THE STRESS ULCER SYNDROME

Het stress ulcus syndroom

PROEFSCHRIFT

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Chapter 1.

Introduction

Stress ulcers (SU) are acute ulcers which develop in the stomachs of severely ill patients. Erosions and acute hemorrhagic gastritis are included in the term stress ulcers. Bleeding from such a lesion is called a stress bleed (SB). The oldest description of SU is probably that of Aulus Cornelius Celsus (1) who described its development in Roman soldiers wounded in battle. In 1772 John Hunter (1) reported "malacia of the stomach" at autopsy examinations, and he considered this to be a lesion which developed before death as a result of a serious illnes. Curling described in 1842 the acute duodenal ulcers in patients with severe burns (2). Gastric ulcers occurring in burned patients were later also included in the definition of Curling's ulcers. Rokitansky described "decubity of the gastric mucosa" in the proximal portion of the stomach in 1846 (3). His description was based on post mortem examinations of patients who had died after severe illness. With better medical care and improving prognosis of previously lethal diseases, the realization grew that this type of gastric damage caused clinical problems in the form of hemorrhage. In 1932 Cushing published the association between ulcers in the upper gastrointestinal tract and brain disease (4).

In the second world war a number of patients were reported with burns who survived the initial fase due to administration of plasma and other solutions, but who subsequently developed sepsis complicated by stress bleeds.

During the past 20 years the association between major trauma and hypovolemic shock and SB has become clearer. Stress bleeds often

develop after a number of days in these patients, especially when major trauma is complicated by a shock lung, renal insufficiency or sepsis. These problems were described extensively in casualties in the Vietnam war and following traffic accidents. Major operations performed in older or previously severely ill patients form another group in whom SB is seen.

The problem of SB is a problem of the intensive care department. The following conditions have been reported to predispose to SU or SB: respiratory insufficiency, hypotension, sepsis, peritonitis, renal insufficiency, major operations, major trauma and jaundice (1,5,6,7). These clinical conditions can be called risk factors. Although extensive burns and brain disease can also lead to ulceration in the stomach, they are often associated with duodenal and/or esophageal lesions. The gastrointestinal lesions associated with burns and brain disease are complicated not only by bleeding but also by perforation. For these and other reasons, described in chapter 2 and 3, they differ morphologically and pathophysiologically from the stress ulceration. The gastric ulceration or erosive gastritis associated with the risk factors is practically never associated with perforation but is clinically of importance because it often results in gastrointestinal hemorrhage. The incidence of SU reported in the literature varies. In one group of trauma patients, stress lesions were found in all patients on endoscopy (6). Stress bleeding occurs in 5-20% of patients in an intensive care unit (5,8,9). Clinically manifest bleeding from a SU has a mortality of more than 30% (10).

Optimal medical care is the basis of the prophylaxis of SB. A prompt treatment of complications or risk factors (e.g. sepsis) is essential. The chance of developing SB is related to the number of risk factors (1,5,6). As not all risk factors can be rapidly reversed, specific prophylaxis of SB is desirable.

Hastings et al (7), using guaiac tests for determination of blood loss, showed that the incidence of SB could be reduced from 25% to 6% by titration of gastric contents with antacids to a predetermined pH. Priebe et al (11) compaired antacids with the histamine-2-antagonist cimetidine in stress bleeding prophylaxis. They found that cimetidine

failed to protect against stress bleeding. These findings were confirmed by Zinner et al (9) and Van den Berg et al (12). The role of gastric acids in the development of SU is not clear. The primary damage associated with the above mentioned risk factors is apparently to the gastric mucosa and diminished perfusion of the gastric mucosa seems to play a major role. Prostaglandins have been shown to be of great importance in the maintenance of the integrity of the gastric mucosal barrier. They have been demonstrated to protect the gastric mucosa against damage by acetylsalicylic acid (13) and absolute alcohol (14). This effect of prostaglandins has been called cytoprotection (14,15,16). Although some prostaglandins (PGE_1, PGE_2, PGA_1) can reduce gastric acid production when given in large doses, the cytoprotective effects on the gastric mucosa are not dependent on a reduction of gastric acidity (17).

To determine the possible clinical applications of the cytoprotective effects of prostaglandins in the prophylaxis of SU and SB we performed a clinical study in intensive care patients. In this study we used prostaglandin E_2, the prostaglandin that is normally present in gastric mucosa (18). The results of this study are described in chapter 5. In chapter 2 stress ulcers are discussed further with regard to the localization and the histology. In chapter 3 the pathophysiology of stress ulcers is described in detail, and the evidence for cytoprotection by prostaglandins in chapter 4. The patients, methods and results of the clinical study are reported in chapter 5. In chapter 6 problems associated with the measurement of blood loss in gastric juice are described. In chapter 7 a new method we developed to measure gastrointestinal blood loss quantitatively is reported. Chapter 8 describes DNA measurements in gastric juice. Chapter 9 contains a general discussion on the treatment and prevention of stress ulcers and stress bleeds. Finally, a discussion and summary is given in chapter 10.

1.1 REFERENCES

1. Stremple JF, Mori H, Lev R, Glass GBJ. The stress ulcer syndrome. Curr Probl Surg, April 1973.
2. Curling TB. On acute ulceration of the duodenum in cases of burns. Med Chir Trans (London) 1842;25:260.
3. Lucas CE. Stress ulceration: the clinical problem. World J Surg 1981;5:139-151.
4. Cushing H. Peptic ulcers and the interbrain. Surg Gynecol Obstet 1932;55:1-34.
5. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with letal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523-530.
6. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266-273.
7. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding. N Eng J Med 1978;298:1041-1045.
8. Harris SK, Bone RC, Ruth WE. Gastrointestinal hemorrhage in patients in a respiratory intensive care unit. Chest 1977;72:301-304.
9. Zinner MJ, Zuidema GD, Smith PL, Marilyn Mignosa. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet 1981;153:214-220.
10. Cheung LY. Treatment of established stress ulcer disease. World J Surg 1981;5:235-240.
11. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980;302:426-430.
12. Van den Berg B, Van Blankenstein M. Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion 1985;31:1-8.
13. Cohen MM, Gladys Cheung, Lyster DM. Prevention of aspirin-induced

faecal blood loss by prostaglandin E_2. Gut 1980;21:602-606.

14. Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury. Gastroenterology 1979;77:433-443.
15. Robert A. Antisecretory, antiulcer, cytoprotective and diarrheogenic properties of prostaglandins. In: Advances in Prostaglandin and Thromboxane Research. Samuelsson B, Paoletti R (eds). Raven Press, New York. Vol.2, 1976:pp.507-520.
16. Miller TA, Jacobson ED. Gastrointestinal cytoprotection by prostaglandins. Gut 1979;20:75-87.
17. Wilson DE, Kaymakcalan H. Prostaglandins: gastrointestinal effects and peptic ulcer disease. Med Clin North Am 1981;65:773-787.
18. Bennett A, Murray JG, Wyllie JH. Occurrence of prostaglandin E_2 in the human stomach, and a study of its effects on human isolated gastric muscle. Br J Pharmac Chemother 1968;32:339-349.

Chapter 2.

Pathology of stress ulcers

2.1 LOCALIZATION AND MACROSCOPY

Stress ulcers are usually multiple and occur mainly in the proximal part of the stomach. Skillman et al (1) found multiple superficial ulcers in the fundus of the stomach in six patients with respiratory insufficiency, hypotension, sepsis and jaundice who had had massive gastrointestinal hemorrhage. The antrum was involved in only one patient, in addition to the lesions in the fundus. The lesions varied in size from 0.2 cm. to 4.0 cm. in diameter. Erosions are almost always present at the same time as ulcers (2,3). Ulcers develope from erosions, as has been shown by the studies of Lucas et al (4) who performed serial gastrophotography studies in 42 seriously ill patients with sepsis and/or trauma. Within the first 24 hours pale areas were seen in the proximal portion of the stomach. After 24 hours erosions with a red base and petechia were seen in the same portion of the stomach, mainly on the greater curvature. After 48 hours larger erosions (2 to 25 mm. in diameter), which were slightly deeper with a dark base were seen. These were situated more distally, but still within the corpus. Damage limited to the antrum was not observed. The three patients who did have erosions in the antrum also had multiple lesions in the proximal area of the stomach. In the patients who had recurrent bleeds, the erosions remained throughout 3 weeks. On the other hand in patients who were recovering the erosions became more superficial, the base changed in colour from black to red and finally a completely normal mucosa was seen. The predilection for the corpus

of the stomach was confirmed by Stremple et al (3) in 14 patients with major trauma and gastrointestinal bleeding. Solitary ulcers were never seen, all patients had multiple (mainly 3 to 6) ulcers with a mean diameter of 1 cm. One ulcer had penetrated deeply into the muscularis propria. In all investigated patients with a bleed a large artery was seen in the base of an ulcer. In addition to the ulcers, multiple erosions were seen. These authors described the ulcers as lying between the gastric mucosal folds. An explanation for the development of stress ulcers in the proximal portion of the stomach with sparing of the antrum, is given in chapter 3.

The concept of stress ulcers should not be limited to the stomach (5). In the seriously ill patient the small and large bowel can also be involved. Stremple et al (3) found extensive hemorrhagic necrosis of the stomach and multiple ulcers in the small bowel in a patient with a gunshot wound of the chest and the thoracic spine. At operation they also found duodenal ulcers which, in view of the description - ulcer craters with raised, firm edges - were probably preexistant and should be regarded as chronic rather than acute ulcers and therefore not as stress ulcers. Of greater importance is the fact that they found lesions in the colon of 8 patients; in 5 of these there was simultaneous gastroduodenal ulceration. Lucas et al (6) found hyperemic areas at endoscopy of the small and large bowel. These patients also had acute erosive gastritis. The duodenum and the terminal ileum appeared to be the most susceptible parts of the small bowel for stress lesions (7). Isolated or confluent red (hyperemic) areas can progress into mucosal ulcers which are small, superficial and of irregular form. Perforation is rare. The mesenteric arteries are open and there is no relationship between the position of the lesions and the topography distribution of the abdominal arteries (8,9,10). The risk factors for the development of lesions in small and large intestine, described in the literature, are the same as those for stress ulcers in the stomach, except for jaundice. Heart disease has been cited as an additional risk factor (8,9,10).

2.2 MICROSCOPY

The stress ulcer (or erosion) is characterized histologically by loss of the surface epithelium, with loss of cells which can continue into the submucosa and occasionally into the muscularis propria. There is edema and hemorrhage (3,4). In the immediate vicinity there is usually some acute inflammatory infiltration (4,11). In Fig.1 a stress erosion is shown.

Fig.1. Cross section of the gastric mucosa with centrally located in this photograph a superficial mucosal defect. Underneath this erosion a dilated capillary vessel is seen (hematoxylin-eosin, 60x).

Typically there is no evidence for chronic inflammation (11). Lesions which are some days old, show a fibrinous exsudate and signs

of regeneration (1,3). Various changes may be seen in the adjoining blood vessels. Lucas et al (4) found no thrombosed vessels in the early stages of stress ulcers. Stremple et al (3) found in some patients organized thrombi in the submucosal vessels. Margaretten et al (10) found in approximately two thirds of patients with hemorrhagic lesions in the digestive tract, on post mortem examination fibrin thrombi in the microcirculation of the mucosa and submucosa of stomach and intestine. These changes, taken together with changes in the clotting parameters, could be explained by diffuse intravascular coagulation. As mentioned above, Stremple et al found a large artery in the base of the ulcer in all patients with hemorrhage (3). This is in contrast to others who have postulated that hemorrhage is always derived from small, superficial vessels.

Three dimensional topographic photography of the gastric mucosa has shown that in the early phase the apical membrane of the epithelial cells is lost, with release of cell contents (4). When the cells are subsequently completely destroyed, erosions develop and fibrin bundles with entrapped erythrocytes are seen (4,5). In the macroscopically non-involved parts of the gastric mucosa, the cells are morphologically intact with normal mucus content of the mucus cells and, on electron macroscopy, normal cell junctions are seen between epithelial cells (3,5).

The microscopy of the gastric lesions is similar to that of the lesions in the small and large intestine (9). The destruction of cells is usually limited to the mucosa, but can continue into the submucosa and occasionally into the muscularis propria. There is also edema and hemorrhage. Few inflammatory changes are seen, except in patients with lesions of longer duration. Continuation of the process leads to replacement of the mucosa by a membrane composed of cell debris and fibrin. In general fibrin thrombi, emboli or obstructive arterial disease are absent. Margaretten et al have found fibrin thrombi in the microcirculation of the mucosa and submucosa, as described above (10). Levine states that the main characteristics are mucosal hemorrhage and thrombosis of the mucosal capillaries (8). Obstruction of larger vessels has not been described.

2.3 DIFFERENTIATION FROM OTHER ULCERS

A. Ulcers occurring in patients with extensive burns (Curling's ulcers) are found either in the stomach, mainly in the fundus and corpus in the earlier phases (12,13) or in the duodenum in the later phase (13). Lesions are usually found in both the stomach and the duodenum (12). The lesions in the stomach are multiple and superficial and have the macroscopic appearance of stress ulcers, but they sometimes progress to perforation (14). In the duodenum usually a solitary ulcer is found with histologically chronic inflammation and deep penetration into the submucosa and muscularis propria. Perforation is not uncommon.

B. Ulcers occurring in association with cerebral or spinal column lesions (Cushing's ulcers) are to be found not only in the stomach but also in esophagus and duodenum (15,16). These ulcers are frequently deep with extensive necrosis and they often lead to perforation (15).

C. A chronic peptic ulcer occurs at some stage in 5 to 10% of the population (17). Peptic ulcers are found four times more often in the duodenum than in the stomach (17). In the stomach peptic ulcers are to be found mainly in the antrum and on the lesser curvature and, in the duodenum, most commonly in the duodenal bulb (18). Endoscopically these ulcers are usually solitary, and are often deep with a raised edge. Histologically, chronic inflammatory infiltrates are present with fibrosis. Penetration into the deeper layers and perforation are not rare.

D. Ulcers and erosive gastritis caused by drugs such as aspirin and other non-steroidal analgetic and anti-inflammatory agents, and by alcohol form a separate entity. The lesions are morphologically identical to stress lesions, but they are localized mainly in the distal rather than the proximal part of the stomach (2,19,20).

These four forms of ulcers must therefore be differentiated from stress lesions on the basis of both localization and histology. The pathophysiology of these lesions is also different, as will be described in the next chapter.

2.4 REFERENCES

1. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523-530.
2. Skillman JJ, Silen W. Stress ulcers. Lancet 1972;2:1303-1306.
3. Stremple JF, Mori H, Lev R, Glass GBJ. The stress ulcer syndrome. Curr Probl Surg. April 1973.
4. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266-273.
5. Lucas CE. Stress ulceration: the clinical problem. World J Surg 1981;5:139-151.
6. Lucas CE, Sugawa C, Friend W, Walt AJ. Therapeutic implications of disturbed gastric physiology in patients with stress ulcerations. Am J Surg 1972;123:25-34.
7. Menguy R. Role of gastric mucosal energy metabolism in the etiology of stress ulceration. World J Surg 1981;5:175-180.
8. Levine MA. The entity of hemorrhagic necrosis of the intestine. Am J Gastroent 1970;54:490-495.
9. Bounous G. Acute necrosis of the intestinal mucosa. Gastroenterology 1982;82:1457-1467.
10. Margaretten W, McKay DG. Thrombotic ulcerations of the gastrointestinal tract. Arch Intern Med 1971;127:250-253.
11. Skillman JJ, Silen W. Stress ulceration in the acutely ill. Ann Rev Med 1976;27:9-22.
12. Cjaza AJ, McAlhany JC, Pruitt BA. Acute gastroduodenal disease after thermal injury: an endoscopic evaluation of incidence and natural history. N Engl J Med 1974;291:925-929.
13. Sevitt S. Duodenal and gastric ulceration after burning. Br J Surg 1967;54:32-41.
14. Pruitt BA, Foley FD, Moncrief JA. Curling's ulcer: a clinical-pathological study of 323 cases. Ann Surg 1970;172:523-539.

15. Cushing H. Peptic ulcers and the interbrain. Surg Gynecol Obstet 1932;55:1-34.
16. Kamada T, Fusamoto H, Kawano S, Noguchi M, Hiramatsu K, Masuzawa M, Sato N. Acute gastroduodenal lesions in head injury. Am J Gastroent 1977;68:249-253.
17. Kurata JH, Haile BM. Epidemiology of peptic ulcer disease. Clin Gastroenterol 1984;13:289-307.
18. Shearman DJC, Finlayson NDC. Peptic ulceration. In: Diseases of the gastrointestinal tract and liver. (Shearman DJC and Finlayson NDC, eds.) Churchill Livingstone, London 1982:pp.134-168.
19. Gilbert DA, Surawicz CM, Silverstein FE, Weinberg CR, Saunders DR, Feld AD, Sanford RL, Bergman D, Washington P. Prevention of acute aspirin-induced gastric mucosal injury by 15-R-15 methyl prostaglandin E_2: an endoscopic study. Gastroenterology 1984;86:339-345.
20. Burbige EJ, Lewis DR, Halsted CH. Alcohol and the gastrointestinal tract. Med Clin North Am 1984;68:77-89.

Chapter 3.

Pathophysiology of stress ulcers

3.1 INTRODUCTION

In general stress ulcers and erosive gastritis are limited to the mucosa of the stomach and do not penetrate into deeper layers. In man mucosal changes can be detected within 24 hours of the development of the serious clinical condition (1). In animal experiments microscopical changes have been found in the mucosa of the gastric fundus within minutes of the onset of hemorrhagic shock; macroscopical lesions were visible within one hour (2). These lesions could also be induced in the terminal ileum and in the colon.

