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REVIEW ARTICLE

GASTRIC CYTOPROTECTION

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Abstract : The term 'cytoprotection' means protection against gastric mucosal injury by a mechanism other than inhibition or neutralisation of gastric acid. Several mechanisms of gastric cytoprotection have been proposed like increased mucus and bicarbonate secretion, strengthening of gastric mucosal barrier, increased gastric mucosal blood flow, decreased gastric motility, increased formation of prostaglandins and sulfhydryls, scavenging of free radicals, stimulation of cellular growth and repair, decreased release of leukotrienes etc. Some of the drugs widely used in therapy of peptic ulcer are cytoprotective e.g. sucralfate, colloidal bismuth and aluminium containing antacids. As the concept of gastric cytoprotection is becoming widely accepted, the list of drugs which have shown a cytoprotective action in animal experiments is growing rapidly. This list includes zinc sulphate, meciadanol, propranolol, dipyridamole etc.

Key words : blood flow prostaglandins sulfhydryls gastric motility

INTRODUCTION

Peptic ulcer is one of the common diseases affecting mankind. 'It kills few but troubles many' (1). The incidence has been estimated variously as ranging from 3-10% but 'as a result of excessive advertising of antacids the public has come to believe that man is constantly fighting a battle against acidity' (2). However, the pathogenesis of peptic ulcer is far from clear and so is the mechanism of anti-ulcer drugs.

It is well known that the gastric mucosa can resist auto-digestion though it is exposed to numerous 'insults' like high concentration of hydrochloric acid, pepsin, reflux of bile, spicy food, microorganisms and at times alcohol and irritant drugs. It is thus evident that the integrity of the gastric mucosa is maintained by defence mechanisms against these 'aggressive' damaging factors.

Traditionally drugs used in peptic ulcer have been directed only against a single luminal damaging agent i.e. hydrochloric acid (3). Hence a plethora of drugs like antacids, anticholinergics, histamine H_2 antagonists and so on, directed against acid, flooded the market. However an increase in 'aggressive' factors like acid and pepsin is found only in a minority of peptic ulcer patients. Further, these factors do not alter during or after spontaneous healing (4). Thus attention has been focussed on gastroduodenal defence mechanisms leading to the concept of 'cytoprotection'.

The term 'cytoprotection' was first introduced by Andre Robert in 1979 (5). He used this term to refer to protection by prostaglandins against experimentally induced acute gastric lesions, in doses which do not affect gastric secretion in the rat. Now the term 'cytoprotection' is used in a broader sense to mean protection against gastric mucosal injury by a mechanism other than inhibition or neutralisation of gastric acid. However, it is found that surface cells are often not protected by cytoprotective agents though deep haemorrhagic necrosis is prevented (6). This made Szabo and Szelenyi (7) suggest the term

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'gastroprotection'. But the term 'cytoprotection' continues to be in popular use and hence is preferred in this review.

The most commonly used model employed to evaluate the cytoprotective effect of a drug is ethanol-induced acute gastric haemorrhagic lesion as it is an acid independent injury and antisecretory drugs like H_2 antagonists have no effect (5, 8). Other necrotising agents used include bile acids, taurocholate and glychenodeoxycholate, hypertonic urea, sodium hydroxide, hydrochloric acid and boiling water.

MECHANISM OF CYTOPROTECTION

Though the concept of cytoprotection has come to stay, there are diverse opinions as to the exact mode of action of cytoprotective agents. Various mechanisms have been suggested:–

1. *Increase in mucus secretion :* The relative importance of mucus as a protective mechanism is still controversial. It has been shown that diffusion of hydrogen ions across mucus gel is four times slower than through a similar layer of water (4). The mucus gel structure in patients with gastric ulcer has been found to be abnormal in that it contains less glycoprotein (9) and several cytoprotective drugs have been shown to increase mucus gel thickness like carbenoxolone, prostaglandins (10).

However microscopic studies (6), question the role of mucus in gastric cytoprotection as it has been shown that prostaglandin treatment which produces a thicker mucus gel layer, does not protect the surface injury (though it prevents deeper damage). Morris et al (11) have demonstrated by electron microscopy that the unstressed rat gastric mucosa is only partially covered by an interconnected but discontinuous layer of mucus 'ropes' 'sheets' and 'mats'; thus allowing ulcerogenic agents direct access to surface epithelial cells. This finding also goes against the generally accepted protective role of mucus. However, several studies have suggested that mucus may play an important role in protecting the mucosa from further damage after the initial insult by providing a thick 'cap' over the rapidly migrating epithelial cells favouring a rapid reepithelialization of the mucosa (11, 12).

2. *Increase in bicarbonate secretion :* Flemstrom in 1977 (13) first demonstrated the existence of bicarbonate secretion from fundic and antral mucosa which occurs by a metabolically dependent process as well as by passive diffusion. Vagal stimulation increases both acid and alkali secretion. This 'alkaline tide' during hydrogen ion secretion increases bicarbonate delivery to the surface epithelium.

However, the rate of bicarbonate secretion is only 5 to 10 per cent of the maximal acid output (14). Thus bicarbonate alone cannot lower sufficiently the hydrogen ion concentration but it can complement the action of mucus, forming what is known as the 'mucus-bicarbonate barrier' (15). This has been confirmed experimentally using pH sensitive micro-electrodes which have shown a marked pH gradient from lumen to cell surface (16).

It has been seen that in duodenal ulcer, there is a defective bicarbonate response to an acid load (17). However, though some prostaglandins cause an increase in bicarbonate secretion (18) other cytoprotective prostaglandins do not (19), thus casting doubts on the importance of bicarbonate secretion as a mechanism of cytoprotection.

