical trials,[10,11] arbaprostil was effective in healing both duodenal and gastric ulcer and was much better tolerated than the 15*S* isomer. In a multicenter duodenal ulcer study, arbaprostil at a dose of 100 μg four times a day produced a cure rate of 67% at 4 weeks vs. 39% for placebo. However, the incidence of diarrhea was quite high (34%). A possible drawback to the clinical use of arbaprostil is related to the epimerization of the 15-hydroxy group. Since the rate of epimerization is pH dependent,[12] variations in gastric juice acidity of patients could produce an inconsistent therapeutic outcome. Although the ulcer trials have not indicated a problem of inconsistency thus far, an insufficient conversion to the 15*S* isomer was suggested as an explanation for the ineffectiveness of arbaprostil in preventing gastrointestinal bleeding.[13] Efforts have also been made to increase the chemical stability of these compounds, particularly 16,16-dimethyl-PGE_2. For example, a large number of substituted phenyl and naphthyl esters was prepared to induce crystallinity and, hopefully, improve stability.[14] However, none of these derivatives is currently under investigation. Another strategy to increase stability was the replacement of the 9-ketone of 16,16-dimethyl-PGE_2 with a methylene group which removes the driving force for elimination of the carbon-11 hydroxyl group.[15] This compound, metenep-

Scheme III. Synthetic Development of Misoprostol



rost, while stable, possesses only weak gastric antisecretory activity and is being studied for gynecological indications instead of ulcer therapy.

Trimoprostil, the 11-methyl derivative of 16,16-dimethyl-PGE_2, was also prepared with stability considerations in mind. In the synthetic program, the labile hydroxy group at carbon 11 was replaced with a variety of stable substituents, but the methyl derivative was the most promising. Although less active than the parent compound as an inhibitor of gastric acid secretion, trimoprostil presented fewer side effects in animals and was generally well tolerated in phase I clinical studies.[16] In phase II trials, trimoprostil (750 μg four times daily) was less effective than cimetidine (200 mg three times daily and 400 mg at bedtime) in healing duodenal ulcer at 4 weeks (62% vs. 90%). Of the 30 patients who received trimoprostil, 19 had untoward events, and five were withdrawn from the study because of continuing ulcer pain, nausea, and vomiting.[17] Other modifications which have been made to improve stability are 11-deoxy compounds,[18] 10,10-dimethyl derivatives,[19] and 9-ketal and enol derivatives.[20] In general, these structures possess weak gastric antisecretory activity and have not warranted further study. A possible exception to this generalization is the 11-deoxy compound M&B 28,767 (Table I).

A second major advance in the development of antiulcer prostaglandins was the discovery that moving the 15-hydroxy group of natural prostaglandins to the adjacent