It is an intriguing observation that the antrum of the stomach is very rarely involved. The acid producing portion of the stomach (the fundus and the corpus), is apparently more vulnerable. Although gastric acid plays a role in the development of stress ulcers, it is not clear whether this is the only or even the most important factor. Stress lesions in ileum and colon do not arise in an acid environment and stress ulcers have also been found in stomachs of patients with atrophic gastritis (2). The fundamental change is a rapid loss of the integrity of the gastric mucosal barrier under influence of the risk factors.

In this chapter mucosal defense mechanisms will be described. The risk factors which predispose to stress ulcers are discussed. Stress ulcers do not develop as a consequence of only one of these risk factors. It is the combination of risk factors that is able to overwhelm the mucosal barrier.

3.2. GASTRIC MUCOSAL BARRIER

A precise description of the gastric mucosal barrier, which forms the boundary between the highly acidic, pepsin containing fluid in the stomach and the vulnerable cell layer, is difficult to give. A hydrogen ion-gradient is maintained from pH 2 to 3 (lumen) to pH 6 to 8 (cell surface). The gastric mucosal barrier can therefore be defined as the factors that prevent back-diffusion of secreted hydrogen ions. Davenport (3), who has investigated extensively situations where back-diffusion of hydrogen ions occurs, considered the gastric mucosal barrier to be mainly determined by the tight junctions between cells. He ascribed the back-diffusion of acid under influence of salicylates to an increased permeability of the mucosa, and suggested that the mucosal damage developes from this back-diffusion. However it is difficult to accept that the gastric mucosal damage is directly dependent on the back-diffusion of a certain amount of acid, as specified amounts of acids diffusing back within a certain time will give rise to mild damage in the presence of aspirin but no damage in the absence of aspirin (4,5). In other studies it has not been possible to demonstrate back-diffusion of acid in experimental shock (6,7,8).

Kivilaakso et al (9) considered the low intramural pH of the gastric mucosa in shock to be mainly due to a decreased acid secretion in shock. The question of decreased acid secretion versus back-diffusion of secreted acid has not been solved (6). Aspirin, other non-steroidal anti-inflammatory drugs, bile acids, alcohol and hypertonic salt solutions all cause morphological changes in the gastric mucosa - namely loss of epithelial cells (10). That this loss of epithelial cells is associated with back-diffusion of acid into the mucosa is not surprising. The gastric mucosal barrier can also be regarded as the epithelial layer of the gastric mucosa (6), and damage to the mucosal barrier as loss of this cell layer or at least loss of the apical membrane of these cells with or without maintenance of the tight junctions (11).

Apart from influx of hydrogen ions this is associated with efflux

of sodium and potassium ions and organic material and hydrogen ions from the parietal cells.

3.3 MUCUS LAYER

The gastric mucosa under normal physiological circumstances is covered by a layer of mucus, which consists of 2/3 glycoproteins and approximately 1/3 free proteins (12).

The mucus is produced by the superficial epithelial cells and the neck cells, and is released mainly by exocytosis and apical expulsion and also by exfoliation of the older cells (13). Little is known about the regulation of mucus production (14). Mucus thickness is difficult to measure and the relationship between intracellular mucus, the mucus gel on the mucosa and the free mucus present in gastric juice (dissolved mucus) is not clear. A low intraluminal pH is associated with a greater amount of free mucus (14). Carbenoxolone and prostaglandins facilitate the apical expulsion of mucus (15). Urea causes dissociation of mucus (16). Aspirin decreases the thickness of the mucus layer, lowers the glycoprotein content of the gastric juice and interferes with the production of mucus in the cell (14). Aspirin acts on the apical expulsion of mucus, probably to such an extent that the cell is exposed for prolonged periods to hydrogen ions and pepsin and is damaged after mucus depletion (15). As prostaglandins increase the apical expulsion of mucus, probably in a gradual fashion, and cause a thickening of the mucus layer (15,17) and increase the mucous content of the gastric juice (18), these compounds (19) appear to be of major importance for the mucus layer and mucosal protection.

The rate of diffusion of hydrogen ions to the mucus gel is approximately four times slower than that through the unstirred water layer (20). The mucus layer is therefore not a good barrier against acid. Large molecules, such as pepsin, cannot pass easily through the mucus layer (21). It is not clear how the still larger pepsinogen molecule passes through the mucus to the lumen. With micro-electrodes it has been shown that the pH of the mucus layer is approximately 7

on the epithelial side, and approximately 2 on the luminal side (22,23).

3.4 BICARBONATE

The stomach is capable of producing bicarbonate (14). This is easy to demonstrate in the antrum, but more difficult in fundus and corpus, which are major acid producing areas (21). In the antrum bicarbonate is probably partly passively transported and in the fundus largely actively secreted (14). In animal experiments alkali production has been shown to be 5-10% of the maximal acid output (14). The alkaline secretion is diminished by anoxia and adrenalin and stimulated by gastric acid and probably also by stimulation of the vagus (14). Exogenous prostaglandins stimulate alkaline secretion (14,19,24). Aspirin and other non-steroidal anti-inflammatory agents decrease the secretion of bicarbonate, and this inhibition can be prevented by the prior administration of 16, 16 dimethyl-prostaglandin E_2 (25). There is good evidence that the basal bicarbonate secretion is dependent on endogenous prostaglandin synthesis (14).

3.5 MUCUS-BICARBONATE

Mucus and bicarbonate individually cannot protect the gastric epithelium against gastric acid and pepsin. Mucus alone has little buffering capacity and has no anti-pepsin activity (14). A relatively small amount of bicarbonate by itself would be directly neutralized by the acid which is present in excess. However studies have shown that the mucus layer together with the bicarbonate appear to be capable of maintaining a pH gradient of approximately 2 on the luminal side to approximately 7 on epithelial side of the mucus layer (22,23,26), and thus to protect the gastric mucosa (Fig.1). The mucus gel is constructed in such a way that a small amount of penetrating hydrochloric acid is continually neutralized by bicarbonate coming

from the epithelial side. The mucus-bicarbonate-model implies a continuing secretion of bicarbonate. The pH on the epithelial side is increased by the administration of 16, 16-dimethyl-prostaglandin E_2 and is decreased by aspirin and other non-steroidal anti-inflammatory drugs (21). Aspirin is indeed capable of destroying the whole pH gradient of the mucus layer within a few minutes (14). A very low intraluminal pH (lower than pH 1.4) also results in a lower pH gradient, so that the mucus bicarbonate barrier does not completely protect the cell layer against acid (14).

3.6 MUCUS-BICARBONATE BARRIER IN RELATION TO ACID SECRETION AND CIRCULATION

Gastric acid (hydrochloric acid, HCl) is secreted by the parietal cells in the gastric glands (Fig.1). Hydrogen ions (H^+) leave at the apical membrane of the cell. Intracellularly, bicarbonate (HCO_3^-) is formed, which passes across the basolateral membrane and is released into the interstitium of the lamia propria (14). The intramural pH of the gastric mucosa is increased in this way (46). Gastric mucosa which is actively secreting acid was shown to resist high concentrations of intraluminal acid better than resting mucosa (9,46).

Gannon et al (27) described blood flow in the mucosal exchange vessels (capillaries) occuring only in a unidirectional fashion, from the serosal to the luminal aspect. They hypothesized a vascular transport of HCO_3^-, released interstitially by secreting parietal cells, and taken away by fenestrated capillaries, from deep within the mucosa toward the gastric surface, thereby providing an optimal acid-base status for the superficial epithelial cells to secrete HCO_3^-, or for the neutralization of back-diffusing H^+. HCO_3^- is secreted into the mucus layer, which is formed by superficial epithelial cells and by mucus cells in the gastric glands. Continuous secretion of HCO_3^- maintains a pH gradient across the mucus layer. These aspects are shown schematically in Fig.1.

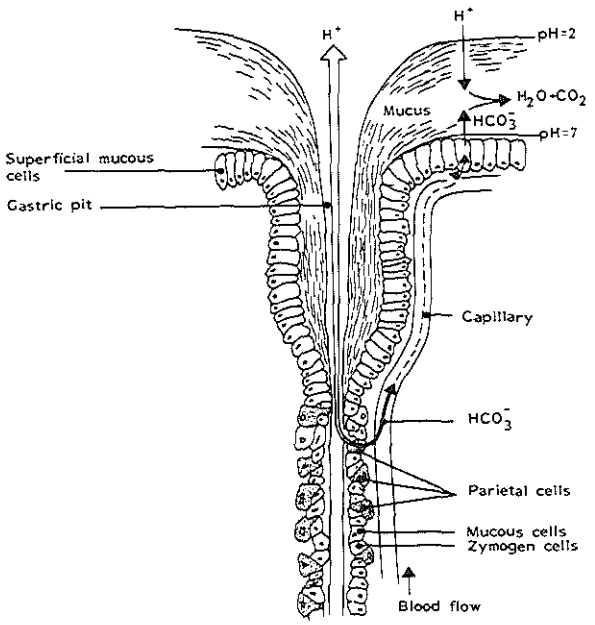

Fig.1. Schematic diagram of the gastric mucus-bicarbonate barrier, and proposed relation to acid secretion and capillary circulation.

3.7 GASTRIC ACID AND PEPSIN

Many authors have stated that acid and pepsin are necessary for the development of stress ulcers (7,8,16,28,29). However stress ulcers are also seen in the absence of acid, notably in the small and large bowel. Prophylactic administration of antacids or histamine-2-receptor-antagonists do not result in complete prevention of bleeding from the upper gastrointestinal tract (30,31,32,33,34). In general, acid production is not increased in patients under stress, and in the first days after onset of the stress situation acid secretion is often decreased (16,35,36). An increased gastric acid secretion develops during prolonged stress, after several days (1,36,37). The role of gastric acid in the development of stress

ulcers therefore is still not clear (2). The early decrease in acid production occurs at the same time as a decrease in blood flow through the gastric mucosa, which has been regarded as being a major factor in the development of acute mucosal lesions (6). The mucosal lesions caused by ischemia and other risk factors can in second instance become larger and deeper by the actions of acid and pepsin.

3.8 GASTRIC MUCOSAL BLOOD FLOW; THE ROLE OF HYPOTENSION

Mucosal ischemia appears to be the most important factor in the development of stress ulcers (6,16,35,38). Shock results, by the sympathetic nervous system, in constriction of the splanchnicus blood vessels. The effect of adrenalin on intestinal blood flow in shock and stress is not always inhibitory, the alpha-effect being vasoconstriction and the beta-effect being vasodilation (39). In experimental animals in general a decreased mucosal blood flow is necessary for the development of stress ulcers (16,38). An increased mucosal perfusion caused by intra-arterial infusion of isoprenaline can prevent gastric ulcers in dogs with hemorrhagic shock (40). In clinical situations stress lesions often develope in patients in whom the gastric mucosal blood flow has been reduced for only a brief period. Ischemia can give rise to mucosal lesions within in relatively short period (some hours) (1,37). The mucosal blood flow of the stomach can theoretically be circumvented by submucosal arteriovenous anastomoses, but there is still some discussion whether such anastomoses exist (27,41). Decreased mucosal blood flow results initially in an energy deficit, but eventually causes cell necrosis. Shortage of oxygen interferes with adenine nucleotide metabolism (2). Menguy and co-workers (42) showed in rats that hemorrhagic shock resulted in a greater lowering of adenosine triphosphate (ATP) in the gastric mucosa than in the liver or skeletal muscle. Energy metabolism of the gastric mucosa is therefore much more sensitive to ischemia than the liver or skeletal muscle, possibly due to the relatively lower glycogen level. These authors demonstrated a lesser decrease in

the ATP concentration in the antrum of rabbits than in the corpus or fundus of the stomach (2,43). In these experiments with rats and rabbits corrections were made for possible local differences in blood flow. In addition the authors found that hemorrhagic shock following fasting resulted in larger stress lesions and lower ATP levels than in the post-prandial situation (44). Low ATP levels were also found in the small bowel following shock and especially in areas where ulcers first develop, namely the duodenum and the terminal ileum (2). ATP shortage reduces the activity of the sodium pump and at a certain level more sodium ions and water will enter the cell, resulting in cell death (2).

The findings of Menguy and co-workers appear to provide a better explanation for the development of stress ulcers than those of Silen and co-workers (6,28), who ascribed the consequences of mucosal ischemia to the development of a low pH in the mucosa due to increased back diffusion of hydrogen ions and a decreased buffering capacity for acid in the gastric mucosa. Silen and co-workers postulated that this lowering of intramural pH, which not only comes from back-diffusion of hydrogen ions but also by a decreased venous removal of hydrogen ions and a decreased arterial supply of bicarbonate, taken together with the associated systemic acidosis, results in loss of mucosal areas. Increased intraluminal hydrogen ion concentrations results in an increase in blood flow through the gastric mucosa (45) so that the intramural pH does not decrease. However above a certain hydrogen ion concentration the perfusion does not increase further and intramural pH can decrease. The buffering bicarbonate is also supplied by actively secreting parietal cells (22). The histamine stimulated stomach is more resistent to ulceration than the metiamide inhibited stomach (46), which could be related to the high and/or low hydrogen ion concentration in the gastric mucosal cell. These theories, however, do not explain why back diffusion of hydrogen ions should increase in stress.

3.9 UREMIA

Stress ulcers in uremia develop mainly in the corpus of the stomach but also in the duodenum (47). Fifteen-30% of the circulating urea diffuses into the gastrointestinal lumen (47). In patients with uremia a raised urea level has been found in gastric juice and it has been shown that high concentrations of urea can dissolve human gastric mucus (48). Urea in high concentrations also causes direct damage to the superficial cells of the stomach without dissolution of the tight junctions (49). Cronic renal failure is often accompanied by various forms of gastric lesions, which can not always be differentiated from stress lesions. Stress ulcer may develop in patients suffering from renal failure together with other risk factors.

3.10 BILE ACIDS

In severely ill patients biliary reflux from the duodenum into the stomach is often seen, caused amongst other things by paralytic ileus. Closure of the pylorus decreases the development of gastric ulcers in dogs subjected to hemorrhagic shock, and stress ulcers can be provoked by administration of taurochlorate into the stomach (50,51).

Martin and co-workers (52) showed that bile salts are capable of changing the physical characteristics of the mucous layer. Damage to the superficial cells of the stomach by bile salts occurs despite an intact tight junction (49). Although an increased back-diffusion of hydrogen ions following the effect of bile has often been suggested (9,10,53), the back-diffusion appears to be more the result of the lesions caused by bile salts than the cause of the lesion. Bile salts have differing effects at differing pH levels (9,54), depending on the PKa. Taurochlorate (PKa 1.8), for example, only damages an intact stomach at a low intraluminal pH. Deconjugated bile salts and dihydroxy bile salts give rise to more mucosal lesions than do conjugated bile salts and trihydroxy bile salts (55). Deconjugated bile salts however, precipitate at low pH and become inactive because

their PKa is higher than 5 (9,54).

Ritchie (55) performed a series of elegant studies in dogs in which he showed that gastric mucosal lesions only developed in the presence of the combination of acid, bile salts and mucosal ischemia. He also studied intensive care patients and showed that this combination of factors is necessary for the development of gastric lesions in humans, and that in patients bile salts also play a role. He was able to demonstrate an increased gastric mucosal blood flow following exposure of the gastric mucosa to bile salts at a low pH, and that the blood flow was directly related to the hydrogen ion back-diffusion.

In practice it is important to know that bile salts in physiological concentrations and at low pH (that is below the PKa of the toxic bile salts) can give rise to gastric lesions in the presence of mucosal ischemia. This is in agreement with the clinical observation that stress lesions often are seen shortly after gastric juice with a low pH becomes bile tinted (56). Probably, biliary reflux into the stomach in combination with one or more risk factors - and not only mucosal ischemia - can lead to stress ulcer formation.

3.11 JAUNDICE

In the most extreme example of jaundice, namely acute liver insufficiency, upper gastrointestinal bleeding occurs in approximately 50% of patients (57).

Skillman and co-workers (58) and Lucas and co-workers (1) already regarded jaundice as a risk factor. The manner in which jaundice promotes the development of stress ulcers is not clear. It is possible that the mechanism is related to the associated disturbances in clotting, which exacerbate bleeding from erosions or ulcers resulting from other risk factors (57).

3.12 SEPSIS AND PERITONITIS

As not every sepsis is associated with shock, stress ulcers in septic patients can not always be explained by hypotension.

Le Gall and co-workers (59) showed endoscopically that sepsis by itself could give rise to stress ulcers in intensive care patients. Sepsis is often associated with a hyperdynamic circulation, and this should not necessarily be associated with a decrease in gastric blood flow. In septic animals an increased blood flow to the stomach, including the gastric mucosa, has indeed been observed (56). Sepsis, like shock, probably causes a redistribution of blood flow to the detriment of the subepithelial capillaries of the gastric mucosa, resulting in epithelial hypoxia (60). Little is known about the role of endotoxins in the development of stress ulcers. Sepsis often causes hypofibrinogenemia, thrombocytopenia and thrombocytopathy, which can increase or prolong blood loss. Sepsis complicating shock or trauma causes a marked increased risk of stress ulcers developing (56). In general gram negative bacteria are involved (36). The chance of stress ulcers developing is also dependent on the source of the sepsis: intraperitoneal and pulmonary infections result in a greater chance of stress ulcers than cellulitis, phlebitis and soft tissue abcesses (56).

3.13 RESPIRATORY INSUFFICIENCY

Bleeding from stress ulcers occurs in approximately 20% of patients with respiratory insufficiency, and the incidence is much higher when adult respiratory distress syndrome is the cause of the respiratory insufficiency (61). The mechanism for the development of stress ulcers is probably tissue hypoxia (34) together with an increased gastric acid production (61).