3. *Strengthening of gastric mucosal barrier :* Many studies have provided evidence that surface epithelial cells have intrinsic barrier properties and play an important role in the first line defense of the stomach. Davenport (20) proposed that the apical membrane or tight junctions between epithelial cells are relatively impermeable to hydrogen ions and therefore form a physical barrier to back diffusion of acid. He called this the 'gastric mucosal barrier'. More recent studies (21) have shown the existence of surface active phospholipids which form a hydrophobic lining on the luminal surface of the gastric epithelium and retard the passage of water-soluble ions such as hydrogen ions. NSAIDs have been shown to eliminate surface hydrophobicity and disrupt the mucosal barrier to hydrogen ions. On the

TABLE I : Proposed mechanisms of cytoprotection involved in the action of drugs in clinical use for peptic ulcer.

Mechanism	*Drugs*
Increased mucus	carbenoxolone, misoprostol sucralfate
Increased bicarbonate	misoprostol, sucralfate
Increased phospholipid	colloidal bismuth, misoprostol
Increased blood flow	misoprostol
Decreased motility	misoprostol
Increased prostaglandins	al-containing antacids, colloidal bismuth, sucralfate
Increased sulfhydryls	al-containing antacids, sucralfate
Increased epidermal growth factor	colloidal bismuth
Increased repair	misoprostol

other hand, cytoprotective agents like prostaglandins increase the concentration of surface-active phospholipids (22).

4. *Increase in mucosal blood flow :* Several recent studies have demonstrated that vascular injury to subepithelial capillaries with increased vascular permeability and circulatory stasis, is an early pathogenetic factor in experimental gastric lesions (23). These changes lead to functional impairment of gastric micro-circulation, the decrease in mucosal blood flow correlating with the extent of haemorrhagic erosions (23).

Increase in mucosal blood flow has been shown to protect against mucosal damage (24). The mucosal micro-circulation is extremely important in maintaining oxygenation and supplying nutrients. The anatomical design of the gastric vasculature is such that the 'alkaline tide' from secreting oxyntic cells is readily available to the basal aspect of surface epithelial cells (25). Thus if blood flow is adequate there can be an almost unlimited supply of bicarbonate neutralization of back diffused hydrogen ions. In addition enhanced blood flow ensures that the absorbed injurious agent is diluted within the subepithelial capillaries.

However some studies raise doubts about the importance of mucosal blood flow in cytoprotection. For example PGF_2 alpha, a vascoconstrictor has been shown to exert a gastric cytoprotective effect similar to that of the vasodilator PGE_2 (5). Further, agents like histamine and acetycholine have been shown to increase gastric mucosal blood flow and yet cause gastric ulceration (26). Studies in our laboratory have also shown no correlation between gastric cytoprotection and blood flow. For example the ACE inhibitor captopril which is known to increase gastric mucosal blood flow (27) does not affect ethanol-induced gastric lesions (28) while the non-selective ß-antagonist propranolol which decreases gastric blood flow (29) has a marked gastroprotective effect (30).

5. *Decrease in gastric motility :* Various studies have suggested that changes in gastric motility may play a role in the development and prevention of experimental gastric lesions (31). It has been consistently observed that gastric injury caused by necrotising agents occurs as band-like lesions, at the crest of mucosal folds and is preceded by violent gastric contractions. As the lesions occur at the site of the greatest mechanical stress, 'mucosal compression' by gastric hypercontraction probably accounts for necrosis and ulceration of epithelium (31).

As the formation of mucosal folds relates closely to muscle action, specially circular muscle, an inhibiting effect on gastric motility may protect the gastric mucosa through flattening of the folds. This will lead to an increase in the mucosal surface area exposed to ulcerogens and thereby reduce the volume of the irritant on specific sites of the mucosa (rugal crests).

Studies using prostaglandins, mast cell stabiliz-

TABLE II : Proposed mechanisms of cytoprotection involved in the action of experimental cytoprotective agents.

Mechanism	*Drugs*
Increased blood flow	adenosine
Decreased motility	SH drugs, mast cell stabilizers, dopamine
Increased prostaglandins	papaverine, dipyridamole, propranolol, interleukin 1 B
Increased sulfhydryls	dipyridamole
Decreased free radicals	vit E, dipyridamole
Decreased leukotrienes/ amines	mast cell stabilizers, meciadanol.