(6) Robert, A.; Magerlein, B. J. *Adv. Biosci.* **1973**, *9*, 247.
(7) Robert, A.; Schultz, J. R.; Nezamis, J. E.; Lancaster, C. *Gastroenterology* **1976**, *70*, 359.
(8) Karim, S.; Fung, W. P. *Adv. Prostaglandin Thromboxane Res.* **1976**, *2*, 529.
(9) Robert, A.; Yankee, E. W. *Proc. Soc. Exp. Biol. Med.* **1975**, *148*, 1155.
(10) Vantrappen, G.; Janssens, J.; Popiela, T.; Kulig, J.; Tytgat, G. N. J.; Huibregtse, K.; Lambert, R.; Pauchard, J. P.; Robert, A. *Gastroenterology* **1982**, *83*, 357.
(11) Fung, W. P.; Karim, M. M. *Med. J. Aust.* **1976**, *2*, 127.
(12) Merritt, M. V.; Bronson, G. E. *J. Am. Chem. Soc.* **1978**, *100*, 1891.
(13) Skillman, J. J.; Lisbon, A.; Long, P. C.; Silen, W. *Am. J. Surg.* **1984**, *147*, 451.
(14) Morozowich, W.; Oesterling, T. O.; Miller, W. L.; Lawson, C. F.; Weeks, J. R.; Stehle, R. G.; Douglas, S. L. *J. Pharm. Sci.* **1979**, *68*, 833.
(15) Bundy, G. L.; Kimball, F. A.; Robert, A.; Aiken, J. W.; Maxey, K. M.; Sebek, O. K.; Nelson, N. A.; Sih, J. C.; Miller, W. L.; Hsi, R. S. P. "Advances in Prostaglandin and Thromboxane Research"; Samuelsson, B., Ramwell, P. W., Paoletti, R., Eds.; Raven Press: New York, 1980; Vol. 6, p 355.
(16) Friedman, G. *Am. J. Gastroenterol.* **1983**, *78*, 387.
(17) Bardhan, K. D.; Whittaker, K.; Hinchliffe, R. F. C.; Cleur, K.; Rose, K. *Gut* **1984**, *25*, A580.
(18) Lippmann, W.; Seethaler, K. *Experientia* **1973**, *29*, 993.
(19) Hamon, A.; Lacoume, B.; Pasquet, G.; Pilgrim, W. R. *Tetrahedron. Lett.* **1976**, 211.
(20) Cho, M. J.; Bundy, G. L.; Biermacher, J. J. *J. Med. Chem.* **1977**, *20*, 1525.

16-position significantly reduced many of the typical prostaglandin side effects yet did not decrease gastric antisecretory activity.[2] This discovery was made independently at Searle and Lederle[21] in the early 1970s. The key compound, 15-deoxy-16-hydroxy-PGE_1 methyl ester **5** (Scheme III) was approximately equipotent to PGE_1 in inhibiting gastric secretion by intravenous administration. Side effects such as trembling, emesis, and diarrhea, which are usually observed with PGE_1, were absent at effective antisecretory doses of **5**. However, **5** was only weakly active by oral administration, and its duration of action was quite short. Enzymatic studies performed at Searle indicated that the 16-hydroxy group of **5** was also a substrate for the dehydrogenase enzyme which inactivates 15-hydroxy prostaglandins. In an effort to block this oxidative degradation, the 16-methyl, 15,15-dimethyl, and 17,17-dimethyl analogues of **5** were prepared. As was the case with natural prostaglandins, the addition of a methyl group at carbon 16 of **5** dramatically increased the oral potency and duration of action of the resulting compound **6** (SC-29333, misoprostol).[22,23] In contrast, addition of two methyl groups at either carbons 15 or 17 greatly diminished gastric antisecretory activity.[22]

Misoprostol, in general, shows improved selectivity with respect to side effects over 15-hydroxy prostaglandins. For example, the separation of gastric antisecretory and diarrheogenic properties in animals was much greater for misoprostol than for (15*S*)-15-methyl- and 16,16-dimethyl-PGE_2.[24] Furthermore, no evidence of platelet, hypotensive, or hyperostotic effects has been found with misoprostol. One prostaglandin side effect which has not been removed, however, is stimulatory activity on uterine smooth muscle. Although uterotonic activity was neither observed nor suggested by preclinical investigations, recent clinical studies have demonstrated that misoprostol can increase uterine contractility in pregnant women.[25]

Stability problems have also hindered the development of misoprostol, which is susceptible to the same types of chemical degradation as natural E prostaglandins. Indeed, early concerns about misoprostol's instability and noncrystalline nature almost stopped development. Fortunately, pharmaceutical formulation studies produced a solution to both problems. This research established that a dispersion of misoprostol on hydroxypropylmethylcellulose (HPMC) is much more stable than the neat chemical.[26] In fact, the tablets prepared from the solid dispersion have a shelf life of several years at room temperature.

Extensive clinical trials have demonstrated efficacy for misoprostol in both duodenal and gastric ulcer. In a multicenter trial misoprostol (200 μg four times daily) was considerably more effective (79%) than placebo (51%) in healing duodenal ulcer at 4 weeks.[27] A second study established that a dose of 100 μg four times daily was also effective.[28] In gastric ulcer, misoprostol was shown to be equivalent to cimetidine in 4-week healing rates at 200 μg vs. 300 mg, each given four times daily.[29] Side effects in all these studies were minimal. Diarrhea was the most commonly reported complaint but was generally mild and self-limiting.