3.14 MAJOR OPERATIONS AND MULTIPLE TRAUMA

The extent and duration of the operation and severity of trauma are directly related to the risk of developing stress ulcers and stress bleeding (36). Both are often associated with paralytic ileus (62). The majority of the patients described by Beil and co-workers (63) with postoperative hemorrhage had associated infections. Fogelman and co-workers (64) described acute gastrointestinal ulceration after operational trauma in a group of patients with whom more than the half were septic. Lucas and co-workers (1) found within 24 hours gastric lesions in all patients with major trauma. In these patients there was often associated sepsis, renal insufficiency or jaundice. Gastric acid production is in general reduced in the first 2 to 3 days after trauma, but thereafter it is increased with a raised pepsin, protein, DNA and sialic acid content of the gastric juice (65,66). Temporary hypotension appears to play the greatest role in the pathogenesis of stress ulcer both following trauma as well as following major operations.

3.15 CORTICOSTEROIDS

Patients treated on an intensive care are often given corticosteroids. These could theoretically play a role in the development of stress ulcers. The effect of corticosteroids on gastric mucosa is a controversial area. Both harmful (67,68) as well as favourable (69) effects have been described. Conn and Blitzer (70) in a large study were unable to find a clear relationship between corticosteroid treatment and peptic ulcers. A favourable effect of corticosteroids could theoretically be derived from lysosomal stabilisation (71) and deleterious effects of corticosteroids are exemplified by delayed healing of peptic ulcers and reactivation of existing duodenal or gastric ulcers (72). Whether corticosteroids promote the development of stress ulcers is not known. Corticosteroids inhibit the enzyme phospholipase, which converts phospholipids into

arachidonate and other precursors of prostaglandins (73). Prostaglandins are present in relatively high concentrations in gastric mucosa (74,75) and they play an important role in the maintenance of gastric mucosal integrity (75,76). Theoretically therefore corticosteroids could facilitate the development of stress ulcers by prostaglandin depletion.

3.16 PROSTAGLANDINS

Prostaglandins protect the stomach against the damaging effects of aspirin, alcohol, hydochloric acid, sodium hydroxide, hypertonic salt solutions and heat (77,78). Prostaglandins also decrease acid production (78). However they protect against damaging substances at dosage levels which do not decrease gastric acid secretion (75). This effect has been called cytoprotection (76,79), a concept which will be discussed further in the next chapter. Risk factors, such as hypotension, could cause a deficiency of prostaglandins, whereby the gastric mucosa is incapable of withstanding the effects of acid and pepsin, thus leading to the development of stress ulcers.

3.17 REFERENCES

1. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266-273.
2. Menguy R. Role of gastric mucosal energy metabolism in the etiology of stress ulceration. World J Surg 1981;5:175-180.
3. Davenport HW. Salicylate damage to the gastric mucosal barrier. N Eng J Med 1967;276:1307-1312.
4. McGreevey JM, Moody FG, Zalewsky C. Effects of topical 16,16-dimethyl prostaglandin E_2 on aspirin ulcerogenesis. Surg Forum 1978;219:413-415.
5. Chung RSK, Field M, Silen W. Effects of methylprednisolone on hydrogen ion absorption in the canine stomach. J Clin Invest 1978;62:262-270.
6. Marrone GC, Silen W. Pathogenesis, diagnosis and treatment of acute gastric mucosal lesions. Clin Gastroenterol 1984;13:635-650.
7. Moody FG, Aldrete JS. Hydrogen permeability of canine gastric secretory epithelium during formation of acute superficial erosions. Surgery 1971;70:154-160.
8. Zinner MJ, Turtinen L, Gurll NJ. The role of acid and ischemia in the production of stress ulcers during canine hemorrhagic shock. Surgery 1975;77:807-816.
9. Kivilaakso E, Silen W. Pathogenesis of experimental gastric mucosal injury. N Engl J Med 1979;301:364-369.
10. Ritchie WP. Pathogenesis of acute gastric mucosal injury. Viewpoints on Digest Dis 1983;15:17-20.
11. Eastwood Gl. Effect of pH on bile salt injury to mouse gastric mucosa: a light-and electron-microscopic study. Gastroenterology 1975;68:1456-1465.
12. Allen A. Structure of gastrointestinal mucus glycoproteins and the viscous and gel forming properties of mucus. Br Med Bulletin 1978;34:28-33.
13. Zalewsky CA, Moody FG. Mechanisms of mucus release in exposed

canine gastric mucosa. Gastroenterology 1979;77:719-729.

14. Rees WDW, Turnberg LA. Biochemical aspects of gastric secretion. Clin Gastroenterol 1981;10:521-554.
15. Moody FG, Zalewsky CA, Larsen KR. Cytoprotection of gastric epithelium. World J Surg 1981;5:153-163.
16. Skillman JJ, Gould SA, Chung RSK, Silen W. The gastric mucosal barrier: clinical and experimental studies in critically ill and normal man, and in the rabbit. Ann Surg 1970;172:564-584.
17. Bickel M. Effect of 16,16-dimethyl prostaglandin E_2 on gastric mucus gel thickness. Prostaglandins 1981;21 (suppl.) 63-65.
18. Johansson C, Kollberg B. Stimulation by intragastrically administered E_2 prostaglandins of human gastric mucus output. Eur J Clin Invest 1979;9:229-232.
19. Bolton JP, Palmer D, Cohen MM. Stimulation of mucus and nonparietal cell secretion by the E_2 prostaglandins. Dig Dis 1978;23:359-364.
20. Williams SE, Turnberg LA. Retardation of acid diffusion by pig gastric mucus: a potential role in mucosal protection. Gastroenterology 1980;79:299-304.
21. Garner A, Flemström G, Allen A. Gastroduodenal alkaline and mucus secretions. In: Basic science in gastroenterology: Physiology of the gut. Polak JM, Bloom SR, Wright NA, Butler AG (Eds.) Glaxo Group Research Limited; Ware. 1984:pp.207-223.
22. Williams SE, Turnberg LA. Demonstration of a pH gradient across mucus adherent to rabbit gastric mucosa: evidence for a "mucus-bicarbonate" barrier. Gut 1981;22:94-96.
23. Ross IN, Bahari HMM, Turnberg LA. Studies of the gastric "mucus-bicarbonate" barrier: the influence of aspirin and n-acetyl cysteine on the pH gradient across gastric mucus in vivo. Gut 1980;21:A929.
24. Garner A, Heylings JR. Stimulation of alkaline secretion in amphibian-isolated gastric mucosa by 16,16-dimethyl PGE_2 and PGF_{2alpha}: A proposed explanation for some of the cytoprotective actions of prostaglandins. Gastroenterology 1979;76:497-503.
25. Garner A, Flemström G, Heylings JR. Effects of antiinflammatory

agents and prostaglandins on acid and bicarbonate secretions in the amphibian-isolated gastric mucosa. Gastroenterology 1979;77:451-457.

26. Flemström G, Kivilaakso E. Demonstration of a pH gradient at the luminal surface of rat duodenum in vivo and its dependence on mucosal alkaline secretion. Gastroenterology 1983;84:787-794.
27. Gannon B, Browning J, O'Brien P, Rogers P. Mucosal microvascular architecture of the fundus and body of human stomach. Gastroenterology 1984;86:866-975.
28. Kivilaakso E, Fromm D, Silen W, Relationship between ulceration and intramural pH of gastric mucosa during hemorrhagic shock. Surgery 1978;84:70-78.
29. Silen W, Merhav A, Simson JNL. The pathophysiology of stress ulcer disease. World J Surg 1981;5:165-174.
30. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled, randomized trial in 100 critically ill patients. N Engl J Med 1978;298:1041-1045.
31. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W, Antacid versus cimetidine in preventing acute gastrointestinal bleeding: a randomized trial in 75 critically ill patients. N Engl J Med 1980;302:426-430.
32. Van den Berg B, van Blankenstein M. Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion 1985;31:1-8.
33. Zinner MJ, Zuidema GD, Smith PL, Mignosa M. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet 1981;153:214-220.
34. Fiddian-Green RG, McGough E, Pittenger G, Rothman E. Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. Gastroenterology 1983;85:613-620.
35. McClelland RN, Shires GT, Prager M. Gastric secretory and splanchnic blood flow studies in man after severe trauma and hemorrhagic shock. Am J Surg 1971;121:134-142.

36. Stremple JF, Mori H, Lev R, Glass GBJ. The stress ulcer syndrome. Curr Probl Surg, April 1973.

37. Menguy R. The prophylaxis of stress ulceration. N Engl J Med 1980;302:461-462.

38. Goodman AA, Osborne MP. An experimental model and clinical definition of stress ulceration. Surg Gynecol Obstet 1972;134:563-571.

39. Granger DN, Richardson PDI, Kvietys PR, Mortillaro NA. Intestinal blood flow. Gastroenterology 1980;78:837-863.

40. Ritchie WP, Shearburn EW. Influence of isoproterenol and cholestyramine on acute gastric mucosal ulcerogenesis. Gastroenterology 1977;73:62-65.

41. Granger DN, Barrowman JA. Microcirculation of the alimentary tract. I. Physiology of transcapillary fluid and solute exchange. Gastroenterology 1983;84:846-868.

42. Menguy R, Desbaillets L, Masters YF. Mechanisms of stress ulcer: influence of hypovolemic shock on energy metabolism in the gastric mucosa. Gastroenterology 1974;66:46-55.

43. Menguy R, Masters YF. Mechanisms of stress ulcer. II. Differences between the antrum, corpus and fundus with respect to the effects of complete ischemia on gastric mucosal energy metabolism. Gastroenterology 1974;66:509-516.

44. Menguy R, Masters YF. Mechanism of stress ulcer. IV. Influence of fasting on the tolerance of gastric mucosal energy metabolism to ischemia and on the incidence of stress ulceration. Gastroenterology 1974;66:1177-1186.

45. Starlinger M, Schiessel R, Hung CR, Silen W. H^+ back diffusion stimulating gastric mucosal blood flow in the rabbit fundus. Surgery 1981;89:232-236.

46. Kivilaakso E, Fromm D, Silen W. Effect of the acid secretory state on intramural pH of rabbit gastric mucosa. Gastroenterology 1978;75:641-648.

47. Fischer RP, Stremple JF. Stress ulcers in post-traumatic renal insufficiency in patients from Vietnam. Surg Gynecol Obstet 1972;134:790-794.

48. Edward DW, Skoryna SC. Properties of gel mucin of human gastric juice. Proc Soc Exp Biol Med 1964;116:794-799.

49. Eastwood GL, Kirchner JP. Changes in the fine structure of mouse gastric epithelium produced by ethanol and urea. Gastroenterology 1974;67:71-84.

50. Hamza KN, DenBesten L. Bile salts producing stress ulcers during experimental shock. Surgery 1972;71:161-167.

51. Guilbert J, Bounos G, Gurd FN. Role of intestinal chyme in the pathogenesis of gastric ulceration following experimental hemorrhagic shock. J Trauma 1969;9:723-743.

52. Martin GP, Marriott C, Kellaway IW. Direct effect of bile salts and phospholipids on the physical properties of mucus. Gut 1978;19:103-107.

53. Davenport HW. Destruction of the gastric mucosal barrier by detergents and urea. Gastroenterology 1968;54:175-181.

54. Harmon JW, Doong T, Gadacz TR. Bile salts are not equally damaging to the gastric mucosa. Surgery 1978;84:79-86.

55. Ritchie WP. Role of bile acid reflux in acute hemorrhagic gastritis. World J Surg 1981;5:189-198.

56. Lucas CE. Stress ulceration: the clinical problem. World J Surg 1981;5:139-151.

57. Macdougall BRD, Baily RJ, Williams R. H_2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure. Lancet 1977;I:617-619.

58. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523-530.

59. Le Gall JR, Mignon F, Bader JP, Rapkin M. Injury of gastric mucosa in sepsis: letter to the editor. N Engl J Med 1975;292:1242.

60. Bowen JC. Invited commentary. In: Silen W, Merhav A, Simson JNL. Pathophysiology of stress ulcer disease. World J Surg 1981;5:165-174.

61. Pingleton SK. Gastrointestinal hemorrhage. Med Clin North Am

1983;68:1215-1231.

62. Gurd FN, McClelland RN. Trauma workshop report: the gastrointestinal tract in trauma. J Trauma 1970;11:1089-1091.

63. Beil AR, Mannix H, Beal JM. Massive upper gastrointestinal hemorrhage after operation. Am J Surg 1964;108:324-330.

64. Fogelman MJ, Garvey JM. Acute gastroduodenal ulceration incident to surgery and disease: analysis and review of eighty-eight cases. Am J Surg 1966;112:651-656.

65. Stremple JF. Prospective studies of gastric secretion in trauma patients. Am J Surg 1976;131:78-85.

66. Lucas CE, Sugawa C, Friend W, Walt AJ. Therapeutic implications of disturbed gastric physiology in patients with stress ulcerations. Am J Surg 1972;123:25-34.

67. Chung RSK, Field M, Silen W. Effects of methyl-prednisolone on hydrogen ion absorption in the canine stomach. J Clin Invest 1978;62:262-270.

68. Messer J, Reitman D, Sacks HS, Smith H, Chalmers TC. Association of adrenocorticoid therapy and peptic-ulcer disease. J Engl J Med 1983;309:21-24.

69. Ozdemir IH, Zimmerman B. The effect of adrenalectomy and endocrine substances on restraint-induced acute gastric ulceration. Surg Forum 1970;21:304-305.

70. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976;294:473-479.

71. Himal HS, Mowat C. Methyl prednisolone and ethanol induced lysosomal instability. Gastroenterology 1982;82:1084 (Abstract).

72. Domschke S, Domschke W. Gastroduodenal damage due to drugs, alcohol and smoking. Clin Gastroenterol 1984;13:405-436.

73. Metz SA. Anti-inflammatory agents as inhibitors of prostaglandin synthesis in man. Med Clin North Am 1981;65:713-757.

74. Bennett A, Murray JG, Wyllie JH. Occurrence of prostaglandin E_2 in the human stomach, and a study of its effects on human isolated gastric muscle. Br J Pharmac Chemother 1968;32:339-349.

75. Wilson DE, Kaymakcalan H. Prostaglandins: gastrointestinal effects and peptic ulcer disease. Med Clin North Am

1981;65:773-787.

76. Robert A. Cytoprotection by prostaglandins. Gastroenterology 1979;77:761-767.

77. Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats: prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl, and thermal injury. Gastroenterology 1979;77:433-443.

78. Robert A. Antisecretory, antiulcer, cytoprotective and diarheogenic properties of prostaglandins. In: Advances in Prostaglandin and Thromboxane Research. Samuelsson B, Paoletti R (eds). Raven Press, New York. Vol.2,1976:pp.507-520.

79. Miller TA, Jacobson ED. Gastrointestinal cytoprotection by prostaglandins. Gut 1979;20:75-87.

Chapter 4.

Prostaglandins: gastrointestinal effects and cytoprotection

4.1 INTRODUCTION

Prostaglandins (PGs) are synthesized in all nucleated cells of the body. These biologically active substances are thought to be local regulators of cell and tissue functions rather than circulating hormones. Only small amounts of PG are found extracellulary, as they are unstable and are also rapidly broken down by local enzymes.

4.2 CHEMISTRY

PGs are derivatives of polyunsaturated fatty acids, in humans mainly of arachidonate. The chemical structure of PGs is characterized by a cyclopentane ring connected with two fatty acid chains; one of these chains has a terminal carboxyl group. PGs are called A, B, C, D, E, F according to their substituents at the cyclopentane ring. The suffix 1 or 2 or 3 indicates the number of double bonds in the fatty acid chains, e.g. PGE_2. In addition, alpha or beta can be added to indicate the stereometry of the hydroxyl group at the C_9 position of the ring, e.g. PGF_{2alpha}.

4.3 BIOSYNTHESIS AND DEGRADATION

PGs are synthesized by membrane bound enzymes. Polyunsaturated

fatty acids are used as a substrate. These are obtained as essential fatty acids in food and are stored in the membranes as phopholipids. The enzyme phospholipase A_2 hydrolyzes these phospholipids at the membranes, and the released arachidonate is metabolized by a microsomal enzyme called cyclooxygenase, to endoperoxides. The endoperoxides are the precursors of PGs and also of prostacyclin and thromboxanes.

In mammals PGE_2 and PGF_{2alpha} are quantitatively the most important prostaglandins. PGs are not stored but are used immediately after their synthesis. Most PGs are stucturally unstable. They are rapidly degraded by enzymes. If PGs of the E or F group enter the circulation they are catabolized rapidly by enzymes in the liver and the lungs, usually in a single passage. Degradation is mainly by oxidation of the C_{15} group, followed by reduction of the double bond between C_{13} and C_{14} (1).

4.4 INHIBITION OF SYNTHESIS

Acetylsalicylic acid and other nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin inhibit PG synthesis by selective inhibition of cyclooxygenase. Their action is detectable within one to ten minutes (2).

Corticosteroids inhibit PG release by inhibition of the enzyme phospholipase. This effect can be seen only after several hours or sometimes days of treatment, because the action is via newly synthesized proteins (2).

4.5 GASTROINTESTINAL MOTILITY

PGs act on smooth muscles of the whole gastrointestinal tract (3). In general, longitudinal muscle is contracted by E and F PGs. Circular smooth muscle is relaxed by E series and contracted by F series PGs. PGs cannot be called neurotransmitters but they modulate and modify

synaptic function. PGE_1 and PGE_2, when administered exogenously, relax the lower esophageal sphincter. The oral administration of PGE in man was found to be associated with reflux of bile into the stomach, due to relaxation of the pyloric sphincter (4,5). Gastric emptying is not markedly affected. PGE can induce diarrhea as a result of increased motility and accelerated intestinal passage (6). The small intestine is the site of the described responses (3) and diarrhoea limits clinical applications of PGs. The release of PGs is increased by intestinal muscle contraction. Indomethacin, which acts as a PG synthesis inhibitor, diminishes colonic muscle activity (7). This suggests a possible role for PGs in modulating colonic motility.