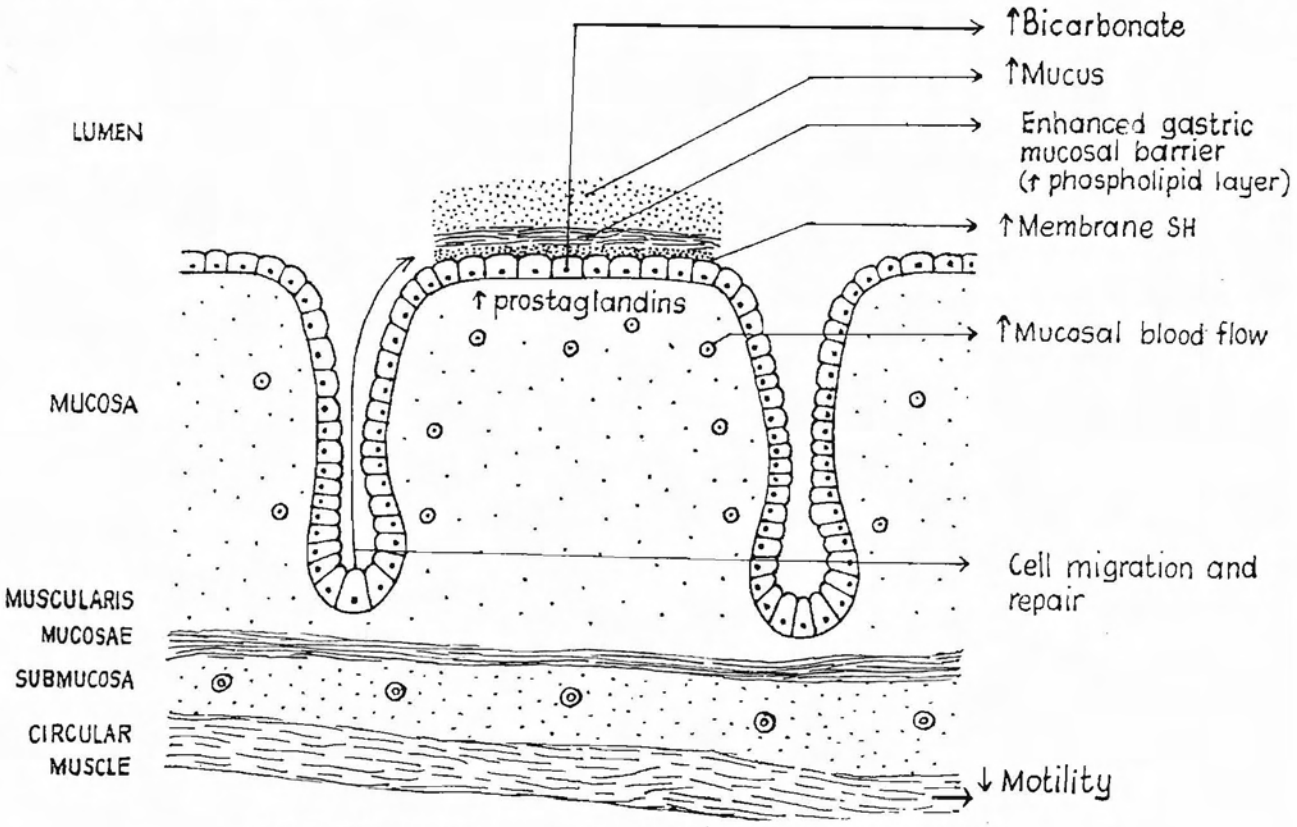

Fig. 1: Diagrammatic representation of gastric cytoprotective mechanisms.

ers and sulfhydryl compounds have confirmed that inhibition of gastric motility is associated with their cytoprotective action in the rat (32). Studies in our laboratory on a group of antihypertensive drugs also showed a correletion between gastric cytoprotection and a decrease in ethanol-induced contraction of circular muscle of rat fundus (unpublished observation).

6. *Increased release of endogenous mediators/of gastric cytoprotection: (a) Prostaglandins :* Prostaglandins were the first endogenous compounds implicated in gastric cytoprotection (5). The importance of endogenous prostaglandins in mucosal defense mechanism is evident from the observation that NSAIDs damage gastric mucosa. Since prostaglandins increase mucosal blood flow (33) this has been suggested to be responsible for their gastroprotective effect. However various other mechanisms have also been postulated like dilution of noxious agent by prostaglandin-stimulated mucus secretion (34), stimulation of basal bicarbonate secretion (35), increase in the concentration of surface-active phospholipids (22), stimulation of cyclic AMP (36), stabilisation of lysosomes (37), decrease in gastric motility and dissolution of gastric mucosal folds (31) and maintenance of mucosal sulfhydryl groups (38). Prostaglandins probably also have a repair function by stimulating rapid resolution of disrupted surface epithelium (39). It has been shown that prior exposure of gastric mucosa to mild irritants protects it from damage by more noxious agents. This 'adaptive' cytoprotection is mediated by prostaglandins (40). *(b) Sulfhydryls :* Szabo et al (38) observed that the naturally occurring sulfhydryl (SH)-containing amino acids L-cysteine and methionine as well as sulfhydryl containing drugs protect rats from ethanol-induced gastric lesions whereas sulfhydryl blocking drugs counteract the cytoprotective effect of PGE_2. They proposed that endogenous sulfhydryls may be

one of the mediators of cytoprotection. Various mechanisms have been suggested: Synthesis of prostaglandins as well as prostaglandin receptor action are dependent on endogenous sulfhydryls (41). In addition, by influencing membrane permeability or production of free radicals they may be directly involved in mucosal defense (42). On the other hand, Robert et al (43) reported that depletion of endogenous sulfhydryls paradoxically had a gastro-protective effect. *(c) Epidermal growth factor :* This polypeptide, a potent inhibitor of gastric acid secretion, is found in salivary glands as well as other sources like duodenal mucosa and pancreas (44). It has been reported to have a gastric cytoprotective action in non-antisecretory doses (45). Perhaps this effect is mediated through endogenous sulfhydryl group rather than prostaglandins or alkali secretion (42). In addition, other studies (46) have shown its efficacy in preventing stress ulcers and in healing chronic duodenal ulcers in rats. At present, however, its exact role in human gastric cytoprotection is still being elucidated.

7. *Scavenging of free radicals :* The involvement of oxygen - derived free radicals, specially the superoxide radical in ischemic gastric mucosal damage has been suggested but the exact mechanism is not yet defined. Probably free radicals result in lipid peroxidation and damage to intracellular components (47). Antioxidants like Vit E and selenium have been shown to have a protective effect on the gastric mucosa against stress and chemically induced lesions (48, 49).

8. *Decreased release of endogenous mediators of gastric injury : Vasoactive amines and leukotrienes*-It has been shown that at least part of the injurious action of ethanol on gastric microcirculation is due to release of mediators. Mast cell stabilizers like disodium cromoglycate and doxantrazol and H_1 receptor antagonists decrease ethanol-induced haemorrhagic mucosal damage (50). Further, ethanol-induced gastric lesions are also less in mice genetically deficient in mast cells (51). In addition to mast cells and vasoactive amines, leukotrienes have been proposed as endogenous mediators of acute gastric mucosal damage. Leukotrienes have been shown to induce gastric vasoconstriction (52) and to increase vascular permeability (53). Mucosal levels of leukotrienes are increased after exposure to ethanol (54). In addition, inhibition of synthesis of LTC_4 & LTD_4 in the gastric mucosa protects against damage by noxious agents.