Exploitation of the 16-hydroxy lead has been inexplicably limited to a few research groups. In addition to the efforts at Searle, only investigators at Lederle and Miles have explored this area to any significant degree. From these respective laboratories have come two structural relatives of misoprostol, CL-115,574 and rioprostol. Rioprostol is simply the 1-alcohol derivative of misoprostol, whereas CL-115,574 contains an unusual hydroxymethyl keto function in place of the carboxylate moiety. Although metabolic studies have not been reported for either compound, their pharmacological activity may be dependent on in vivo conversion to the free acid of misoprostol. Phase I clinical results[30,31] indicated that these compounds were less active than misoprostol in inhibiting gastric acid secretion and had no significant advantages over misoprostol.

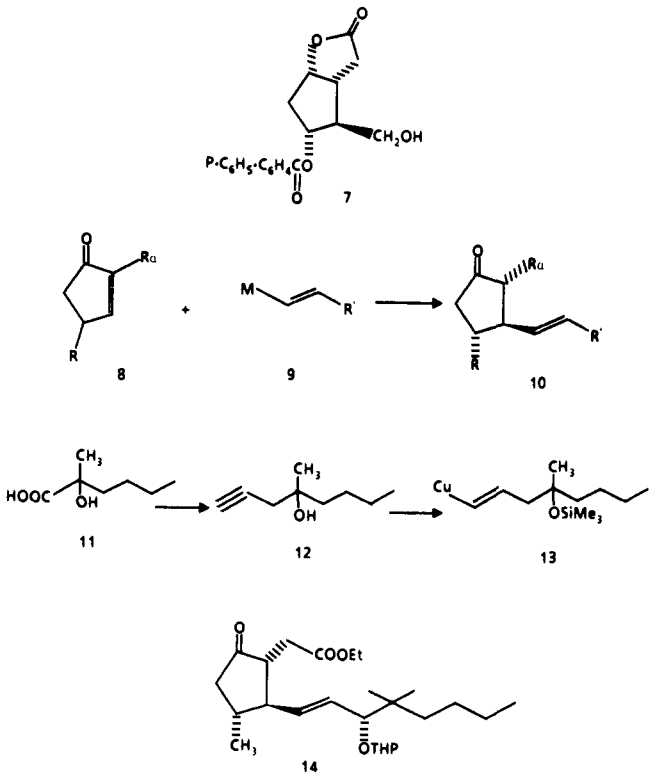
A considerable amount of effort has also been directed toward blocking or impeding β oxidation of the α side chain of prostaglandins. Strategies such as placing alkyl or halogen substituents at carbons 2, 3, or 4, substitution of heteroatoms (oxygen and sulfur) for carbons 3 or 5, insertion of double or triple bonds into various positions of the α chain, or incorporation of aromatic rings into the side chain have encountered limited success because these modifications generally reduced or eliminated gastric antisecretory activity. Two compounds in which this objective has been successfully met, however, are enisoprost and enprostil. Enisoprost in the Δ^4 cis analogue of misoprostol. The synthesis of enisoprost was based on reports that this modification impeded β oxidation[32] but did not alter gastric antisecretory activity.[33] In dogs, orally administered enisoprost was about 10 times more active in inhibiting gastric secretion than misoprostol and also had a longer duration of action.[24]

Enprostil has a very interesting structure, but details about its synthesis, metabolism, and pharmacology have not been published. One can surmise, however, that the allene was introduced to block β oxidation and the phenoxy group was added to prevent oxidation of the 15-hydroxy group and to avoid ω oxidation. Information from meeting abstracts[34] indicates that enprostil is a potent, orally active gastric antisecretory agent in animals and man with an exceptionally long duration of action. In duodenal ulcer trials, enprostil was very effective in healing ulcers at 4 weeks at doses of 35 and 70 μg twice daily with diarrhea being the only reported side effect. The extent of potential problems such as uterotonic activity and chemical instability is unclear at this point.