4.6 EFFECTS ON GASTRIC SECRETION

PGE_1, PGE_2, PGA_1 and PGA_2 inhibit gastric acid secretion (8,9). Naturally occuring PGs, when administered orally, have no or at most a very small inhibitory effect on gastric acid secretion (8,9).

These PGs are metabolized by the gastrointestinal tract and inactivated by the liver and the lungs following absorption. Parenteral administration of PGs results in a marked reduction of gastric acid secretion. Synthetic analogs of PGs, such as 16,16-dimethyl PGE_2 and 15(R)15-methyl PGE_2 have been shown to be more potent inhibitors and their effectivity is not lost by oral administration (3,8,9).

PGs decrease gastric secretion volume as well as total acid output, the effect on acid output being greater than that on volume. Total pepsin output diminishes parallel to reduction of gastric secretion volume. Natural PGE_2 has been found in man to decrease gastric acid secretion when given intravenously (10), while no effect could be shown using the oral route (9,11). Recently however, Reele and Bhan (12) described inhibition of liquid protein meal-stimulated gastric acid secretion in man, following oral administration of PGE_2. This effect was seen with dosages of 1.0 mg and more. Another study confirmed this effect of natural PGE_2 during vagal stimulation of acid

production (13).

The mechanism by which PGs inhibit acid secretion is probably by a direct effect on parietal cell (3,14). Soll and co-workers observed an inhibitory effect of PGs on the histamine-mediated stimulation of adenyl cyclase and on production of cAMP in parietal cells (15,16). PGs seem to have a physiological role in modulating gastric acid secretion (13).

4.7 EFFECTS ON INTESTINAL SECRETION

PGE stimulates the secretion of water and electrolytes from the jejunum (3). The cholera toxin acts in a similar way (3). PGE_2 mediated secretory diarrhea from a villous adenoma has been reported (17).

4.8 EFFECTS ON PANCREAS AND BILE SECRETION

Inhibition as well as stimulation by PGs of cholecystokinin-stimulated exocrine pancreatic secretion has been reported (3). PGE_1 and PGA_1 probably increase the bile flow in the dog (3).

4.9 CYTOPROTECTION

Cytoprotection was originally defined as the ability of PG to protect the gastrointestinal epithelium against potentially noxious agents, which otherwise would cause necrosis (18,19,20). This protective effect is not dependent on inhibition of gastric acid secretion, as cytoprotection can be shown with dosages too low to give such inhibition. The studies and publications of Robert have made this cytoprotective effect of PG well known (19,20,21). He found, for example, that PGs protected against absolute alcohol, concentrated solutions of hydrochloric acid and of sodium hydroxide, hypertonic

sodium chloride and thermal injury in rats (21).

Gastric cytoprotection is rapidly achieved. When given orally one minute before administration of absolute alcohol, PGs reduce the number and the severity of gastric lesions by 80%. When given two minutes before ethanol the protection is complete. The protection lasts approximately 2 hours after administration of PGE_2 (22).

In a recent publication Robert et al (23) pointed out that part of the gastric mucosa is not protected, i.e. the monolayer epithelium which covers the mucosa. Robert was prompted to change the definition of cytoprotection, which is now "the property of certain PGs to protect gastric mucosal tissue located under the surface epithelium from becoming hemorrhagic and necrotic after exposure to noxious agents" (23).

Cytoprotection by PGs is also demonstrated in the prevention of gastrointestinal ulceration induced by NSAIDs and corticosteroids (20,24,25,26,27). Evidence of this cytoprotective effect has been shown in animals (24,26) and in man (25,27,28). A protective action by PGs against taurochlorate-induced gastric hemorrhage in rats has also been reported (26).

4.10 MECHANISMS OF CYTOPROTECTION

Although the exact mechanism of cytoprotection is not known, some facts have emerged. First, orally and topically administered PGs have a three to five fold more powerful cytoprotective action than parenterally administered PGs (21). Secondly, PGs act immediately, i.e. their maximal cytoprotective effect is reached within one minute (21).

There is evidence for the following mechanisms in cytoprotection:

1. Stimulation of bicarbonate secretion (29);
2. Stimulation of mucus secretion (30);
3. Increase of mucosal blood flow (32);
4. Stimulation of the sodium transport from mucosa to serosa (33) and of gastric chloride transport (34), together with an increase in

electrical potential difference of the mucosa (35);

5. Increase of mucosal coating with phospholipids (36);
6. Lysosomal stabilization (37);
7. Stimulation of intracellular cyclic AMP (33,37).

Mucosal penetration of noxious agents is not prevented by PGs (22). PGs therefore seem to act at cellular level, and luminal factors are probably less important than intramucosal processes. As was shown by Tarnawski et al (38), PGs protect the mucosal proliferative zone, from which rapid migration of cells toward the luminal surface follows injury by alcohol. Microscopic lesions may be seen after ethanol despite PG-pretreatment, but cells in the gastric pit base are spared, and reepithelialization is detectable within 60 minutes (39).

Therefore in studying cytoprotection not only should macroscopically detectable mucosal lesions be taken into account, but also light microscopical and electron microscopical lesions (37). Cytoprotection should always be defined histologically (40).

4.11 ADAPTIVE CYTOPROTECTION

Mildly irritating substances have a cytoprotective action against necrotizing agents, if they are administered prior to the necrotizing agent (41). For instance, in rats a ten percent alcohol solution given intragastrically protects against subsequent instillation of absolute alcohol. This effect develops within 15 minutes. Pretreatment with certain mildly irritating substances also has a cytoprotective effect against necrotizing agents with a quite different chemical structure (37). Indomethacin blocks this adaptive effect, thus providing evidence for a PG mediated mechanism (37). Intragastric administration of a mildly irritating agent results in an increased synthesis of PGE_2 and other PGs in the gastric mucosa, especially in the corpus (41). Adaptive cytoprotection seems to be a normal physiological mechanism, mediated by PGs.

4.12 PROSTAGLANDIN RECEPTORS IN GASTRIC MUCOSA

Tepperman et al (42) provided evidence for a specific binding site with high affinity for PGE_2 in the porcine gastric mucosa. They found a much higher affinity in the fundus than in the antrum of the stomach, which itself had higher affinity than the esophagus, duodenum, ileum or colon (43).

4.13 CLINICAL APPLICATIONS OF PROSTAGLANDINS IN GASTROENTEROLOGY

In the mouse PGE_2 has a protective effect on diet-induced pancreatitis (44). Investigations in man have shown some beneficial biochemical effects of PGE_2 in acute pancreatitis, given in a dose of 0.1 mg/kg body weight per 24 h intravenously (45).

Sepsis-induced gastric erosions can be prevented in dogs by 16,16-dimethyl PGE_2, with dosages not inhibiting gastric acid secretion, as was shown by Odonkor et al (46). Other animal experiments using PGs showed the prevention of the restraint ulcer (47) exertion ulcers (48) and shock-induced ulcers (47). These findings suggest a possible use of PGs in critical care medicine.

Natural PGE_2, in a 1 mg four times daily dosage, can prevent gastrointestinal blood loss induced by aspirin in man (28). A 1 mg three times daily dosage has the same protective effect against indomethacin (49). For these applications PGE_2 should be given before or simultaneously with NSAIDs. Endoscopic studies showed the prevention of aspirin-induced gastroduodenal lesions by 15(R)15-methyl PGE_2 (arbaprostil) and by enprostil, which are synthetic analogs of PGE_2 (25,50).

Healing of active duodenal ulcer is promoted by PGE_2 at a dosage of 0.5 mg three times daily, without concomitant reduction in gastric acid secretion (11). Arbaprostil accelerates the healing of duodenal ulcer, but has also a significant inhibitory effect on gastric acid secretion (51). This ulcer healing effect cannot be explained by changes in basal or meal-stimulated serum gastrin, as was shown by

Tytgat and Huibregtse (52). Gastric ulcer healing too, is facilitated by treatment with PGE_2 analogs (53,54).

Some case reports have been published in which stress bleeding was stopped using 15(R)15-methyl PGE_2, after treatment failures with different other drugs (55,56). Long term treatment with 15(R)15-methyl PGE_2 leads to an increased thickness of gastric mucosa via decreased exfoliation of mucus cells (57).

From the gastric-protective effects of PGs in animals and man described above, one could expect a beneficial effect of PGs in the prevention of stress-induced ulcers. In the next chapter a clinical trial is described, which was aimed to test the clinical usefulness of PGE_2 in the prophylaxis of stress-induced ulcers.

4.14 REFERENCES

1. Samuelsson B, Granstrom E, Green K, Hamberg M. Metabolism of prostaglandins. Ann NY Acad Sci 1971;180:139-161.
2. Metz SA. Anti-inflammatory agents as inhibitors of prostaglandin synthesis in man. Med Clin North Am 1981;65:713-757.
3. Wilson DE, Kaymakcalan H. Prostaglandins: gastrointestinal effects and peptic ulcer disease. Med Clin North Am 1981;65:773-787.
4. Horton EW, Main I, Thompson CJ. Effects of orallly administered prostaglandin E_1 on gastric secretion and gastrointestinal motility in man. Gut 1968;9:655-658.
5. Dilawari JB, Newman A, Poleo J, Misiewicz JJ. Response of the human cardiac sphincter to circulating prostaglandins F_{2alpha} and E_2 and to anti-inflammatory drugs. Gut 1975;16:137-143.
6. Misiewicz JJ, Wallller SL, Kiley N, Horton EW. Effect of oral prostaglandin E_1 on intestinal transit in man. Lancet 1969;1:648-651.
7. Bruch HP, Schmidt E, Laven R, Kehrer G, Wasner KH. The role of prostaglandins in peristalsis of the human colon. Acta Hepato-Gastroenterol 1978;25:303-307.
8. Robert A, Kane G, Reele SB. Dose response inhibition in man of meal stimulated gastric acid secretion by 15(R)15-methyl prostaglandin E_2, given orally. Gut 1981;22:728-731.
9. Karim SMM, Carter DC, Bhana D, Adaikan Ganesan P. Effect of orally administered prostaglandin E_2 and its 15-methyl analogues on gastric secretion. Br Med J 1973;1:143-146.
10. Newman A, Moraes-Filho PP, Philippakos D, Misiewicz JJ. The effect of intravenous infusions of prostaglandins E_2 and F_{2alpha} on human gastric function. Gut 1975;16:272-276.
11. Kollberg B, Slezak P. The effect of prostaglandin E_2 on duodenal ulcer healing. Prostaglandins 1982;24:527-536.
12. Reele SB, Bohan D. Oral antisecretory activity of prostaglandin E_2 in man. Dig Dis Sci 1984;29:390-393.
13. Befrits R, Johansson C. Oral PGE_2 inhibits gastric acid secretion in man. Prostaglandins 1985;29:143-152.

14. Robert A, Schultz JR, Nezamis JE, Lancaster C. Gastric antisecretory and antiulcer properties of PGE_2, 15-methyl PGE_2, and 16,16-dimethyl PGE_2. Gastroenterology 1976;70:359-370.
15. Soll AH. Prostaglandin inhibition of histamine-stimulated amino-pyrine uptake and cyclic AMP generation by isolated canine parietal cells. Gastroenterology 1978;74:1146 (abstract).
16. Levine RA, Kohen KR, Schwartzel EH, Ramsay CE. Prostaglandin E_2-histamine interactions on cAMP, cGMP, and acid production in isolated fundic glands. Am J Physiol 1982;242:G21-26.
17. Steven K, Lange P, Bukhave K, Rask-Madsen J. Prostaglandin E_2-mediated secretory diarrhea in villous adenoma of rectum: effect of treatment with indomethacin. Gastroenterology 1981;80:1562-1566.
18. Miller TA, Jacobson ED. Gastrointestinal cytoprotection by prostaglandins. Gut 1979;20:75-87.
19. Robert A. Cytoprotection by prostaglandins. Gastroenterology 1979;77:761-767.
20. Robert A. Antisecretory, antiulcer, cytoprotective and diarrheogenic properties of prostaglandins. In: Advances in Prostaglandins and Thromboxane Research. Samuelsson B, Paoletti R (eds.). Raven Press, New York, Vol.2,1976:pp.507-520.
21. Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats: prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl, and thermal injury. Gastroenterology 1979;77:433-443.
22. Robert A. Current history of cytoprotection. Prostaglandins 1981;21(suppl.):89-96.
23. Robert A, Lancaster C, Davis JP, Field SO, Wickrema Sinha AJ, Thornburgh BA. Cytoprotection by prostaglandin occurs in spite of penetration of absolute ethanol into the gastric mucosa. Gastroenterology 1985;88:328-333.
24. Robert A. An intestinal disease produced experimentally by a prostaglandin deficiency. Gastroenterology 1975;69:1045-1047.
25. Gilbert DA, Surawicz CM, Silverstein FE, Weinberg CR, Saunders DR, Feld AD, Sanford RL, Bergman D, Washington P. Prevention of acute

aspirin-induced gastric mucosal injury by 15-R-15 methyl prostaglandin E_2: an endoscopic study. Gastroenterology 1984;86:339-345.

26. Carmichael HA, Nelson L, Russel LI, Chandra V, Lyon A, Cochran KM. Effect of prostaglandin 15(R)15 methyl-E_2 ester on aspirin and taurocholic acid-induced gastric mucosal haemorrhage in rats. Gut 1976;17:33-36.
27. Johansson C, Kollberg B, Nordemar R, Samuelson K, Bergström S. Protective effect of prostaglandin E_2 in the gastrointestinal tract during indomethacin treatment of rheumatic diseases. Gastroenterology 1980;78:479-483.
28. Cohen MM, Cheung G, Lyster DM. Prevention of aspirin-induced faecal blood loss by prostaglandin E_2. Gut 1980;21:602-606.
29. Garner A, Heylings JR. Stimulation of alkaline secretion in amphibian-isolated gastric mucosa by 16,16,-dimethyl PGE_2 and PGF_{2alpha}: a proposed explanation for some of the cytoprotective actions of prostaglandins. Gastroenterology 1979;76:497-503.
30. Bolton JP, Palmer D, Cohen MM. Stimulation of mucus and nonparietal cell secretion by the E_2 prostaglandins. Dig Dis 1978;23:359-364.
31. Kauffman GL, Reeve JJ, Grossman MI. Gastric bicarbonate secretion: effect of topical and intravenous 16,16-dimethyl prostaglandin E_2. Am J Physiol 1980;239:G44-48.
32. Konturek SJ, Robert A. Cytoprotection of canine gastric mucosa by prostacyclin : possible mediation by increased mucosal blood flow. Digestion 1982;25:155-163.
33. Chaudhury TK, Jacobson ED. Prostaglandin cytoprotection of gastric mucosa. Gastroenterology 1978;74:59-63.
34. Schiessel R, Matthews J, Barzilai A, Merhav A, Silen W. PGE_2 stimulates gastric chloride transport: possible key to cytoprotection. Nature 1980;283:671-673.
35. Müller P, Fischer N, Kather H, Simon B. Prevention of aspirin-induced drop in gastric potential difference with 16,16-dimethyl-prostaglandin E_2. (Letter to the Editor) Lancet 1981;1:333-334.

36. Lichtenberger LM, Richards JE, Hills BA. Effect of 16,16-dimethyl prostaglandin E_2 on the surface hydrophobicity of aspirin-treated canine gastric mucosa. Gastroenterology 1985;88:308-314.
37. Miller TA. Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am J Physiol 1983;245:G601-623.
38. Tarnawski A, Hollander D, Stachura J, Krause WJ, Gergely H. Prostaglandin protection of the gastric mucosa against alcohol injury - a dynamic time-related process. Role of the mucosal proliferative zone. Gastroenterology 1985;88:334-352.
39. Schmidt KL, Henagan JM, Smith GS, Hilburn PJ, Miller TA. Prostaglandin cytoprotection against ethanol-induced gastric injury in the rat. A histologic and cytologic study. Gastroenterology 1985;88:649-659.
40. Silen W, Ito S. Cytoprotection: a word of caution. (Letter to the Editor). Gastroenterology 1982;83:944-950.
41. Robert A, Nezamis JE, Lancaster C, Davis JP, Field SO, Hanchar AJ. Mild irritants prevent gastric necrosis through "adaptive cytoprotection" mediated by prostaglandins. Am J Physiol 1983;245:G113-121.
42. Tepperman BL, Soper BD. Prostaglandin E_2-binding sites and cAMP production in porcine fundic mucosa. Am J Physiol 1981;241:G313-320.
43. Tepperman BL, Soper BD. Distribution of prostaglandin E_2 binding sites in the porcine gastrointestial tract. Prostaglandins 1981;22:205-212.
44. Manabe T, Steer ML. Protective effects of PGE_2 on diet-induced acute pancreatitis in mice. Gastroenterology 1980;78:777-781.
45. Stanfield NJ, Kakkar VV. Prostaglandins and acute pancreatitis - experimental and clinical studies. Br J Surg 1983;70:573-576.
46. Odonkor P, Mowat C, Himal HS. Prevention of sepsis-induced gastric lesions in dogs by cimetidine via inhibition of gastric secretion and by prostaglandin via cytoprotection. Gastroenterology 1981;80:375-379.
47. Robert A, Kauffman GL. Stress ulcers. In: Gastrointestinal

Disease. Sleisenger MH, Fordtran JS (eds.). W.B. Saunders Company, Philadelphia 1983:pp.612-625.