Since the two products of arachidonic acid pathway -prostaglandins and leukotrienes- have opposite effect on gastric mucosa, it is possible that the balance between production of prostaglandins and leukotrienes may play an important role in mucosal integrity. There is experimental evidence to indicate

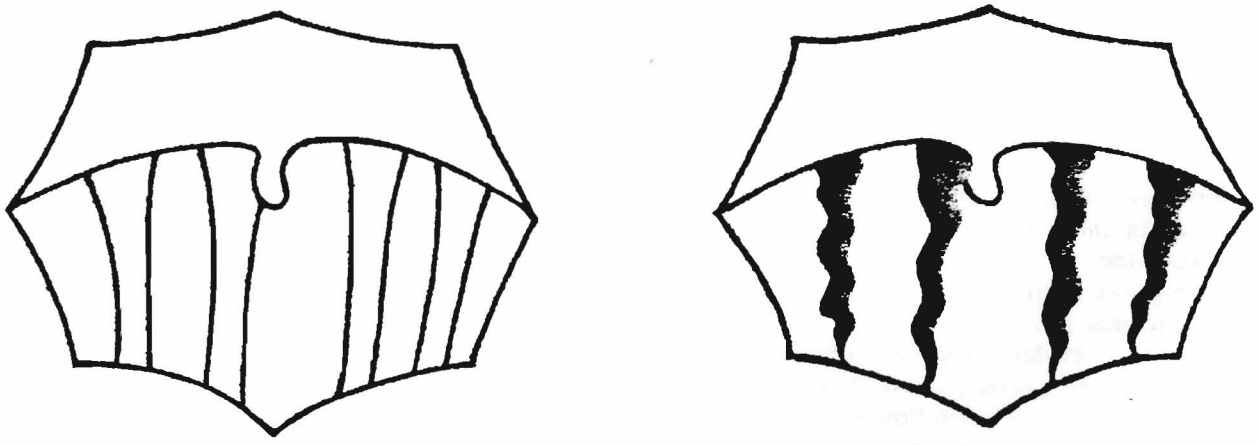

Fig. 2: Simplified diagrammatic representation of rat gastric mucosa *Left :* Normal mucosa showing mucosal folds. *Right :* Ethanol-induced haemorrhagic lesions along the mucosal folds.

that decreased synthesis of leukotrienes may be more significant as compared to increased levels of prostaglandins (55).

9. *Stimulation of cellular growth & repair :* It is well known that rapid epithelial restitution of the damaged mucosal surface takes place by migration of cells from deep within the gastric pits, which recover the denuded basal lamina (56). Following injury with agents like ethanol, aspirin and hypertonic saline, mucosal reepithelialization occurs within as short a time as 30 minutes (57). It should be noted that an intact basal lamina is vital for the cells to migrate during this repair process. The integrity of the basal lamina is maintained by a medium with high pH (58). On the other hand, if the luminal pH is low (acid) reepithelialization is hampered (59).

In general it can be said that there is a plethora of mechanisms of gastric cytoprotection, their relative importance and interdependence being far from clear. This itself is a pointer that gastric cytoprotection may be a multifactorial phenomenon.

CYTOPROTECTIVE DRUGS

In clinical use for peptic ulcer

The drugs that follow are well known and widely used in the treatment of peptic ulcer. Their pharmacological profile is well established. So we are limiting ourselves mainly to their 'cytoprotective' aspect.

Sucralfate : The beneficial effect of sucralfate in peptic ulcer has been attributed to its ability to bind to the ulcer crater and prevent access of acid & pepsin to the ulcerated tissue (60). Many studies, however, have demonstrated that it also has a cytoprotective effect (61, 62). Pretreatment with endomethacin decreases by more than 50% the protective effect of sucralfate against ethanol-induced gastric lesions, showing that it is partly mediated by release of endogenous prostaglandins (63). Other mechanisms proposed are: increase in mucus (64) and bicarbonate secretion (65), involvement of endogenous sulfhydryls (66), protection against damage to proliferative zone (67) and preservation of vascular integrity (68).

Tripotassium Dicitrato Bismuthate : This colloidal bismuth salt chelates proteins in the ulcer crater, forming a protective coating against acid, pepsin and probably bile (69). It also destroys campylobacter pylori (70). In addition colloidal bismuth subcitrate has been shown to prevent a variety of experimental gastric mucosal lesions in the rat (71). Its cytoprotective effect has been attributed to stimulation of prostaglandins, increased luminal availability of epidermal growth factor and stimulation of phospholipid - rich mucus (62, 72, 73). Its effect on prostaglandin synthesis is, however, controversial as indomethacin did not affect its cytoprotective action in cold-immobilization stress model (74).

Carbenoxolone : Carbenoxolone is an anti-ulcer drug obtained from glycyrrhiza. The cytoprotective action of carbenoxolone has been attributed to endogenous prostaglandins (75). However, other actions have been implicated like increasing gastric mucus, decreasing the exfoliation and increasing the half life of gastric mucosal cells (10). It has been shown to enhance healing of gastric and duodenal ulcers (76) but because of its frequent adverse effects resulting from mineralocorticoid action, it has fallen into disrepute.

Antacids : Aluminium-containing antacids have been reported to significantly decrease ethanol - induced injury in rats (77). Aluminium hydroxide gel also protected against gastric mucosal barrier disruption by sodium taurocholate. As indomethacin only partly blocked this protective effect, it appears that in addition to prostaglandins, other mechanisms may be involved like non-protein sulfhydryls (78).

Omeprazole : This H^+ K^+ ATPase inhibitor is a potent antisecretory agent. Kollbert et al (79) have shown that antisecretory doses of omeprazole administered orally but not intraperitoneally prevent ethanol-induced gastric lesions in rats. The cytoprotective effect of omeprazole requires its direct contact with the gastric mucosa and appears to be independent of its antisecretory effect (as in-

traperitoneal omeprazole was not protective). A recent study using quantitative histological techniques (80) failed to demonstrate any cytoprotective effect of omeprazole even in doses sufficient to cause some inhibition of gastric secretion.