The compounds discussed thus far currently are the most likely candidates for successful clinical development in this area. However, a number of other synthetic analogues have been reported to have good antisecretory and cytoprotective properties and are at various stages of

(21) Floyd, M. B.; Schaub, R. E.; Weiss, M. J. *Prostaglandins* **1975**, *10*, 289.
(22) Dajani, E. Z.; Driskill, D. R.; Bianchi, R. G.; Collins, P. W.; Pappo, R. *Am. J. Dig. Dis.* **1976**, *21*, 1049.
(23) Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152.
(24) Collins, P. W.; Dajani, E. Z.; Pappo, R.; Gasiecki, A. F.; Bianchi, R. G.; Woods, E. M. *J. Med. Chem.* **1983**, *26*, 786.
(25) Herting, R. L.; Nissen, C. H. *Dig. Dis. Sci.*, in press.
(26) Sanvordeker, D. U.S. Patent 4 301 146, 1981.
(27) Brand, D. L.; Roufail, W. M.; Thomson, A. B. R.; Tapper, E. J. *Gastroenterology* **1984**, *86*, 1034.
(28) Sontag, S. J.; Mazure, P. A.; Pontes, J. F.; Beker, S. G.; Dajani, E. Z. *Dig. Dis. Sci.* **1985**, *30*, 159S.
(29) Shield, M. F. *Dig. Dis. Sci.* **1985**, *30*, 178S.
(30) Demol, P.; Wingender, W.; Weihrauch, T. R.; Graefe, K. H. *Arzneim.-Forsch* **1985**, *35*, 861.
(31) Wilson, D. E.; Levendoglu, H.; Adams, A.; Ramsamooj, E. *Prostaglandins* **1984**, *28*, 5.
(32) Green, K.; Samuelson, B.; Magerlein, B. J. *Eur. J. Biochem.* **1976**, *62*, 527.
(33) Walker, E. R. H. "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergamon Press: New York, 1979; p 326.
(34) Garay, G. L.; Muchowski, J. M. *Ann. Rep. Med. Chem.* **1985**, *20*, 93.

Scheme IV. Synthetic Processes



preclinical and clinical study. Among these are EMD-33,290 (tiprostanide),[35] MDL-646,[36] M&B 28,767,[37] and HOE-260[38] (Table I).

Synthesis and Stereochemistry

The successful development of a therapeutic agent obviously depends upon the availability of an efficient and cost effective process for producing large quantities of the compound. Attainment of this goal has been especially challenging in the case of synthetic prostaglandins because of stereochemical requirements, multiplicity of steps, stability and purification problems, and the use of sophisticated synthetic methodology. For the most part, however, the challenges have been met quite successfully and have not impeded developmental progress of these therapeutic agents. Currently two general processes are used to prepare most of the synthetic prostaglandins under clinical investigation.

One process utilizes the Corey lactone[39] **7** (Scheme IV) or related intermediates[40] as starting materials to which are attached the appropriate side chains via Wittig or similar type chemistry. The synthesis of the optically active intermediates involves a number of steps as well as a traditional resolution procedure. Nevertheless, the general approach is attractive because of its versatility, stereochemical control, and adaptability to large-scale production. Of the synthetic prostaglandins in Table I, arbaprostil, 16,16-dimethyl-PGE_2, and MDL-646 are prepared industrially by this general approach. All of these compounds are single stereoisomers. They are obtained either by use of optically active ω side chain or by chromatographic separation of the two epimers prepared with racemic side chain.