48. Dajani EZ, Driskill DR, Bianchi RG, Collins PW. Comparative gastric antisecretory and antiulcer effects of prostaglandin E_1 and its methyl ester in animals. Prostaglandins 1975;10:205-215.
49. Johansson C and Kollberg B. Clinical trials with prostaglandin E_2. Prostaglandins 1981;21 (suppl.):161-164.
50. Cohen MM, McCready DR, Clark L, Sevelius H. Protection against aspirin-induced antral and duodenal damage with enprostil: a double blind endoscopic study. Gastroenterology 1985;88:382-386.
51. Vantrappen G, Janssens J, Popiela T, Kulig J, Tytgat GNJ, Huibregtse K, Lambert R, Pauchard JP, Robert A. Effect of 15 (R)15-methyl prostaglandin E_2 (arbaprostil) on the healing of duodenal ulcer: a double blind multicenter study. Gastroenterology 1982;83:357-363.
52. Tytgat GNJ, Huibregtse K. The effect of 15(R)-15-methyl prostaglandin E_2 on basal and meal stimulated serum gastrin in duodenal ulcer patients. Prostaglandins 1981;21 (suppl.):53-56.
53. Fung W-P, Karim SMM, Tye CY. Effect of 15(R)15 methylprostaglandin E_2 methylester on healing of gastric ulcers: controlled endoscopic study. Lancet 1974;2:10-11.
54. Gibinski K, Rybicka J, Mikoś E, Nowak A. Double-blind clinical trial on gastroduodenal ulcer healing with prostaglandin E_2 analogues. Gut 1977;18:631-639.
55. Weiss JB, Peskin GW, Isenberg JI. Treatment of hemorrhagic gastritis with 15(R)-methyl prostaglandin E_2: report of a case. Gastroenterology 1982;82:558-560.
56. Groeger JS, Dazza SJ, Carlon GC, Turnbull AD, Pierri MK, Howland WS. Prostaglandin therapy in a case of refractory stress ulcer bleeding. Crit Care Med 1982;10:486-487.
57. Offerhaus GJA, Van Minnen A, Everts V, Samson G, Tytgat GNJ. Invloed van 15(R)-15-methylprostaglandine E_2 op maagslijmvlies. Ned T Geneesk 1985;7:332 (abstract).

PREFACE TO CHAPTER 5.

In this chapter a clinical trial on the prevention of gastrointestinal bleeding in Intensive Care Unit (ICU) patients is described.

Two or more risk factors were taken as an inclusion criterion as bleeding in patients with only one risk factor is rare (1,2). Three days' duration of the study was assumed to be a minimal prerequisite for adequate evaluation, as stress bleeding is rarely seen within 48 hours after the onset of a serious clinical condition (3) and ulcer formation takes at least 48 hours (4). The observation period was arbitrarily extended over seven days, mainly for practical reasons.

Stress bleeding prophylaxis is basically aimed at preventing stress ulcers and erosions. Theoretically, we should do endoscopies at regular intervals to document these lesions. However, this can hardly be accomplished for practical and ethical reasons. Assuming that blood loss is a feature of mucosal injury, we determined blood contents in gastric aspirates, using the ^{51}Chromium (^{51}Cr) method. Although colour tests, based on the peroxidase reaction, such as the guaiac and orthotolidine test, have been used, these tests are semiquantitative and are intended for the determination of blood in faeces and urine, rather than in gastric juice. As we had chosen an indirect parameter, i.e. blood loss instead of endoscopy, we needed an accurate test for determination of blood loss. So we prefered the ^{51}Cr-method, which is generally accepted to be the best quantitative test for blood loss (5), although it is more laborious than colour test strips. Previous work at our department (6) had shown that most ICU patients had less than 5 ml blood loss per 24 h, while another small group of patients had more than 15 ml blood loss per 24 h. Therefore we took more than 15 ml blood loss as a criterion of bleeding and as evidence of mucosal injury.

REFERENCES

1. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled randomized trial in 100 critically ill patients. N Engl J Med 1978;298:1041-1045.
2. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding: a randomized trial in 75 critically ill patients. N Engl J Med 1980;302:426-430.
3. Skillman JJ, Bushnell LS, Goldman H, Silen W. Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523-530.
4. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266-273.
5. Rhys Davies E. Radionuclide investigations. Clin Gastroenterol 1984;13:205-233.
6. Van den Berg B, van Blankenstein M. Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion 1985;31:1-8.

Chapter 5.

Intragastric prostaglandin E_2 and the prevention of gastrointestinal hemorrhage in ICU patients

5.1 ABSTRACT

The effects of intragastric prostaglandin E_2 (PGE_2) on the occurrence of acute gastrointestinal hemorrhage in intensive care patients were investigated in a prospective, double-blind, placebo-controlled study. Ninety patients with two or more risk factors (major surgery, multiple trauma, respiratory insufficiency, renal insufficiency, jaundice, hypotension, peritonitis, sepsis) were randomized for treatment with either prostaglandin E_2 (0.5 mg) or placebo, administered every 4 h via a nasogastric tube. Blood loss in gastric aspirates was measured by ^{51}Cr-erythrocyte labeling and a peroxidase test (orthotolidine). Of 57 patients, who could be evaluated, 29 received PGE_2 and 28 received placebo. Hemorrhage occurred in nine PGE_2 patients and 13 placebo-treated patients, not a significant difference. The occurrence of hemorrhage was related to the number of risk factors, and gastrointestinal hemorrhage was rarely the major factor determining mortality. Results of the orthotolidine test were not positively correlated with those of erythrocyte labeling, indicating that peroxidase tests should not be relied upon to detect blood in gastric aspirates.

5.2 INTRODUCTION

Acute gastrointestinal bleeding from stress ulcers can be

life-threatening in severely ill patients. Factors which promote the development of stress ulcers are: respiratory insufficiency, hypotension, sepsis, peritonitis, renal insufficiency, major surgery, major trauma, and jaundice. [1-3] Stress ulcers are often multiple, localized in the corpus or fundus of the stomach, and do not penetrate beyond the submucosa; they may be preceded or accompanied by erosions. [2,4]

Extensive burns, and/or brain damage can be accompanied by bleeding from a different type of ulcer. [5,6] In contrast to stress ulcers this ulcer is usually solitary and is found not only in the stomach but also in the esophagus and duodenum. It is often deep and perforation may occur; this ulcer probably has a different pathophysiology from the stress ulcer.

The reported incidence of stress ulcer varies; endoscopic evidence of stress lesions has been found in 100% of patients suffering acute trauma, [2] and 5% to 20% of ICU patients may develop a gastrointestinal bleed. [1,7,8] Clinically manifest bleeding from a stress ulcer is accompanied by a mortality of more than 30%. [9]

The role of gastric acidity in the development of stress ulcers is not completely clear. [10-13] The incidence of bleeding from the upper gastrointestinal tract in ICU patients can be reduced by titrating the gastric contents with antacids [14]; however, several studies [8,10,11,15] have failed to show a beneficial effect of cimetidine in the prevention of stress bleeding.

The integrity of the gastric mucosa is adversely affected by the risk factors for stress ulcers, especially shock which leads to ischemia and anoxia. Prostaglandins play an important role in the maintenance of an intact gastric mucosal barrier. To examine the possible clinical applications of prostaglandins in the prevention of bleeding from stress lesions in ICU patients, we performed a prostective double-blind study. Prostaglandin E_2 (PGE_2), which is normally present in the gastric mucosa, [16] was chosen as the therapeutic agent. We used a dose which does not inhibit gastric acid production, so that any prevention of bleeding could be ascribed to cytoprotection rather than to decreased gastric acidity.

5.3 PATIENTS AND METHODS

All patients admitted either to the surgical or medical ICU were considered for inclusion in the study. The criteria for exclusion were: previous esophageal or gastric surgery, the presence of esophageal varices or extensive burns, evidence of gastrointestinal bleeding on ICU admission, and expected discharge and/or expected oral feeding within 3 days. Eligible patients had two or more of the following risk factors for the development of stress ulcers [14]: major surgery; respiratory insufficiency, defined as need for artificial respiration; renal insufficiency, defined as serum creatinine level of more than 170 umol/L or an oliguria of less than 300 ml/day; multiple trauma; peritonitis, confirmed by laparotomy or ascites tap; hypotension, defined as a systolic blood pressure of less than 100 mm Hg for 2 h or longer, or cardiopulmonary resuscitation or hypotension requiring treatment with adrenergic agents and/or MAST (Medical Anti Shock Trousers); sepsis, defined as a positive blood culture or the combination of fever, hypotension, leukocytosis and an infective focus; and/or jaundice, defined as a serum bilirubin level of more than 80 umol/L.

Patients were randomly assigned to receive placebo or prostaglandin therapy, in a double-blind fashion. Treatment was started within 24 hours of ICU admission. Prostaglandin patients received 0.5 mg of prostaglandin E_2 (PGE_2, Upjohn) dissolved in 20 ml of water. Placebo patients received only water. Both fluids were administered every 4 h via the gastric tube. After administration the tube was flushed with 20 ml of water and clamped for 30 min. The clamp was then removed, and the gastric contents allowed to drain by gravity until the next PGE_2 or placebo administration.

At the start of the study, before administering the first dose, a sample of gastric juice was obtained to determine pH, using a combined glass/calomel electrode (Metrohm E350B, Herisau). The gastric pH was remeasured every 24 h. In order to examine the effect of gastric acidity on the development of stress ulcers, we calculated the number of days in which the pH was less than 3.5. [10,14]

Gastric blood loss was qualitatively measured every 3.5 h by inspection for manifest hemorrhage and by a peroxidase test based on the orthotolidine reaction (Multistix), and quantitatively measured every 24 h by ^{51}Cr-chromate labeling of the erythrocytes. For ^{51}Cr-chromate labeling, 10 ml of blood was withdrawn from the patient; the erythrocytes were then labeled with 30 uCi (1.11 MBq) of ^{51}Cr-chromate and readministered. [17] The collections of gastric juice were pooled daily and their radioactivity measured in a large-volume gamma counter (Armac 3002, Packard, Brussels, Belgium). Ten ml of blood was withdrawn daily and used as standard. More than 15 ml of blood loss from the upper gastrointestinal tract was considered to be evidence of mucosal damage in the stomach. Clinically manifest bleeding was also regarded as evidence of mucosal damage. When possible, patients with either occult or manifest bleeding, underwent acute gastroscopy.

The study lasted from 3 to 7 days. Treatment was discontinued if enteral feeding was given within the first 3 days, if the gastric tube was removed, if the patient was discharged from the ICU, if gastric or duodenal surgery was required after the beginning of the study, or if the patient had a gastrointestinal hemorrhage following ICU admission.

Fisher's exact test and the Chi-square test with Yates' correction were used for statistical comparisons of placebo and PGE_2 groups.

5.4 RESULTS

Ninety patients were admitted to the study in the period November 1981 to September 1983. Of these patients, three were excluded when retrospective evaluation indicated noncompliance with the entry criteria. Twelve other patients received enteral feeds or underwent gastric tube removal within the first 3 days. Eight patients were excluded because gastrostomy was performed within the first 3 days (one patient), no chromium labeling was performed (one patient), or ICU discharge was within the first 3 days (six patients). Finally, nine patients died within the first 3 days without signs of bleeding.

The remaining 58 patients complied with the requirements of the protocol. Of these, 29 received PGE_2 and 29 were given a placebo. The two groups were similar with regard to sex distribution, age, and number and nature of risk factors (Table 1).

Table 1. Patient characteristics

	PGE_2	Placebo
Number of patients	29	29
Sex ratio (men:women)	15:14	19:10
Mean age (yr)	51,9 (17-80)	54,8 (18-78)
Medical ICU	14	11
Surgical ICU	15	18
Mean number of risk factors	3.2	3.0

Lesions causing hemorrhage were in the stomach, duodenum and/or esophagus. Hemorrhage occurred in nine (31%) of the 29 PGE_2 patients and in 13 (46%) of the 28 placebo patients. In the PGE_2 group, hemorrhage was clinically manifest in four patients (three with hematemesis, one with melena) and detected by the ^{51}Cr-method in five patients. In the placebo group, clinically manifest hemorrhage occurred in four patients (three with hematemesis, one with bloody stools via a colostomy), and hemorrhage was detected by the ^{51}Cr-method in nine. One other patient in the placebo group exhibited bleeding from a traumatic lesion in the pharynx, and this patient was therefore left out of the further calculations. The difference in frequency of hemorrhage between the PGE_2 and placebo group was not statistically significant. The results of the orthotolidine reactions in a number of the same gastric aspirates did not correlate with the results of the 24-h blood loss as measured by the ^{51}Cr-method (see chapter 6).

The patients with hemorrhage were treated with antacids (Regla-pH 15 every 2 h) in the medical ICU, and with cimetidine sometimes

together with antacids in the surgical ICU. One PGE_2 patient underwent a laparotomy for a gastric perforation after 18 days of cimetidine treatment. One placebo patient's bleeding duodenal ulcer was treated by electrocoagulation during gastroscopy. The overall mortality of the bleeding patients was high: eight of the nine PGE_2 patients and seven of the 13 placebo patients died. In most patients death was due to the underlying disease and its complications and not to gastrointestinal bleeding. Patients with hemorrhage had more risk factors than patients who did not bleed (Table 2). The number and nature of risk factors for bleeding patients was similar in PGE_2 and placebo groups.

There was no great difference in gastric acidity between the PGE_2 and placebo groups, nor between patients with bleeding and those without bleeding (Table 3). There was also no statistical difference in gastric acid output (mmol/24 h) between these groups.

Table 2. Risk factor distribution

Category	No. of Patients	No. of Risk Factors
Hemorrhage		
PGE_2 patients	9	3.8
Survived	1	3.0
Died	8	3.9
Placebo patients	13	3.5
Survived	6	3.3
Died	7	3.0
Total	22	3.6
Survived	7	3.3
Died	15	3.5
No hemorrhage		
PGE_2 patients	20	2.9
Placebo patients	15	2.5
Total	35	2.7

Table 3. Duration of gastric pH $\leqslant$3.5

Category	Duration of treatment (days)	Duration pH $\leqslant$3.5 (days)	Percentage
PGE_2 patients			
Hemorrhage	26	19	73.1%
No hemorrhage	102	83	81.4%
Total	128	102	79.7%
Placebo patients			
Hemorrhage	31	28	90.3%
No hemorrhage	75	58	77.3%
Total	106	86	81.1%

5.5 DISCUSSION

Previous clinical trials with histamine-2-receptor antagonists have failed to demonstrate any clear-cut prevention of stress lesions.[8,10,11,15] Titration of the gastric juice with antacids to achieve a constant pH appears to be effective,[14] but is very difficult to accomplish in practice.

Prostaglandins have a cytoprotective effect[18-20] against injurious substances such as acetyl salicylic acid.[21] Although some prostaglandins (PGE_1, PGE_2, PGA_1) reduce gastric acid secretion when administered in high doses, cytoprotection is not dependent on changes in gastric acidity.[22] The following changes probably play a role in cytoprotection: an increase in electric potential difference generated by an increased sodium transport from the lumen of the stomach[23]; increased chloride transport towards the lumen[24]; increased bicarbonate and mucus secretion by the gastric mucosa[25,26]; and an increased mucosal blood flow.[27] Prostaglandins also increase the intracellular cyclic AMP.[23]

We found no clear-cut evidence that PGE_2 prevented intestinal bleeding. Duodenal ulceration was also not prevented, although a small clinical trial by Johansson and Kollberg [28] found that 2.5 mg/day of PGE_2 seemed to cure duodenal ulcer. A larger study population would possibly show a statistically significant difference in the incidence of bleeding between PGE_2 and placebo groups. However, because we were trying to find a highly effective means of preventing stress bleeding, and because statistical significance does not always mean clinical significance, extension of this study seems unjustified.

In our study the PGE_2 dose was below that which suppresses gastric acid secretion, but at a level reported to provide cytoprotection. Although we failed to demonstrate a beneficial effect with a PGE_2 dose of 3 mg/day, a higher dose could be effective. However, this seems unlikely as Cohen [29] showed protective effects while using much lower dosages. Moreover giving more than 3 mg of PGE_2 can cause undesirable side-effects.

Our findings do not agree with theories that acids are the only cause of stress ulcers. On the other hand, the problem is very complicated. Reflux of alkaline duodenal fluids into the stomach could lower its acid content and favor the development of stress ulcers through detergent action of the bile salts. The damaged gastric mucosa also loses acid through back-diffusion.[30]

The spectrum of upper intestinal lesions should be considered when evaluating stress-induced bleeding. Sampling gastric fluid through an intraluminal tube and measuring its blood content with the ^{51}Cr-method detects not only gastric bleeding sources but also esophageal and duodenal lesions, as evidenced by our findings. However, only gastric ulcers and erosions should be considered true stress lesions, i.e. due to physiologic stress. Duodenal ulcers have been related to psychologic stress, which is also present in ICU situations. Esophageal lesions are mainly due to mechanical factors, such as gastric tube irritation and recumbent posture.

We found no correlation between peroxidase test results and the ^{51}Cr-method. However, in all cases of bleeding indicated by the ^{51}Cr-method a bleeding site was confirmed by endoscopy. This suggests

that bleeding documented only by guaiac or orthotolidine tests, as done in previous studies, [8,14,15,31] is not reliable without endoscopic confirmation. Future studies on the prevention of stress bleeding should be based on the ^{51}Cr-method and, ideally, endoscopy.