Misoprostol : This is a synthetic PGE_1 analog. Its cytoprotective effects have been well documented in various experimental gastric injury models in animals, in doses much lower than the dose required to inhibit gastric acid secretion by 40% in the rat (81). Though its cytoprotective activity has also been reported in clinical studies in human beings (82, 83, 84), doses of Misoprostol which are currently employed (200 μg four times daily) produced marked suppression of acid secretion (85).

Experimental agents

In addition to the drugs described above which are in clinical use for peptic ulcer, studies in several laboratories all over the world have focused on testing a variety of drugs for their possible cytoprotective action.

Dopamine : An association between dopamine deficiency and peptic ulcer was first reported by Strang (86). He noticed a higher incidence of duodenal ulcer in patients with Parkinsonism. On the other hand, duodenal ulcers are rare in schizophrenics who have excess or hyperactivity of brain dopamine. Subsequently several studies have demonstrated the protective effect of parenterally administered dopamine agonists like bromocriptine, lergotrile and apomorphine as well as the dopamine precursor levodopa and the MAO-B inhibitor deprenyl (87, 88, 89). Pretreatment with the peripheral dopamine receptor antagonist domperidone, prevents the protective effect of dopaminergic agonists (87) while the dopamine receptor antagonist haloperidol given parenterally itself induces gastric lesions in rats (90). Based on studies employing selective dopamine DA_1 and DA_2 agonists and antagonists (95), it appears that dopamine DA_1 receptors are involved in gastric cytoprotection.

Meciadanol : This is a new synthetic flavonoid which is an inhibitor of histidine decarboxylase. It has no effect on gastric acid or pepsin (92). Meciadanol has been shown to prevent gross and histological ethanol induced gastric lesions in rat (93), as well as those caused by acidified aspirin (92). As pretreatment with indomethacin does not affect the cytoprotective effect of meciadanol (93), endogenous prostaglandins are probably not involved. It has been shown that meciadanol inhibits mast cell degranulation, thus preventing release of histamine and other mediators of gastric injury (94).

Dipyridamole : This anti-platelet drug has been shown to protect against gastric injury due to a variety of necrotizing agents (95). The cytoprotective effect was prevented by prior treatment with indomethacin suggesting the involvement of mucosal prostaglandins. Other mechanisms cited for its action are replenishment of gastric mucosal non-protein sulfhydryls and inhibition of superoxide anion generation.

Propranolol : This non-selective β adrenoceptor antagonist has been shown to have a protective effect on ethanol-induced gastric lesions in mice (30). The effect was more marked after oral administration and appears to be mediated partly by the prostaglandin pathway and partly by its membrane stabilising action.

Others : Other drugs reported to have a gastric cytoprotective effect are zinc sulphate (96), Vit A (97), Vit E (48), antibiotics like neomycin, bacitracin & polymyxin B (98); papaverine (77), interleukin 1 β (99) and adenosine (100).

As the concept of gastric 'cytoprotection' is gaining more and more recognition all over the world, investigators are vying with one another to test the known anti-ulcer agents, as well as new drugs, for a possible cytoprotective effect. As a result of this today it is 'easier to say what is not cytoprotective than to list the rapidly growing list of cytoprotective drugs' (7). We hope that in the ensuing decade this vast explosion of knowledge will fructify so that peptic ulcer patients derive significant practical benefit.