The second major process consists of a 1,4 conjugate addition of an organometallic derivative of the appropriate ω side chain **9** (Scheme IV) to a cyclopentenone **8** already having the desired α chain attached. The advantages of this approach are its convergent nature, its selective production of the desired ring stereochemistry, and its efficiency and facile adaptability to large-scale synthesis. The lengthy part of this process is the preparation of the cyclopentenone, and a number of procedures have been developed for this purpose.[23,41] Most of the synthetic prostaglandins in Table I are prepared on a large scale by this general process. The synthesis of misoprostol, enisoprost, rioprostil, and CL-115,574 involves the conjugate addition of the same 16-hydroxy vinyl copper species **13** to the particular cyclopentenones. Misoprostol, enisoprost, and CL-115,574 are mixtures of two racemates or four stereoisomers. Even though the cuprate reaction is stereoselective, the use of racemic cyclopentenone and side chain produces two racemates. Preparation of a single stereoisomer or racemate is complicated by the fact that chromatographic separation of racemates in the 16-methyl-16-hydroxy series is difficult and presently cannot be done on a practical scale. Thus the only effective way a single isomer can be obtained is by resolution of both cyclopentenone and side chain or by a combination of resolution and asymmetric induction. Although reasonably efficient methods have been developed to resolve the cyclopentenones,[42,43] no good method has been found to resolve or induce asymmetry in tertiary alcohols in general or for the particular alcohol **12** (Scheme IV) required for the synthesis of these compounds. Instead, rather circuitous routes to resolved **12** have been devised and carried out.[44,45] At Searle, the hydroxy acid **11** was resolved via its naphthylethylamine salt and then converted to **12** by a series of chemical manipulations. Though not feasible on a commercial scale, this procedure has been utilized to prepare each of the four stereoisomers of misoprostol and enisoprost for pharmacological evaluation. Gastric antisecretory activity resides almost entirely in the 11*R*,16*S* isomer which has the same absolute configuration as natural PGE_1.[46] Interestingly, rioprostil is a mixture of only two isomers. It is prepared from resolved cyclopentenone and racemic side chain resulting in the production of two diastereomers.

The development of industrial processes for producing trimoprostil and enprostil have followed similar pathways. Both compounds were initially prepared by Corey lactone methodology but are now synthesized by conjugate ad-

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dition chemistry or a combination of the two processes. Trimoprostil is a single stereoisomer obtained by the conjugate addition of a resolved vinyl zirconium reagent to a resolved cyclopentenone having a truncated α chain. The intermediate 14 is then converted to trimoprostil by using Corey lactone chemistry.[47] Enprostil is a mixture of two racemates or four stereoisomers. The number of possible stereoisomers for this compound is doubled by the presence of the chiral allene functionality. Originally, enprostil was synthesized from the Corey lactone by using methodology developed by Crabbé for allene formation.[48] The industrial process has not been published, but it utilizes racemic starting materials and probably involves conjugate addition chemistry on a truncated cyclopentenone[49] and subsequent elaboration of the α chain.

Gastric Antisecretory Activity

The exact mechanism for the gastric antisecretory action of prostaglandins remains unclear. The fact that prostaglandins block the gastric stimulating action of a wide variety of secretagogues suggests that they interfere with very basic cellular processes. The interaction of prostaglandins with the cyclic AMP system has been postulated as a mechanism, but the experimental evidence to support this possibility has been contradictory and inconclusive. However, studies[50-52] with PGE_2 in isolated canine parietal cells have helped to resolve some of the controversy. The results from these experiments established that cyclic AMP stimulates acid secretion and suggested that prostaglandins inhibit gastric acid secretion by preventing histamine activation of histamine-sensitive adenylate cyclase. Furthermore, because the in vivo response of parietal cells to gastrin and acetylcholine is dependent upon histamine activity, prostaglandins are able to block their effects as well.

A very interesting property observed with several synthetic prostaglandins is their local antisecretory effect when placed in direct contact with gastric mucosa. A local gastric antisecretory activity was clearly demonstrated with 16,16-dimethyl-PGE_2 by administering the drug to one pouch of dogs prepared with two Heidenhain pouches. Secretion was inhibited in the drug treated pouch, whereas no inhibition occurred in the second pouch until the dose was increased 7–10 times.[53] With both misoprostol[22] and enprostil[54] gastric secretion was inhibited at much lower doses when given to the pouch of Heidenhain dogs than when given to the main stomach. No such differences were observed with cimetidine. Thus prostaglandins appear to have a combination of local and systemic antisecretory effects.