5.6 REFERENCES

1. Skillman JJ, Bushnell LS, Goldman H, et al: Respiratory failure, hypotension, sepsis and jaundice: A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 1969;117:523.
2. Lucas CE, Sugawa C, Riddle J, et al: Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266.
3. Stremple JF, Mori H, Lev R, et al: The stress ulcer syndrome. Curr Probl Surg, Year Book Medical, April 1973.
4. Menguy R, Masters YF: Mechanism of stress ulcer: II. Differences between the antrum, corpus and fundus with respect to the effects of complete ischemia on gastric mucosal energy metabolism. Gastroenterology 1974;66:509.
5. Czaja AJ, McAlhany JC, Pruitt BA: Acute gastroduodenal disease after thermal injury: An endoscopic evaluation of incidence and natural history. N Engl J Med 1974;291:925.
6. Kamada T, Fusamoto H, Kawano S, et al: Acute gastroduodenal lesions in head injury. Am J Gastroenterol 1977;68:249.
7. Harris SK, Bone RC, Ruth WE: Gastrointestinal hemorrhage in patients in a respiratory intensive care unit. Chest 1977;72:301.
8. Zinner MJ, Zuidema GD, Smith PL, et al: The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet 1981;153:214.
9. Cheung LY: Treatment of established stress ulcer disease. World J Surg 1981;5:235.
10. Van den Berg B, Van Blankenstein M: Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion 1985;31:1.
11. Van den Berg B, Van Blankenstein M: Cimetidine in the prevention of stress-induced upper gastrointestinal bleeding. Abstr. Gut 1980;21:464.
12. Eiseman B, Heyman MRL: Stress ulcers-a continuing challenge. N Engl J Med 1970;282:372.
13. Menguy R: Role of gastric mucosal energy metabolism in the

etiology of stress ulceration. World J Surg 1981;5:175.

14. Hastings PR, Skillman JJ, Bushnell LS, et al: Antacid titration in the prevention of acute gastrointestinal bleeding. N Engl J Med 1978;298:1041.

15. Priebe HJ, Skillman JJ, Bushnell LS, et al: Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980;302:426.

16. Bennett A, Murray JG, Wyllie JH: Occurrence of prostaglandin E_2 in the human stomach, and a study of its effects on human isolated gastric muscle. Br J Pharmacol Chemother 1968;32:339.

17. The International Committee for Standardization in Hematology: Recommended Methods for Radioisotope Red Cell Survival Studies. Blood 1971;38:378.

18. Robert A: Antisecretory, antiulcer, cytoprotective and diarrheogenic properties of prostaglandins. In: Advances in Prostaglandin and Thromboxane Research. Vol.2. Samuelsson B, Paoletti R (Eds). New York, Raven Press 1976,pp 507-520.

19. Miller TA, Jacobson ED: Gastrointestinal cytoprotection by prostaglandins. Gut 1979;20:75.

20. Robert A, Nezamis JE, Lancaster C, et al: Cytoprotection by prostaglandins in rats: Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury. Gastroenterology 1979;77:433.

21. Cohen MM, Cheung G, Lyster DM: Prevention of aspirin-induced faecal blood loss by prostaglandin E_2. Gut 1980;21:602.

22. Wilson DE, Kaymakcalan H: Prostaglandins: Gastrointestinal effects and peptic ulcer disease. Med Clin North Am 1981;65:773.

23. Chaudhury TK, Jacobson ED: Prostaglandin cytoprotection of gastric mucosa. Gastroenterology 1978;74:58.

24. Schiessel R, Mattheus J, Barzilai A, et al: PGE_2 stimulates gastric chloride transport: Possible key to cytoprotection. Nature 1980;283:671.

25. Bolton JP, Palmer D, Cohen MM: Stimulation of mucus and nonparietal cell secretion by the E_2 prostaglandins. Dig Dis Sci 1978;23:359.

26. Johansson C, Kollberg B: Stimulation by intragastrically administered E_2 prostaglandins of human gastric mucus output. Eur J Clin Invest 1979;9:229.

27. Lindt S, Baggiolini M: Effect of a PGE_2 analogue on the vascularization of the gastric mucosa in the rat. Experientia 1976;32:802.

28. Johansson C, Kollberg B: Clinical trials with prostaglandin E_2. Prostaglandins 1981;21 (suppl.):161.

29. Cohen MM: Prevention of aspirin-induced fecal blood loss with oral prostaglandin E_2: dose-response studies in man. Prostaglandins 1981;21 (suppl.):155.

30. Davenport HW: Back diffusion of acid through the gastric mucosa and its physiological consequence. Prog Gastroenterol 1970;Vol.2:42.

31. Pingleton SK, Hadzima SK: Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med 1983;11:13.

Published in Critical Care Medicine 1985;13:957-960.

Co-authors: M. van Blankenstein, J.H.P. Wilson, B. van den Berg, H.A. Bruining.

Chapter 6.

Orthotolidine test not to be used for detection of blood in gastric juice

6.1 INTRODUCTION

A peroxidase test for detecting occult blood in gastric aspirates has been used as a criterion for haemorrhage in several studies on stress-induced upper intestinal bleeding. Hastings et al (1), Priebe et al (2) and Zinner et al (3) used the guaiac test while Pingleton and Hadzima (4) based their study on the orthotolidine method. Both tests depend on the peroxidase activity of iron-containing haemoglobin derivates, which catalyse the oxidation of guaiac or orthotolidine in the presence of hydrogen peroxide. The guaiac test is intended for the investigation of faeces, the pH of which varies between 6 and 8. The orthotolidine test is usually employed to detect occult blood in faeces or urine. It is questionable whether such tests are suitable for the detection of blood in gastric aspirates which have a much lower pH. However conclusions regarding the prevention of stress ulcers have been based on the results of such colorimetric tests (1-4).

During a study of prophylaxis of stress-bleeding in intensive care patients, we encountered marked discrepancies between results of the orthotolidine test in gastric juice and those based on ^{51}Cr-labelling of the patient's erythrocytes, which suggest that the orthotolidine method is not suitable for gastric juice analysis, and which cast doubt on the conclusions drawn in the studies cited.

6.2 METHODS

Twenty-one patients admitted to a medical or surgical intensive care ward were investigated. The study was done within the scope of a prospective stress-bleeding prophylaxis trial, which was approved by the Medical Ethics Committee of our hospital. The patients were randomized to receive prostaglandin E_2 or placebo. Patients who were fed enterally were excluded from the study. No antacids or histamine-2 antagonists were given. Ten milliliters of blood were taken, labelled with 1.11 MBq ^{51}Cr-chromate and readministered intravenously to the patient (5). Blood content in gastric juice was determined in 24-h collections in a large volume gamma counter (Armac, Brussels), using 10 ml of the patient's blood taken on the same day as a standard. Gastric juice was obtained by a nasogastric tube and collected in 4-h portions which were kept refrigerated at 4°C until the 24-h collection period was completed. The colour of the gastric juice was noted and the pH measured.

Multistix$^{(R)}$ (Ames, IN, USA) was used as the orthotolidine test. The reagent contains 9.0% w/w cumene hydroperoxide, 2,4% w/w orthotolidine, 22% w/w buffer and 66.6% nonreactive ingredients. The gastric juice was diluted 1:20 with water, as we had determined previously that a blood loss of about 10 ml/24 h would give a 3+ reaction at this dilution. Subsequently, a series of 23 samples was tested undiluted and in a 1:10 dilution with water. To investigate the effect of adjusting the pH of the gastric juice on the test result, the test was repeated in portions of gastric juice in which the pH had been brought to pH 7.0 with $NaHCO_3$ during dilution. The test strip was dipped into the gastric aspirate and read after 40 s.

The following colour classification was used: yellow, negative; yellow-green, trace; green, +; blue-green, 2+; blue, 3+.

6.3 RESULTS

The results are shown in Tables I and II and in Fig. 1.

Table I.

Twenty-four hours' gastric juice analysis of 11 patients

Volume (ml)	Colour	pH	Multistix 1:20 dil.	Blood (^{51}Cr) (ml/1 gj [a])
903	green	1.7	trace	<1
1,154	green	2.6	trace	<1
634	green	1.7	+	<1
1,884	green	2.5	+	<1
979	green	1.8	+	<1
578	green	1.4	+	<1
992	gray	1.6	+	<1
1135	green	2.3	+	<1
1,539	yellow	2.4	+	1
566	green	1.4	+	2
924	green	1.4	+	3
920	green	1.3	+	3
988	green	4.1	2+	<1
998	green	1.3	2+	1
734	green	1.3	2+	3
475	green	1.2	2+	4
425	green	1.5	2+	4
312	green	1.4	2+	4
617	green	1.4	2+	5
1,300	green	1.2	2+	5
287	green	1.4	2+	5
366	green	1.5	2+	5
480	green	1.4	2+	5
609	green	1.9	2+	5
417	green	1.5	2+	7
602	green	1.5	2+	8
479	brown	1.6	2+	16
703	brown	3.1	2+	30
505	brown	5.3	3+	12
710	green	3.5	3+	12
253	brown	1.7	3+	22

[a] gj, Gastric juice.

Table II.

Twenty-four hours' gastric juice analysis of 10 patients

Volume (ml)	Colour	pH	Multistix undil.	1:10 dil.	1:20 dil.	Blood (^{51}Cr) (ml/1 gj [a])
617	yellow	1.6	trace	trace	trace	<1
1,374	yellow	1.5	trace	trace	trace	<1
2,487	green	1.1	trace	2+	+	2
258	green	2.0	+	+	+	<1
623	yellow	1.9	+	trace	trace	<1
845	green	1.4	+	+	trace	<1
1,197	green	1.3	+	2+	trace	2
954	brown	1.2	+	2+	2+	11
1,427	green	1.8	2+	+	+	<1
573	bs [b]	7.3	2+	+	+	<1
405	green	4.3	2+	3+	2+	<1
460	bs	7.1	2+	2+	+	<1
629	bs	6.8	2+	+	+	1
529	green	1.7	2+	2+	+	2
500	green	1.6	2+	2+	2+	2
926	green	1.8	2+	2+	+	3
972	green	3.6	2+	2+	2+	5
590	green	1.4	2+	2+	2+	9
909	brown	1.9	2+	2+	+	18
590	green	1.5	3+	2+	2+	1
657	green	2.3	3+	2+	2+	2
461	green	6.9	3+	3+	2+	5
468	brown	3.1	3+	3+	2+	149

[a] gj, Gastric juice.

[b] bs, Bile-stained.

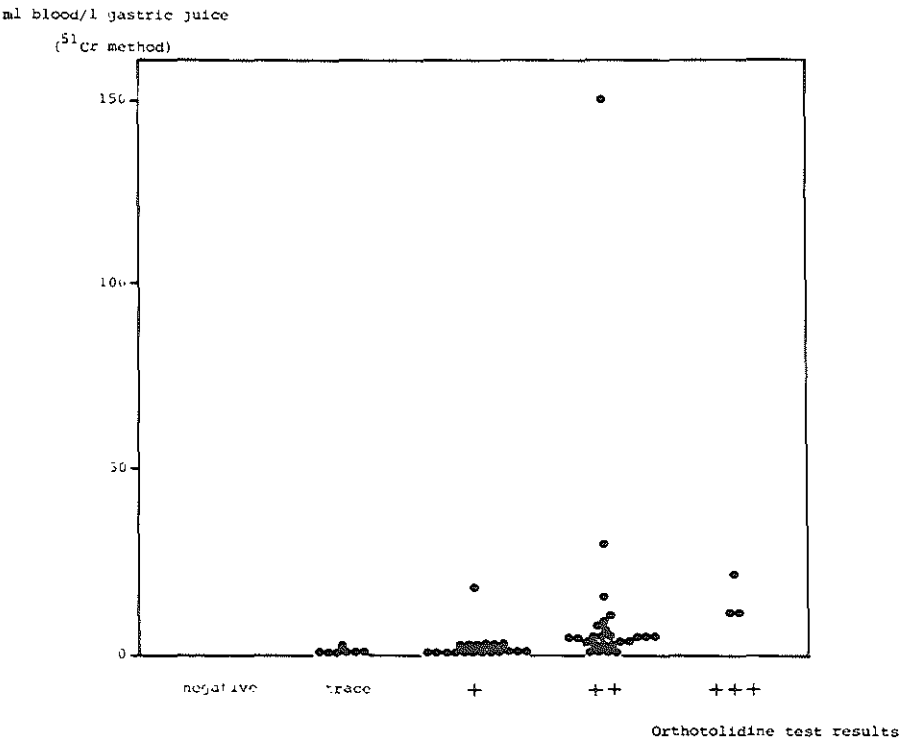

Fig.1. Comparison of 24-h collections gastric juice. Concentration of blood as measured by ^{51}Cr-method and colour classifications from orthotolidine tests after 1:20 dilution of the same gastric juice samples.

The orthotolidine method did not correlate with blood loss per 24 h nor with the concentration of blood in the gastric juice, as measured by the ^{51}Cr-method. Lower colour scores were sometimes found in undiluted gastric juice than in the 1:10 and 1:20 dilutions.

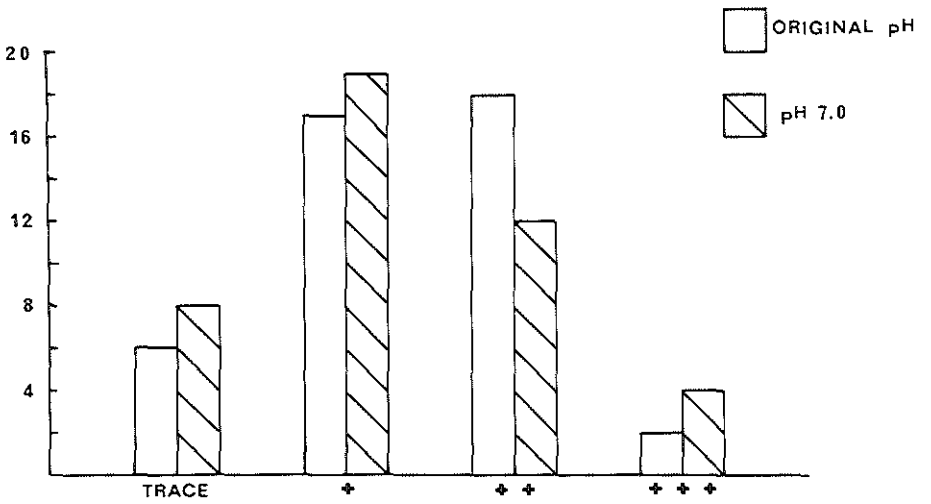

Fig.2. Total numbers of gastric juice samples with particular colour test results before and after neutralization.

Adjusting the pH of the gastric juice to 7.0 did not cause a significant change in the orthotolidine test results (Fig.2) and failed to improve the correlation with the ^{51}Cr-method.

Under these test conditions we failed to find a constant quantitative relationship between blood content as measured by the ^{51}Cr-method and test strip readings.

6.4 DISCUSSION

The ^{51}Cr-method of determining gastrointestinal blood loss is generally regarded as the most reliable method available (6). The results we obtained using this method were not reproduced by the colorimetric method based on the peroxidase reaction. Fisher and Hunt (7) showed in 1976 that the effect of haemoglobin on the conversion of orthotolidine is decreased at a low pH. The manufacturers of Multistix

warn that a high specific gravity or a high protein concentration decrease the reactivity of the test. The presence of reducing substances can also lead to false negative results; oxidizing substances can give false positive results. Multistix is intended to detect occult blood in urine. Layne et al (8) have drawn attention to the effects of antacids, cimetidine and the gastric pH on the reaction. Adjusting the pH of the gastric juice did not improve the correlation with ^{51}Cr-method in this study.

In light of our findings, the peroxidase method cannot be regarded as a reliable method for detecting blood loss from the upper gastrointestinal tract. This study also casts doubt on the validity of conclusions concerning the prevention of stress-bleeding which were based on the peroxidase reaction in gastric aspirates as a criterion of gastrointestinal haemorrhage.

6.5 REFERENCES

1. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding. N Engl J Med 1978;298:1041-1045.
2. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980;302:426-430.
3. Zinner MJ, Zuidema GD, Smith PL, Mignosa M. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynaecol Obstet 1981;153:214-220.
4. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med 1983;11:13-16.
5. The international Committee for Standardization in Hematology. Recommended methods for radioisotope red cell survival studies. Blood 1971;38:378-386.
6. Rhys Davies E. Radionuclide investigations. Clin Gastroenterol 1984;13:205-233.
7. Fisher MA, Hunt JN. A sensitive method for measuring haemoglobin in gastric contents. Digestion 1976;14:409-414.
8. Layne EA, Mellow MH, Lipman TO. Insensitivity of guaiac slide tests for detection of blood in gastric juice. Ann Intern Med 1981;94:774-776.

Published in Clinica Chimica Acta 1985;150:255-259.

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Chapter 7.

Determination of haemoglobin in gastric aspirates

7.1 SUMMARY

The haemoglobin content of gastric aspirates can be quantitated by conversion of non-fluorescent haem to fluorescent porphyrins by heating gastric aspirates with oxalic acid and ferrous sulphate. Recovery of haemoglobin added to gastric aspirates was 92 ± 9%, variation coefficient, n = 52, day to day variation was less than 8%. This method was used to calculate blood (haemoglobin) loss in 211 (24 hours) gastric aspirates obtained from 58 intensive care patients. Gastric blood loss was also measured by the ^{51}Cr radiolabelled erythrocytes method in the same samples. There was a good linear correlation ($r = 0.942$, $p < 0.001$) between the two methods. The fluorimetric method of quantitating haem is therefore suitable for detecting and measuring blood loss in gastric contents.