REFERENCES

1. Lawrence DR, Bennett PN, eds. Clinical Pharmacology: Edinburgh; Churchill Livingstone. 1987; 611-20.
2. Harvey SC. Gastric antacids, miscellaneous drugs for the treatment of peptic ulcers, digestants and bile acids. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F. eds. The Pharmacological Basis of Therapeutics; New York; MacMillan Publishing Co. 1985; 980-93.
3. Brooks FP. The pathophysiology of peptic ulcers: an overview. In: Brooks FP, Cohen S, Soloway RD. eds. Contemporary issues in gastroenterology: peptic ulcer disease; New York; Churchill Livingstone: 1985; 45-149.
4. Shorrock CY, Rees WDW. Overview of gastroduodenal mucosal protection. *Am J Med* 1988; 84: 25-34.
5. Robert A. Cytoprotection by prostaglandins. *Gastroenterology* 1979; 77: 761-67.
6. Lacy ER, Ito S. Microscopic analysis of ethanol damage to rat gastric mucosa after treatment with a prostaglandin. *Gastroenterology* 1982; 83: 619-25.
7. Szabo S, Szelenyi I. "Cytoprotection" in gastrointestinal pharmacology. *Trends Pharmacol Sci* 1987; 8: 149-54.
8. Konturek SJ, Mach T, Konturek JW, Bogdal J, Stachura J. Comparison of sucralfate and ranitidine in gastroprotection against alcohol in humans. *Am J Med* 1989; (Suppl) 6 AS; 55-59.
9. Younan F, Pearson J, Allen A, Venables C. Changes in the structure of the mucus gel on the mucosal surface of the stomach in association with peptic ulcer disease. *Gastroenterology* 1982; 82: 827-31.
10. Bickel M, Kaufman G.Gastric mucus gel thickness: effect of distension, 16, 16-dimethyl prostaglandin E_2 and carbenoxolone. *Gastroenterology* 1981; 80: 770-75.
11. Morris GP, Harding PK, Wallace JL. A functional model for extracellular gastric mucus in the rat. *Virchows Arch B*1984; 46: 239-51.
12. Ito S, Lacy ER. Morphology of rat gastric mucosal damage, defense and restitution in the presence of luminal ethanol. *Gastroenterology* 1985; 88: 250-60.
13. Flemstrom G. Gastric secretion of bicarbonate. In: Johnson RL, Christensen J, Grossman MI, Jacobson ED, Schultz SD. eds. Physiology of the GI tract, Vol i, New York: Raven Press, 1983; 603-14.
14. Allen A, Garner A. Progress report — Mucus and bicarbonate secretion in the stomach and their possible role in mucosal protection. *Gut* 1980; 21: 249-62.
15. Rees WDW, Turnberg LA. Mechanisms of gastric mucosal protection: a role for the "mucus-bicarbonate" barrier. *Clin Sci* 1982; 62: 343-48.
16. Williams SE, Turnberg LA. Studies of the "protective" properties of gastric mucus: evidence for a "mucus-bicarbonate" barrier. *Gut* 1981; 22: 94-96.
17. Isenberg JI, Selling JA, Hogan DL, Koss MA. Impaired proximal duodenal mucosal bicarbonate secretion in patients with duodenal ulcer. *N Engl J Med* 1987; 316: 374-79.
18. Bolton JP, Palmer D, Cohen MM. Stimulation of mucus and non-parietal cell secretion by the E_2 prostaglandins. *Am J Dig Dis* 1978; 17: 219-99.
19. Shea-Donahue PT, Nompleggi D, Myers L, Dubois A. A comparison of the effects of prostacyclin and the 15 (S), 15 methyl analogues of PGE_2 and $PGF_2\alpha$ on gastric parietal and non-parietal secretion. *Dig Dis Sci* 1982; 27: 17-22.
20. Davenport HW, Warner HA, Code CF. Functional significance of gastric mucosal barrier to sodium. *Gastroenterology* 1964; 47; 142-52.
21. Hills BA, Butler BD, Lichtenberger LM. Gastric mucosal barrier: hydrophobic lining to the lumen of the stomach. *Am J Physiol* 1983; 244 *(Gastrointest. Liver Physiol 7):* G 561-68.
22. Lichtenberger LM, Richards JE, Hills BA. Effect of 16, 16-dimethyl prostaglandin E_2 on surface hydrophobicity of aspirin-treated canine gastric mucosa. *Gastroenterology* 1985; 88: 308-14.
23. Pihan G, Majzoubi D, Haudenschild C, Trier JS, Szabo S. Early microcirculatory injury in the rat and prevention by 16, 16-dimethyl prostaglandin E_2 and sodium thiosulfate. *Gastroenterology* 1986; 91: 1415-26.
24. McGreavy JM, Moody FG. Protection of gastric mucosa against aspirin-induced erosions by enhanced blood flow. *Surg Forum* 1977; 28: 357-59.
25. Gannon B, Browning J, O'Brien P. The microvascular architecture of the glandular mucosa of the rat stomach. *J Anat* 1982; 135:667-83.
26. Jacobson ED. The circulation of the stomach. *Gastroenterology* 1965; 48: 85-110.
27. Saxena PR, Bolt GR. Haemodynamic profiles of vasodilators in experimental hypertension. *Trends in Pharmacol Sci* 1986; 7: 501-4.
28. Bhounsule SA, Pereira JS, Hede SS, Diniz D'Souza RS. Effect of captopril on oxyphenbutazone and ethanol-induced gastric lesions in the rat. *European J Pharmacol* 1990; 177: 87-90.
29. Van Boom MP, Saxena PR. Tissue blood flow changes in-

duced by propranolol infusion in conscious normotensive and renal hypertensive rabbits. *Arch Int Pharmacodyn* 1983; 264: 96-109.

30. Bhandare PN, D'Souza RD, Mainker A, Dhume VG. Protective effect of propranolol on ethanol-induced gastric lesions in mice. *European J Pharmacol* 1990; 191: 167-72.

31. Mersereau WA, Hinchey EJ. Role of gastric mucosal folds in formation of focal ulcers in the rat. *Surgery* 1982; 91: 150-55.

32. Takeuchi K, Nobuhara Y. Inhibition of gastric motor activity of 16, 16-dimethyl prostaglandin E_2. A possible explanation of cytoprotection. *Dig Dis Sci* 1985; 30: 1181-88.

33. Gaskill HU, Sirinek KR, Levine BA. Prostacyclin on mucosal blood flow. *Surgery* 1982; 92: 220-25.

34. Johansson C, Kollberg B. Stimulation of intragastrically administered E_2 prostaglandin of human gastric mucus output. *Eur J Clin Inv* 1979; 9: 229-32.

35. Smeeton L, Hurst B, Allen A, Garner A. Gastric and duodenal bicarbonate transport in vivo; influence of prostaglandins. *Am J Physiol* 1983; 245: G 751-59.

36. Simon B, Kather H. Prostaglandin sensitive adenylate cyclase in human gastric mucosa. *Pharmacology* 1979, 19: 96-103.

37. Ferguson WW, Edmonds AW, Starling JR, Wangensteen SL. Protective effect of PGE_1 on lysosomal enzyme release in serotonin-induced gastric ulceration. *Ann Surg* 1973; 177: 648-54.

38. Szabo S, Trier JS, Frankel PW. Sulfhydryl compounds may mediate gastric cytoprotection. *Science* 1981; 214: 200-2.

39. Hawkey CJ, Rampton DS. Prostaglandins and the gastrointestinal mucosa: are they important in its function, disease or treatment? *Gastroenterology* 1985; 89: 1162-68.

40. Robert A, Nezamis JF, Lancester C, Davis JP, Field SO, Hanchar AJ. Mild irritants prevent gastric necrosis through "adaptive cytoprotection" mediated by prostaglandins. *Am J Physiol* 1983; 245: G 113-21.

41. Szabo S, Trier JS. Pathogenesis of acute gastric mucosal injury. Sulfhydryls as a protector, adrenal cortex as a modulator and vascular endothelium as target. In: Allen A, Flemstrom C, Garner A, Silen W, Turnberg LA, eds. Mechanisms of mucosal protection in the upper gastrointestinal tract, New York: Raven Press 1984; 287-93.

42. Szabo S. Peptides, sulfhydryls and glucocorticoids in mucosal defense - coincidence or connection? *Gastroenterology* 1984; 87: 228-29.

43. Robert A, Eberle D, Kaplowitz N. Role of glutathione in gastric mucosal cytoprotection. *Am J Physiol* 1984; 247: G 296-304.