Cytoprotection

A third major event in the development of prostaglandins for the treatment of peptic ulcer disease was the discovery that they can protect the gastrointestinal mucosa from injury caused by a variety of noxious agents. This intriguing phenomenon was first demonstrated by Robert in 1975[55] and termed "cytoprotection" by Jacobson.[56] In his original work Robert found that concomitant administration of prostaglandins with indomethacin to rats prevented or diminished the severity of intestinal lesions caused by this agent. Protection was greatest when the animals were treated with the prostaglandin 30 min prior or up to 1 h after indomethacin. Robert suggested that the lesions were due to a deficiency of endogenous prostaglandins caused by indomethacin and that treatment with a prostaglandin prevents the deficiency and thus the damage. Later work extended the phenomenon to gastric protection. In a landmark publication[56] Robert reported that pretreatment of rats with a variety of prostaglandins protected the gastric mucosa from damage caused by administration of ethanol, strong base or acid, hypertonic solutions, or boiling water. This and other work[57] strongly suggested that cytoprotection is independent of inhibition of gastric acid secretion. The basis for this hypothesis is fourfold: (1) Prostaglandins which are devoid of gastric antisecretory properties are cytoprotective. (2) Cytoprotection can be demonstrated at doses far below the acid inhibitory dose of antisecretory prostaglandins. (3) Cytoprotection occurs in acid independent models such as ethanol injury to stomach or indomethacin damage to intestine. (4) Other antisecretory agents such as histamine H_2 receptor blockers and anticholinergic drugs are ineffective in acid independent models.

The specific mechanism(s) of cytoprotection has not been established, but an enormous amount of experimental effort has identified a number of possibilities. Among the prominent theories[57] are (1) prevention of the disruption of the gastric mucosal barrier, (2) stimulation of gastroduodenal mucus and bicarbonate secretion, (3) stimulation of mucosal blood flow, (4) acceleration of mucosal repair, and (5) modulation of endogenous sulfhydryl levels. None of these postulates alone can adequately explain cytoprotection. Thus cytoprotection may well be a multifactorial phenomenon which encompasses these and other, yet to be identified, mechanisms. It is also conceivable that the specific cellular responses may vary with the particular insult and that synthetic prostaglandins may differ in their ability to elicit the various cytoprotective mechanisms. For example, Larsen et al.[58] have demonstrated differences between misoprostol and 16,16-dimethyl-PGE_2 in their ability to protect canine gastric mucosa against an aspirin-shock insult.

There are two important implications of cytoprotection to the development of synthetic prostaglandins as therapeutic agents for gastrointestinal disease. Firstly, cytoprotection provides the basis for a dual mechanism of action for prostaglandins in ulcer healing. Thus these compounds not only reduce the aggressive factor of acid secretion but simultaneously promote the natural defensive mechanisms of stomach and intestinal mucosa against further injury. This combination of effects should offer a much more favorable environment for ulcer healing than acid inhibition alone. Secondly, cytoprotection considerably expands the potential therapeutic role of prostaglandins in gastrointestinal disease. The use of prostaglandins in combination with aspirin and other nonsteroidal antiinflammatory drugs (NSAIDS) to prevent drug induced damage to the gastrointestinal mucosa is an obvious area of potential value. Other areas include reflux esophagitis, stress ulcer, refractory ulcer, and acute upper