7.2 INTRODUCTION

The determination of haemoglobin in gastric aspirates has been used in several studies to detect upper gastrointestinal bleeding (1-4). In most studies a peroxidase assay, using guaiac or orthotolidine, has been used. Such leuko dye tests are qualitative rather than quantitative, and have been shown to be unreliable tests for occult blood in gastric juice (5). A reliable alternative is the quantitative measurement of ^{51}Cr radiolabelled erythrocytes. This method is however

costly, invasive and not suitable for routine use. Recently Schwartz et al (6,7) described a method for measuring haemoglobin in faeces which is based on the removal of iron from haem by heating under reducing acid conditions to convert it to fluorescent porphyrin. This test, which is based on methods described for whole blood and tissues (8), has been shown to be quantitative and specific over a wide range of haemoglobin concentrations in faeces (6). We have applied a modification of their method to the determination of haemoglobin in gastric aspirates, and compared the results obtained by this method to those obtained by ^{51}Cr-labelling of the patient's erythrocytes.

7.3 MATERIALS AND METHODS

Gastric aspirates were obtained from a series of adult intensive care patients participating in a double-blind, placebo-controlled study of the effects of prostaglandin E_2 on the occurrence of upper gastrointestinal haemorrhage in intensive care patients. Details of the patients and of the protocol have been described elsewhere (9). Briefly, either placebo or prostaglandin E_2 was introduced into the stomach by a nasogastric tube at 4 hourly intervals, and gastric contents allowed to drain by gravity between administrations. Gastric contents were kept at 4°C until 24 hour collections could be pooled, after which the 24 hour collections were kept at -20°C. A total of 211 samples obtained from 58 patients were available for both the ^{51}Cr-labelled erythrocytes and the chemical analysis. This study was approved by the Medical Ethics Committee of the University Hospital of Rotterdam.

7.3.1 ^{51}Cr chromate labelling.

Blood (10 ml) was withdrawn from the patient, the erythrocytes were labelled with 1.11 MBq of ^{51}Cr chromate, and readministered to the patient (10). The radioactivity of the pooled collections of gastric

juice was measured in an Armac(R) large volume gamma counter (NV Packard Instruments Brussels, Belgium). Ten ml of blood was withdrawn daily and used as standard. The haemoglobin content of the blood was measured daily by the HiCN method in a Coulter S instrument (Hoek-Loos BV, Schiedam, The Netherlands). The results of the ^{51}Cr-labelling studies, expressed in ml blood per 1 gastric aspirate, were converted to mmol Hb per 1 aspirate using the Hb concentration of peripheral blood on the morning of the collection day.

7.3.2 Fluorimetric method of haemoglobin determination.

This method is based on that described by Schwartz et al (6,7) in which haem is broken down to iron and porphyrins (mainly dicarboxylic porphyrins such as protoporphyrin) by heating with oxalic acid and $FeSO_4$, but is modified in that the resulting porphyrin is extracted from the reaction mixture by isopropanol.

7.3.3 Reagents.

Crystalline haemoglobin was obtained from Sigma, St. Louis, Mo, USA. Haemoglobin stock standard was made by dissolving 20 mg of haemoglobin in 10 ml 9 g/l NaCl, corresponding to 124 umol/L haemoglobin. The following dilutions were made with 9 g/l NaCl: 1:20, 1:10, 1:5, 1:2.5 and these, together with undiluted stock standard were used as standards for the assay.

7.3.3.1 Oxalic acid reagent.

2.5 mol oxalic acid (315 g $C_2H_2O_4$, $2H_2O$), 90 mmol (25 g) $FeSO_4$. $7H_2O$, 50 mmol (8.4 g) uric acid, 50 mmol (9.1 g) mannitol in bidistilled water to 1 l, was made fresh each day and heated to 80°C on a thermostatted hotplate while being mixed constantly with a

magnetic stirrer, during 1 hour, before use. The reagent remains as a suspension, and was kept at 80°C while being stirred until use. A separate volme of reagent, kept at room temperature, was used for the blank determination of each sample.

7.3.4 Procedure.

Collections of gastric juice were mixed well before sampling. In specimens where the contents did not form a homogenous suspension, a solution could be achieved by the addition of NaOH. For the assay, 50 ul of gastric juice was mixed with 50 ul of 9 g/l NaCl in a polypropylene test tube. To this mixture 2 ml of reagent (80°C) was added by means of a graduated 2 ml glass pipette and the tube placed in a waterbath at 100°C with a marble on top to prevent evaporation losses. After 30 min at 100°C the tubes were cooled under running tap water and 2 ml of isopropanol was added when cooled. The contents were then mixed on a vortex mixer followed by centrifugation at 1200 g for 10 minutes. The supernatants were then tranferred to a Perkin Elmer spectrofluorimeter (type 2000) (Perkin-Elmer Nederland BV, Gouda, The Netherlands) with a red sensitive photomultiplier and the fluorescence read at 399 nm excitation and 598 nm emission wavelengths.

Standards were run in a similar way by mixing 50 ul of each haemoglobin standard with 50 ul 0.01 mol/l HCl. Recoveries were determined by adding 50 ul haemoglobin standard to 50 ul sample .

A blank was prepared of each sample and standard. The order of addition of reagents to blanks was first the isopropanol (2 ml), followed by the oxalic acid reagent (2 ml at 20°C). This mixture was left at room temperature for 30 minutes. Centrifugation and subsequent measurements were carried out as described above.

The fluorescence of the sample minus fluorescence of the sample blank was compared with the fluorescence curve of the standards minus standard blank. Recoveries were performed by adding 50 ul of the 1:5 haemoglobin standard to 50 ul of sample. Reproducibility was checked by performing the test on two series of multiple assays on separate

days. All determinations were done in duplicate. Completeness of extraction of porphyrins was checked by measuring the recovery of added protoporphyrin IX (obtained as disodium salt from Pfaltz & Bauer, Flushing, NY, USA) in concentrations ranging from 11.4 to 114 umol/l in gastric aspirates from 3 patients.

7.3.4.1 HPLC of porphyrins.

The nature of the porphyrins, formed by heating gastric aspirates with the oxalic acid reagent and extracted from the mixture into isopropanol, was examined by reversed phase high performance liquid chromatography (11).

7.4 RESULTS

7.4.1 Recovery and reproducibility.

The isopropanol extraction method was found to extract all added protoporphyrin (recovery 100,3 ± 5.4%). Mean recovery of haemoglobin added to gastric aspirates was 92% (variation coefficient 9%, n = 52). Reproducibility was good, e.g. two samples gave 11.86 ± 0.95 (mean ± SD, n = 8) and 51.48 ± 3.39 (n = 6) umol/l haemoglobin.

7.4.2 Comparison with ^{51}Cr-labelled erythrocytes method.

The results of the comparison of the fluorescent method and the radiolabelled erythrocytes method for the 211 gastric aspirate samples is shown in fig.1. A good correlation was found over a wide range of concentrations.

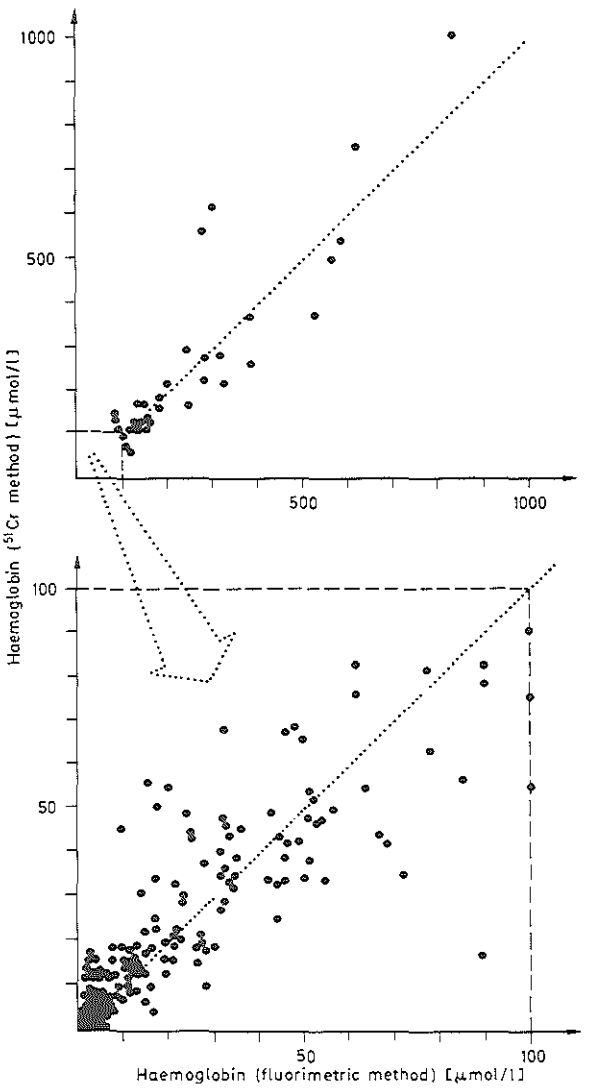

Fig.1. Comparison of haemoglobin concentration in gastric aspirates measured fluorimetrically or by ^{51}Cr-labelled erythrocytes. The dotted line represents the line of identity ($y = 1.03\ x - 0.25$; $r = 0.942$, $p < 0.001$).

7.4.3 HPLC of fluorescent products.

Chromatograms of the porphyrins formed from gastric aspirates and extracted by isopropanol are shown in fig.2.

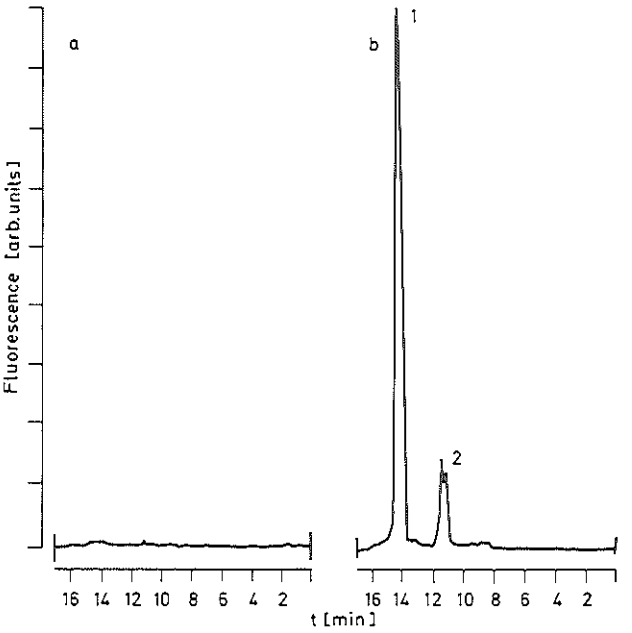

Fig.2. HPLC chromatograms of the porphyrins formed by acid reduction of haemoglobin in a gastric aspirate (b), in comparison with the blank of the same gastric aspirate (a) (protoporphyrin is eluted at 14 min (peak 1), haematoporphyrin between 10 and 12 mins (peak 2).

Most porphyrins found under both situations are dicarboxylic porphyrins - mainly protoporphyrin. There was almost no detectable fluorescence in the blank determination of the specimen.

The fluorescence emission spectra for treated haemoglobin, gastric aspirate and blank are shown in fig.3.

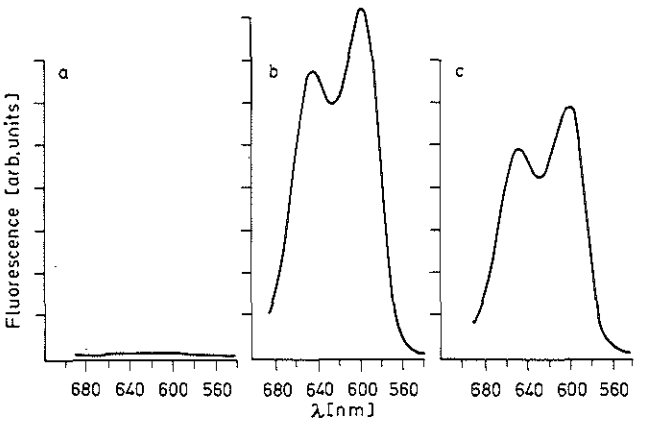

Fig.3. Fluorescence emission spectra of the isopropanol extract of th blank of a gastric aspirate (a), a treated gastric aspirate (b and the treated haemoglobin standard (c) (excitation wavelengt 399 nm).

7.5 DISCUSSION

The fluorimetric method of determining haemoglobin in faeces ha been reported to be quantitative and accurate over a wide range o haemoglobin concentrations (6,7), and this we could confirm. In thi study, measuring haemoglobin in gastric aspirates, we simplified th method described by Schwartz et al (6) for faeces by reducing th extraction of porphyrins after the acid reduction to a single step Isopropanol extracts mainly the lipid soluble porphyrins such as th dicarboxylic porphyrins which are formed when iron is removed fro haem. This single extraction step has proven reliable for measurin haem (haemoglobin) in gastric aspirates, and preliminary studie suggest that it is also applicable to faeces, and that even for faece there is negligible interference by endogenous porphyrins (except i patients with protoporphyria) or by chlorophyll.

This study shows a good correlation between this new quantitativ test of gastric blood loss and the accepted test which use

radiolabelled erythrocytes. The differences in individual values between the two tests in this series could be due to problems in small scale sampling because of the inhomogeneity of gastric juice, and to the difficulties in measuring low levels of blood loss accurately with the radiolabelling technique due to the small amounts of ^{51}Cr in the samples. Blood in gastric aspirates is not distributed evenly, and it is sometimes difficult to obtain a homogenized mixture. Alkaline dilution, however, promotes solubilisation of proteins and haemoglobin and facilitates sampling. The good agreement found in this direct comparison of the two methods suggests that the technically simpler fluorimetric method can be used instead of the radiolabelling technique in clinical studies or clinical practice where detection and quantitation of gastric blood loss is needed. It is suitable for subjects in whom radioisotope studies are contraindicated.

7.6 REFERENCES

1. Hastings, P.R., Skillman, J.J., Bushnell, L.S. & Silen, W. (1978) N.Engl.J.Med. 298,1041-1045.
2. Priebe, H.J., Skillman, J.J., Bushnell, L.S., Long P.C. & Silen, W. (1980) N.Engl.J.Med. 302,426-430.
3. Zinner, M.J., Zuidema, G.D., Smith, P.L., & Mignosa, M. (1981) Surg.Gynecol.Obstet. 153,214-220.
4. Pingleton, S. & Hadzima, S.K. (1983) Crit.Care Med. 11,13-16.
5. Layne, E.A., Mellow, M.H. & Lipman, T.O. (1981) Ann.Intern.Med. 94,774-776.
6. Schwartz, S., Dahl, J., Ellefson, M. & Ahlquist, D. (1983) Clin.Chem. 29,2061-2067.
7. Ahlquist, D.A., McGill, D.B., Schwartz, S., Taylor W.F., Ellefson, M. & Owen, R.A. (1984) Ann.Intern.Med. 101,297-302.
8. Morrison, G.R. (1965) Anal. Chem. 37,1124-1126.
9. Van Essen, H.A., van Blankenstein, M., Wilson, J.H.P., van den Berg, B. & Bruining, H.A. (1985) Crit Care Med. 13,957-960.
10. International Committee for Standardisation in Hematology. Recommend methods for radioisotope red cell survival studies. (1971) Blood 38,378-386.
11. Ford, R.E., Ou, C.N. & Ellefson, R.D. (1981) Clin.Chem. 27,397-401.

Published in: Journal of Clinical Chemistry and Clinical Biochemistry 1985;23:841-844.

Co-authors: J.H.P. Wilson, H. Koole-Lesuis, A. Edixhoven-Bosdijk, J.W.O. van den Berg.

Chapter 8.

DNA in gastric aspirates

8.1 INTRODUCTION

Prostaglandins are thought to have a stimulating effect on the synthesis of desoxyribonucleic acid (DNA) in the stomach mucosa. In rats, acetylsalicylic acid inhibits DNA synthesis in the gastric mucosa. This inhibition and the subsequent ulcer formation could be prevented by administration of prostaglandins (1). Studies in guinea pigs (2) have shown that stress decreases DNA synthesis in gastric mucosa.

Croft and Cotton (3) showed that DNA output in gastric aspirates is a measure of cell turnover in the gastric mucosa, and thus for exfoliation and cellular renewal. The normal gastric juice of humans contains up to 30 mg per day of DNA. A more exact determination of cell renewal than the DNA content, is the measurement of incorporation of titriated thymidine in mucosa. Kim et al (4) and Lipkin et al (5) found that in rats stress results in a decreased mitotic activity in the gastric mucosa. Stremple (6) performed clinical studies in patients with multiple or severe trauma. He found an increase in the DNA output in the gastric juice during the first days of the trauma. The time course of DNA output appeared to be related to the severity of the trauma.

We tried to study whether:

1. Prostaglandin E_2 (PGE_2) influences DNA output in gastric juice; and
2. The DNA output could be related to the number of risk factors for

stress bleeding.

8.2 METHODS

As part of the clinical trial on stress bleeding prophylaxis using PGE_2 versus placebo, described in chapter 5, gastric aspirates from all patients were kept -20°C. The DNA content was measured according the method of Croft and Lubran (7) which is designed to measure DNA in human gastric washings. This is a modified diphenylamine method, which leads to the spectophotometric determination of DNA.

Gastric aspirates of day 1 were not examined as these were initial portions at the moment of starting the study, which did not allow calculation of output. Day 2 was the first complete 24 hour period. To allow statistical evaluation, only the results of patients which completed a minimum of 3 days in the trial, were used. This means that a number of patients who bled during the first days of the study were excluded from the calculations. The DNA output was calculated by multiplying the DNA concentration (ug/ml) by the 24 hour gastric aspirate volume. The DNA output is expressed in mg/day.

Blood loss into gastric aspirates was determined by the ^{51}Cr-labelling method (8).

8.3 RESULTS

DNA outputs over 3 days are given in table 1 and table 2. A trend in the DNA output over these 3 days could not be demonstrated. The total 3 day DNA output is given in table 3 to examine possible effects of PGE_2 on DNA output. For an improved comparison of PGE_2 with placebo, the patients were stratified according to the number of risk factors. A statistically significant quantitated difference in DNA output between the PGE_2 and the placebo group was not found. There was no relationship between the number of risk factors (a measure of the severity of the stress) and DNA output during 3 days.