44. Konturek SJ, Brzozwski T, Dembinski A, Warzecha Z, Konturek PK, Yanaihara N. Interaction of growth hormone releasing factor and somatostatin on ulcer healing and epidermal growth factor. *Digestion* 1988; 41: 121-28.

45. Olsen PS, Poulsen SS, Kirkegaard P, Nexo E. Role of submandibular saliva and epidermal growth factor in gastric cytoprotection. *Gastroenterology* 1984; 87: 103-8.

46. Olsen PS, Poulsen SS, Therkelson K, Nexo E. Oral administration of synthetic human urogastrone promotes healing of chronic duodenal ulcers in rats. *Gastroenterology* 1986; 90: 911-17.

47. Ito H, Guth P. Role of oxygen derived free radicals in haemorrhagic shock-induced gastric lesions in the rat. *Gastroenterology* 1985; 88: 1162-67.

48. Tariq M. Gastric anti-ulcer and cytoprotective effect of Vit E. *Res Commun Chem Pathol* 1988; 60: 87-96.

49. Szabo S. Role of radicals in aspirin-induced gastric mucosal lesions. Abstract, 3rd Inter Science World Conference on inflammation, Monte-Carlo (Principality of Monaco), March 15-18, 1989, 414.

50. Bose R, Brown A, Szabo S. Histochemical and pharmacological studies related to mast cells with ethanol-induced erosions. *Fed Proc* 1985; 44: 733.

51. Galli J, Wershil BK, Bose R, Walker PA, Szabo S. Ethanol-induced acute gastric injury in mast cell-deficient and congenic normal mice: evidence that mast cells can augment the area of damage. *Am J Pathol* 1987, 128: 131-40.

52. Whittle BJR, Oren-Wolman N, Guth PH. Gastric vasoconstrictor actions of leukotrienes C_4, $PGF_2\alpha$ and thromboxane mimetic U-46619 on rat submucosal microcirculation *in vivo*. *Am J Physiol* 1985; 248: G 580-86.

53. Hua HY, Dahlen SE, Lundberg JM, Hammerstroem S, Hedqvist P. Leukotrienes C_4, D_4 and E_4 cause widespread and extensive plasma extravasation in the guinea pig. *Naunyn-Schmiedeberg's Arch Pharmacol* 1985; 330: 136-41.

54. Peskar BM, Lange K, Hoppe U, Peskar BA. Ethanol stimulates formation of leucotrienes C_4 in rat gastric mucosa. *Prostaglandins* 1986; 31: 283-92.

55. Peskar BM, Lange K. Role of leukotriene C_4 in gastric protection by sulfhydryl modulating agents and metals in the rat. *Gastroenterology* 1987; 92: 1573.

56. Svanes K, Ito S, Takeuchi K, Silen W. Restitution of the surface epithelium of in vitro frog mucosa after damage with hyperosmolar sodium chloride. *Gastroenterology* 1982; 82: 1409-26.

57. Rutten MY, Ito S. Morphology and electrophysiology of guinea pig gastric mucosal repair in vitro. *Am J Physiol* 1983, 244; G 171-82.

58. Morris GP, Wallace JL. The roles of ethanol and of acid in the production of gastric erosions in rats. *Virchows Arch (Cell Pathol)* 1981; 38: 23-28.

59. Silen W. Gastric mucosal defense and repair. In: Johnson IR, ed. Physiology of the gastrointestinal tract, 2nd ed. New York: Raven Preess 1987; 1055-69.

60. Koelz HR. Protective drugs in the treatment of gastroduodenal ulcer disease. *Scand J Gastroenterol* 1986; 21: (Suppl 125): 156-63.

61. Tarnawski A, Hollander D, Mach T, Stachura J, Bogdal J. Effect of sucralfate on normal human gastric mucosa. Endoscopic, histologic and ultrastructural assessment (abst). *Gastrointest. Endosc* 1984; 30: 155.

62. Konturek SJ, Stachura J, Radecki T et al. Cytoprotective and ulcer healing properties of prostaglandin E_2, colloidal bismuth and sucralfate in rats. *Digestion* 1987; 38: 103-13.

63. Hollander D, Tarnawski A, Gergely H, Zipser RD. Sucralfate protection of gastric mucosa against alcohol-induced necrosis. A prostaglandin mediated process? *Scand J Gastroenterol* 1984; 19 (Suppl 101): 97-102.

64. Tarnawski A, Hollander D, Krause WJ, Zipser RD, Gergely H. Does sucralfate affect the normal gastric mucosa? Histologic, ultrastructural and functional assessment. *Gastroenterology* 1986; 90: 893-905.

65. Shea-Donahue T, Steel L, Montcalm E, Dubois A. Gastric protection by sucralfate. Role of mucus and prostaglandins. *Gastroenterology* 1986; 91: 660-66.

66. Szabo S, Brown A. Prevention of ethanol-induced vascular injury and gastric mucosal lesions by sucralfate and its components: possible role of endogenous sulfhydryls. *Proc Soc Exp Biol Med* 1987; 185: 493-97.

67. Tarnawski A, Hollander D, Krause WJ, Gergely H. The protective effect of sucralfate against alcohol induced gastric mucosal injury in the rat. Macroscopic, histologic, ultrastructural and functional time sequence analysis. *Gastroenterology* 1985; 88: 366-74.

68. Szabo S, Hollander D. Pathways of gastrointestinal protection and repair: mechanisms of action of sucralfate. *Am J Med* 1989, 86 (Suppl 6A): 23-31.

69. Lam SK. Use of cytoprotective agents in the treatment of gastric ulcers. *Med J Austr* 1985; 142: S21-23.

70. Marshall BJ, Warner JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; 1: 1311.

71. Wierks J, Hespe W, Jaitly KD, Koekkoek PH, Levy U. Pharmacologic properties of colloidal bismuth subcitrate. *Scand J Gastroenterol* 1982; 17 (Suppl 80): 11-16.