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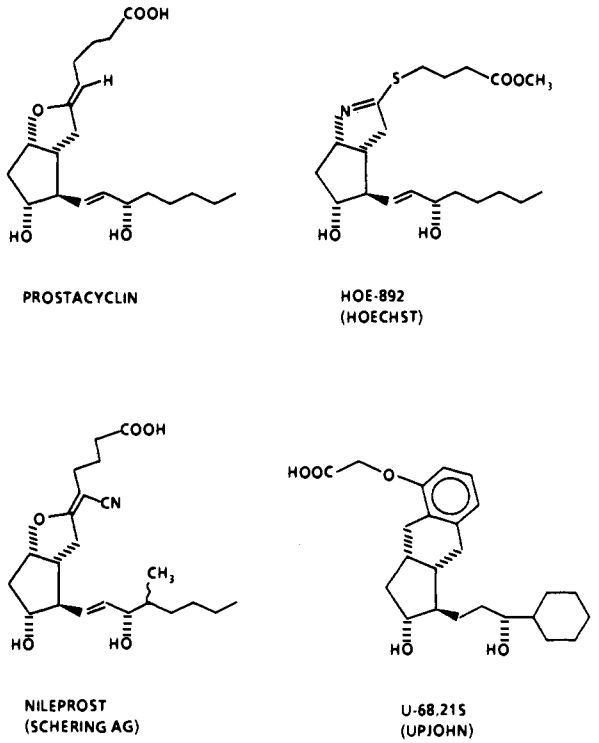
Scheme V. Prostacyclin Analogues



GI bleeding including hemorrhagic gastritis. The latter condition is a life-threatening complication of stress ulcer due to trauma, severe burns, sepsis, hypotension, or pulmonary, renal, or hepatic failure.[59] No effective drug therapy currently exists for hemorrhagic gastritis or upper GI bleeding in general. Cimetidine has been used, but controlled studies have failed to confirm efficacy.[60] Although anecdotal in nature, recent reports have described the successful treatment of hemorrhagic gastritis with synthetic prostaglandins and have suggested the need for controlled clinical trials with these compounds.[61,62]

Recent Developments

Prostacyclin (Scheme V), in addition to its well-known properties of platelet aggregation inhibition and vasodilation, also has gastric antisecretory and cytoprotective effects.[63] The development of prostacyclin analogues for use in peptic ulcer disease has come primarily from programs aimed at producing stable, orally active derivatives for treating cardiovascular diseases. From the hundreds of compounds prepared for cardiovascular intent, a few have recently been identified as potential candidates for ulcer disease therapy. Among these are HOE-892,[64] nileprost,[65] and U-68,215[66] (Scheme V). In general, these compounds are chemically stable and have similar cytoprotective properties but only moderate gastric antisecretory activity relative to synthetic E prostaglandins. However, the side effect profile is quite different. Prostacyclin and its synthetic derivatives are antienteropooling and can actually prevent diarrhea induced by E prostaglandins.[67] Furthermore, U-68,215 has been reported to be devoid of uterotonic activity in pregnant monkeys.[66] Although residual cardiovascular effects are a source of potential concern, prostacyclin derivatives represent a new class of prostaglandin compounds in the peptic ulcer disease area.

Conclusion

Seventy five years ago Schwarz[68] proposed that gastrointestinal ulceration was induced by a disturbance in the balance of aggressive factors such as acid and pepsin and defensive mechanisms such as the mucus layer and mucosal blood flow. His famous dictum "no acid–no ulcer" has been the basis for modern ulcer therapy and has led to the development of a variety of antisecretory drugs such as the anticholinergics, histamine H_2 receptor antagonists, and H^+/K^+ ATPase inhibitors. The discovery of the mucosal protectant properties of prostaglandins now provides a means of addressing the defensive side of Schwarz's theory. Although cytoprotection remains a poorly defined term, more measurable properties of prostaglandins such as the stimulation of bicarbonate and mucus production, enhancement of mucosal blood flow, etc. clearly indicate the ability of prostaglandins to protect the gastrointestinal mucosa against aggressive factors. Thus prostaglandins are capable of restoring the balance between aggressive and defensive factors and represent an ideal treatment for ulcer disease within the context of Schwarz's theory. For this reason prostaglandins will be an important addition to the physician's armamentarium and should eventually play a major role in the treatment of peptic ulcer disease and related conditions.

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