72. Hall DWR, Van Den Hoven WE. Protective properties of colloidal bismuth subcitrate on gastric mucosa. *Scand J Gastroenterol* 1986; 21 (122): 11-13.

73. Tytgat GNJ. Colloidal bismuth subcitrate in peptic ulcer—a review. *Digestion* 1987; 37(2): 31-41.

74. Guth PH. Mucosal coating agents and other nonantisecretory agents - are they cytoprotective? *Dig Dis Sci* 1987; 32: 647-54.

75. Peskar BM. Effect of carbenoxolone on prostaglandin synthesis and metabolizing enzymes and correlation with gastric mucosal carbenoxolone concentrations. *Scand J Gastroenterol 15 (Suppl):* 1980; 109-12.

76. La Brooy S, Taylor R, Hunt R et al. Controlled comparison of cimetidine & carbenoxolone sodium in gastric ulcer. *Br Med J* 1979; 1: 1308-9.

77. Hagel J, Renner H, Hirsh M et al. Gastric cytoprotection by antacids and papaverine in rats. *Hepatogastroenterology* 1982; 29: 271-74.

78. Vergin H, Kori-Lindner C. Putative mechanisms of cytoprotective effect of certain antacids and sucralfate. *Dig Dis Sci.* 1990; 35 (11): 1320-27.

79. Kollbert B, Isenberg JI, Johansson C. Cytoprotective effect of omeprazole on rat gastric mucosa. In: Allen A, Garner A, Turnberg L, eds. Mechanism of mucosal protection in the upper gastrointestinal tract. New York, Raven Press, 1984; 351-56.

80. O'Brien PE, Frydman G, Holmes R, Malcontenti G, Phelan D. Evaluation of putative-cytoprotective properties of anti ulcer drugs using quantitiative histological techniques. *Dig Dis Sci* 1990; 35 (9): 1130-39.

81. Bauer RF. Misoprostol: Preclinical Pharmacology. *Dig Dis Sci* 1985; 30 (11 Nov 1985 Suppl): 118 S-25.

82. Brand DL, Roufail WM, Thomson ABR, Tapper EJ. Misoprostol, a synthetic PGE_1 analog, in the treatment of duodenal ulcers. A multi-centre double blind study. *Dig Dis Sci* 1985; 30 (11 - Nov 85 Suppl): 147 S-58.

83. Monk JP, Clissold SP. Misoprostol: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of peptic ulcer disease. *Drugs* 1987; 33: 1-30.

84. Cohen MM. Gastric mucosal protection with prostaglandins. In: Drugs and peptic ulcer, Vol I, Pfeiffer CJ ed. CRS Press, Boca Raton, 1982; 133-46.

85. Brunton LL. Agents for control of gastric acidity and treatment of peptic ulcers. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P eds. The Pharmacological Basis of Therapeutics, New York, Pergamon Press, 1990; 897-913.

86. Strang R. The association of gastro-duodenal ulceration and Parkinson's disease. *Med J Austral* 1965; 1: 842-43.

87. Hernandez D, Orlando R, Adcock J, Patrick K, Nemeroff C, Prange A. Gastric cytoprotection by dopamine agonists. *Clin Res* 1983; 31: 683 A.

88. Parmar N, Tariq M, Ageel A. Effect of bromocriptine, a dopamine receptor agonist, on the experimentally induced gastric ulcers in albino rats. *Life Sci* 1984; 35: 2035-39.

89. Glavin G, Dugani A, Pinsky C. 1-deprenyl attenuates stress ulcer formation in rats. *Neurosci Lett* 1986; 70: 379-81.

90. Sikiric P, Geber J, Ivanovic D, Suchanek E, Gjuris V, Tucan - Foretic M et al. Dopamine antagonists induced gastric lesions in rats. *Eur J Pharmacol* 1986; 131: 105-9.

91. Glavin GB, Szabo S. Dopamine in gastrointestinal disease. *Dig Dis Sci* 1990; 35(9): 1153-61.

92. Konturek SJ, Kitler ME, Brzozwski T, Radecki T. Gastric protection by meciadanol. A new synthetic flanovoid inhibiting histidine decarboxylase. *Dig Dis Sci* 1986; 31: 847-52.

93. Leung FW, Paulsen G, Lo S, Guth PH. Effect of Zy 15029 on absolute ethanol-induced gastric mucosal injury-cytoprotection without prostaglandin. *Clin Res* 1986; 34: 30A.

94. Jayaraj AP, Lewin MR, Tovey FI, Kitler ME, Clark CG. The protective effect of Meciadanol (o-methyl −3 (+) − catechu) on experimental ulceration. *Eur J Pharmacol* 1988; 147: 265-71.

95. Tariq M, Ageel AM. Gastric antiulcer and cytoprotective effects of dipyridamole in rats. *J Pharmacol Exp Ther* 1990 253 (3): 944-49.

96. Wong SH, Cho CH, Ogle CW. Protection by zinc sulphate against ethanol-induced ulceration: Preservation of the gastric mucosal barrier. *Pharmacology* 1986; 33: 94-102.

97. Javor J, Bata M, Lovasz L, Moron F, Nagy L, Pathy I et al. Gastric cytoprotective effects of Vit A and other carotenoids. *Int J Tissue Reac* 1983; 5: 289-96.

98. Satoh H, Guth PH, Grossman MT. Role of bacteria in gastric ulceration produced by indomethacin in the rat: Cytoprotective action of antibiotics. *Gastroenterology* 1983; 84: 483-89.

99. Wallace JL, Keenan CM, Mugridge KG, Parente L. Reduction of the severity of experimental gastric and duodenal ulceration by interleukin−1B. *Eur J Pharmacol* 1990; 186: 279-84.

100. Cho CH, Ogle CW. Modulatory action of adenosine on gastric function and ethanol-induced mucosal damage in rats. *Dig Dis Sci* 1990; 35(11): 1334-39.