Table 1. PGE_2-group

Patient's No.	No. of RF	DNA output (mg/day) Day 2	Day 3	Day 4	(mg/3 days) Day 2+3+4
1*	5	17,4	9,7	7,3	34,4
2	5	53,5	43,1	24,7	121,3
3*	4	5,6	1,4	1,3	8,3
4	4	26,0	7,7	9,6	43,3
5*T	3	19,5	26,5	11,4	57,4
6	3	13,4	22,0	11,6	47,0
7 T	3	12,0	3,8	12,2	28,0
8	3	6,5	18,2	22,4	47,1
9	3	99,2	84,9	84,3	268,4
10	3	16,7	9,6	17,2	43,5
11	3	6,0	10,5	7,2	23,7
12	3	7,9	3,9	8,8	20,6
13	2	7,9	32,1	39,9	89,9
14	2	9,3	5,1	1,4	15,8
15	2	2,2	8,4	2,3	12,9
16	2	10,2	2,5	2,2	14,9
17	2	20,7	47,0	25,7	93,4

* Patient with bleeding ($\geqslant$15 ml/day)

RF = risk factors

T = trauma patient.

Table 2. Placebo group.

Patient's No.	No. of RF	DNA output (mg/day) Day 2	Day 3	Day 4	(mg/3 days) Day 2+3+4
1*	4	5,1	2,4	5,6	13,1
2*	4	22,1	90,1	28,6	140,8
3	4	1,2	14,1	8,6	23,9
4	3	28,6	22,0	12,5	63,1
5	3	2,2	9,4	4,5	16,1
6	3	20,3	27,3	5,4	53,0
7*	2	11,7	36,9	8,3	56,9
8	2	2,8	2,8	0,9	6,5
9	2	9,6	6,7	11,7	28,0
10	2	11,8	11,6	18,8	42,2
11	2	6,6	1,1	4,0	11,7
12	2	6,0	4,4	5,7	16,1
13	2	4,4	4,5	4,0	12,9

* Patient with bleeding ($\geqslant$15 ml/day)

RF = risk factors.

Table 3. Total DNA output in days 2 + 3 + 4 (mg/3 days) as mean value per patient.

No. of RF	PGE_2	placebo
5	77,9 (2)	- (0)
4	25,8 (2)	59,3 (3)
3	67,0 (8)	44,1 (3)
2	45,4 (5)	24,9 (7)

RF = risk factors.

Numbers of patients in parentheses.

8.4 DISCUSSION

We were unable to confirm in this study the findings of Stremple (6), who found an increase in DNA output during the first days following trauma. This could be due to the fact that a few trauma patients were included in our study, and large number of patients with other serious conditions. The two trauma patients we examined, however, also did not show a change in DNA concentration similar to that observed by Stremple. Patients who bled, did not have obviously different values to patients who did not bleed, nor was there a change in DNA content during the course of 3 days in the patients who had bled. We did not find an obvious effect of PGE_2 on DNA output. The number of risk factors at the start of the study also did not correlate with DNA output. In healthy volunteers Hurst et al (9) was also unable to find an increase in DNA output in gastric juice following administration of PGE_2. The studies described above do not allow the conclusion to be drawn that PGE_2 in stress has no effect on DNA synthesis, as a decreased exfoliation can mask an increased DNA synthesis. A study of a larger number of patients could possibly allow more definite conclusions to be drawn.

8.5 REFERENCES

1. Konturek SJ, Brzozowski T, Piastucki I, Dembinski A, Radecki T, Dembinska-Kiec A, Zmuda A, Gregory H. Role of mucosal prostaglandins and DNA synthesis in gastric cytoprotection by luminal epidermal growth factor. Gut 1981;22:927-932.
2. Ludwig WM, Lipkin M. Biochemical and cytological alterations in gastric mucosa of guinea pigs under restraint stress. Gastroenterology 1969;56:895-902.
3. Croft DN, Cotton PB. Gastrointestinal cell loss in man. Its measurement and significance. Digestion 1973;8:144-160.
4. Kim Y-S, Kerr RM, Lipkin M. Cell proliferation during the development of stress erosions in mouse stomach. Nature 1967;215:1180-1181.
5. Lipkin M, Kerr RM, Kim Y-S. The cellular basis of stress ulcer formation in the stomach. J Clin Invest 1966;45:1042.
6. Stremple JF. Prospective studies of gastric secretion in trauma patients. Am J Surg 1976;131:78-85.
7. Croft DN, Lubran M. The estimation of deoxyribonucleic acid in the presence of sialic acid: application to analysis of human gastric washings. Biochem J 1965;95:612-620.
8. The International Committee for Standardization in Hematology: Recommended Methods for Radioisotope Red Cell Survival Studies. Blood 1971;38:378-386.
9. Hurst BC, Rees WDW, Garner A. Cell shedding by the stomach and duodenum. In: Mechanisms of mucosal protection in the upper gastrointestinal tract. Allen A, Flemström G, Garner A, Silen W, Turnberg LA (eds.) New York, Raven Press, 1984:pp.21-26.

Chapter 9.

Treatment and prevention of stress ulcer and stress bleeding

9.1 INTRODUCTION

The incidence of bleeding from stress ulcers seems to have decreased in recent years (1). This decrease has been ascribed to improved management of risk factors, especially sepsis and shock. Rapid recognition and correction of these predisposing conditions for stress ulcer and stress bleeding, are the mainstay of stress ulcer and stress bleeding prophylaxis and treatment. A significant bleeding, - i.e. manifest hemorrhage requiring blood transfusions - from stress ulcer is associated with a high mortality of more than 30% (2,3).

9.2 TREATMENT

9.2.1. General measures.

Bleeding should prompt the attending doctor to look for and to treat rigorously underlying serious conditions. In suspected sepsis, all efforts should be taken to localize the source, drainage should be performed if possible, and appropriate antibiotic therapy should be given. Shock must be treated vigorously. Coagulation disorders should also be corrected (2,3,4). A large-bore tube should be inserted, in order to allow gastric decompression and to reduce vomiting and aspiration. It will provide also an impression about the rate of

bleeding. Some authors have reported a beneficial effect of gastric lavage (2,3,5). Iced saline lavage has been reported to stop 80% of bleeding episodes (2,6). There is evidence, however, that low temperature may retard clotting (2,4,5). Washing with fluid at room or body temperature is probably better, and, at least, serves to clean the stomach for subsequent gastroscopy.

Intragastrically administered norepinephrine has been used in the treatment of gastric bleeding. There is little evidence that cold saline lavage or lavage with saline plus norepinephrine are better than lavage with room temperature saline for stopping bleeding (5,8).

9.2.2 Antacids.

Recent reviewers recommend the administration of antacids via a gastric tube, and to titrate gastric pH to $\geqslant 7$ (4,9,10). In vitro studies have demonstrated that acid has anticoagulant properties (11). Pepsin promotes platelet disaggregation (11), and is inactivated at high gastric pH. In the majority of patients, bleeding ceases with this type of management (4,9). Titration of gastric pH is, however, a tedious method for the nursing staff.

9.2.3 Histamine-2-antagonists.

The effectiveness of histamine-2-antagonists (H_2-antagonists), such as cimetidine and ranitidine, in stopping upper gastrointestinal bleeding from different sources has not been proven (12,13). The available data indicate that in bleeding from peptic ulceration, rebleeding may be prevented by H_2-antagonists (14,15); combination with antacids seems to improve rebleeding prophylaxis (16). To date, there are no prospective randomized endoscopically controlled studies that indicate that cimetidine is effective in controlling established bleeding from acute gastric mucosal ulceration (10). Rebleeding from stress ulcers can possibly be prevented by H_2-antagonists plus antacids (17).

9.2.4 Tranexamic acid.

Tranexamic acid, an antifibrinolytic drug, was not associated with any decrease in the rate of rebleeding or the need for operation, in bleeding from different upper gastrointestinal sources in a recent study (18). However, stress ulcers were not included.

9.2.5 Somatostatin.

Somatostatin is a hormone that inhibits stimulated gastric acid and pepsin secretion and reduces splanchnic blood flow. It has been reported to be more effective than cimetidine in stopping bleeding from peptic ulcers (19,20). These studies are small and poorly controlled, and do not deal with stress bleeding. In a recent study by Somerville et al (21), 630 patients with bleeding from different upper gastrointestinal lesions were randomly allocated to treatment with somatostatin and placebo. No clear-cut benefit from somatostatin was found.

9.2.6 Prostaglandins.

There are some reports of treating bleeding from stress ulceration succesfully with prostaglandins (22,23). No clinical trials have been reported using prostaglandins for this specific purpose.

9.2.7 Therapeutic angiography.

If bleeding persists, angiography should be considered. Athanasoulis et al (24) reported on their experience with the selective intra-arterial infusion of vasopressin in patients who were bleeding from acute gastromucosal lesions. Hemorrhage was controlled in 84%. The left gastric artery should be canulated and there is need

for an indwelling catheter. Though vasopressin is metabolized by the liver, there is a risk of cardiac side effects. Intravenously administered vasopressin is of no use in upper gastrointestinal tract bleeding, except in hemorrhage from varices (25).

In a recent study, Lieberman et al (26), using gelfoam and/or coil springs had attained control of bleeding in 6 out of 11 patients with stress ulcers, i.e. a success rate of 55% in this small group of patients.

For this hemostatic technique to be effective, one major artery should be supplying the area of bleeding, but in the stomach this is rarely the case as there is an extensive submucosal plexus. Moreover, stress ulcers are often multiple. An infrequent but serious complication of arterial embolization is gastric infarction. It seems reasonable to attempt therapeutic angiography before operation is considered, initially giving intra-arterial infusion of vasopressin. Failures of vasopressin can be followed by transcatheter embolization (27).

9.2.8 Endoscopic therapy.

Endoscopic hemostatic techniques e.g. electrocoagulation and laser coagulation are currently in the investigational stages. This mode of therapy probably offers the best non-surgical means for controlling upper intestinal hemorrhage. Efficacy and safety should be more completely evaluated, before routine clinical use can be advocated. Stress bleeding poses a special problem as stress ulcers are mostly multiple.

9.2.9 Surgical therapy.

In most patients bleeding stops after saline lavage, antacid or others of the aforementioned measures. Surgical intervention should be considered if bleeding persists, as evidenced by the need of multiple

transfusions of blood. Surgery should be viewed as a last resort. In these seriously ill patients an additional surgical procedure for control of bleeding has a mortality of 30 to 40 percent (3,10). A variety of operations has been proposed. The superiority of one from another has not been demonstrated (3). In general, the less extensive procedures are associated with lower mortality rates, but high incidences of rebleeding (3). Truncal vagotomy and pyloroplasty with oversewing of lesions, is probably the best initial operation (3,4). Rebleeding occurs in 10 to 40 percent of cases and should first be treated medically (3). If conservative treatment of rebleeding is not successful, near total gastrectomy should be performed (3,4). Gastric devascularization is a new alternative approach, advocated by Richardson and Aust (28). This operation was reported to have low rates of rebleeding and gastric necrosis was not seen. Mortality, however, remained high, so in this respect gastric devascularization offers no advantage over the other operations.

9.3 PREVENTION

Significant hemorrhage from stress ulcer is associated with a high mortality and therapeutic results are disappointing. Therefore prophylaxis of stress ulcer and bleeding are rational.

It should be emphasized that the best prophylaxis is rapid treatment of underlying serious conditions (risk factors), like sepsis and shock, and giving effective renal and respiratory support (31).

The aim of stress ulcer prophylaxis is to maintain the gastric mucosal integrety, which involves several aspects: mucosal permeability, secretion, mucosal blood flow, acid-base balance, pepsin, and prostaglandins (29). A decreased cellular proliferation of the gastric mucosa has been demonstrated during stress (30). Attempts to influence these facets of gastric mucosal integrety in conditions predisposing to stress ulcers have been made in the laboratory and in patients and will be discussed below.

9.3.1 Vitamin A.

Vitamin A has been used for stress bleeding prophylaxis as a deficiency of this vitamin was suggested in animal experiments. Some data show a possible effect of vitamin A in preventing stress ulcer in rats, but results in humans are anecdotal and inconclusive (31).

9.3.2 Carbenoxolone.

Carbenoxolone, which stimulates the synthesis of gastric mucus and increases the life span of gastric mucosal epithelial cells, was found to reduce the incidence of stress ulcer in the rat model (31). Though carbenoxolone has been used for duodenal ulcer in man, no clinical use in the prophylaxis of stress ulcer has been reported (31).

9.3.3 Gastrin.

Gastrin is a powerful stimulator of gastric acid secretion. In rats, pentagastrin protects against stress ulceration (32). This protective effect is shared by histamine and is probably mediated by stimulation of cells to secrete H^+, thus increasing intramural pH, which enhances the gastric mucosal barrier (29,33). Mucus synthesis is increased by gastrin probably via increased acid output (34). Another biological effect of gastrin is stimulation of growth of gastric mucosa (35), which seems very important in stress conditions.

9.3.4 Secretin.

A double-blind trial by Spilker et al (36) using endoscopic criteria, gave evidence of effective stress ulcer prophylaxis by secretin. They ascribed this effect to reduced gastric acid and pepsin secretion together with a decreased serum gastrin level. The

explanation has a weak theoretical base, as gastrin may on the contrary prevent stress ulcer; moreover, secretin reduces gastric blood flow, which predisposes to stress ulcer formation.

Nevertheless, their findings are of interest, as they performed endoscopies instead of using unreliable tests for detecting occult blood loss. Further studies are necessary before firm conclusions as to the value of secretin in stress ulcer can be drawn.

9.3.5 Cholestyramine.

Reflux of duodenal contents into the stomach plays an important role in stress ulcer pathogenesis (1). Bile acids and lysolecithin cause gastric-mucosal injury (37). Cholestyramine is a bile-acid-binding agent, which was used by Schumpelick and Grossner (38) for stress ulcer prophylaxis in a clinical trial which included 68 subjects. They found only gastric erosions in one patient in the cholestyramine group (8 patients), and gastric stress ulcers in 2 patients in the antacid group (24 patients), the latter being used as a control group. No lesions were found using cholestyramine plus antacids (36 patients).

9.3.6 Vasodilatation.

Selective vasodilatation of gastric vessels with isoproterenol during hemorrhagic shock protects against acute gastric mucosal lesions in dogs (39). This seems to be too complicated for clinical application.

9.3.7 Bicarbonate.

Disturbances of acid-base balance are important pathogenetic factors in stress ulcer. Active acid-secreting gastric mucosa has a

protective effect against stress ulcer (29,33). Administration of bicarbonate on the gastric serosa or intravenously prevents stress ulcer in animals (29,31), and a high arterial bicarbonate concentration possibly reduces the risk of stress bleeding in man (40), but no clinical trials using parenteral administration of bicarbonate in the prophylaxis of stress bleeding have been done.

9.3.8 Antacids.

Gastric acid production is generally not increased in stress ulcer disease, and gastric acid is not the most important factor in its genesis. Nevertheless it has a permissive role in stress ulcer formation (41,43), as gastric mucosal injury is aggravated by the influx of acid.

The effectiveness of antacid in the prevention of bleeding was investigated by Hastings et al (43) in a placebo-controlled trial involving 100 critically ill patients. Hourly titration was used to maintain the pH of gastric contents above 3.5. The reported incidence of bleeding was 25% in the placebo group and 4% in the antacid group. Bleeding criteria were based on frank blood in gastric aspirates and on guaiac tests for occult blood. All patients of the placebo group who were considered to have a bleed (12 out of 49) had "chemical bleeding", i.e. based on guaiac. Only one patient was found to have clinical bleeding (frank blood in gastric aspirate) and this patient was treated with antacids. Two out of 51 patients in the antacid group were assumed to have bled: the one with clinical bleeding and another patient with "chemical bleeding". As is described in chapter 6 of this thesis, peroxidase tests are not applicable to detecting occult blood in gastric juice, so "chemical bleeding" is not a good criterion. Zinner et al (44), using also guaiac tests, had similar results in treating with antacids (5% bleeds) as compared with placebo (20% bleeds). In this study, gastric pH was kept above 4.0, and concomitantly one group of patients was treated with cimetidine (14% bleeds). Each group consisted of 100 patients.

Khan et al (45) reviewed the case records of intubated patients with respiratory failure. In 420 patients massive upper gastrointestinal hemorrhage occurred in 40 of 420 patients (9.5%). In a prospective study hourly antacid gastric neutralization was started, maintaining gastric pH over 5; three of 210 patients treated in this way devcloped bleeding (1.4%). In 110 patients cimetidine 1800 mg daily was given; 3 of them had bleeding (2.7%). These patients had only one risk factor (respiratory failure), so this study has significance for a special group of intensive care patients. Nevertheless, their findings are important as only clinical bleeding was used as a criterion.

In a recent study (46) 65 critically ill patients were given prophylactic antacid treatment to maintain gastric pH of at least 5. Sixty-one patients received no prophylaxis. Microscopic bleeding was diagnosed with tests based on the peroxidase reaction. All patients in both groups developed microscopic bleeding. Moderate visible bleeding was seen in 7 patients of the antacid group (10.8%) as compared to 8 patients in the control group (13.1%). This difference was not significant. One patient in the control group developed severe bleeding due to acute erosive gastritis. The authors conclude that antacids are not required to prevent stress bleeding.

The rate of complications using antacids was 25% in the study of Hastings et al (43). Diarrhea is frequently seen. Metabolic alkalosis can occur. Aspiration pneumonia and hypermagnesemia are dangerous side effects, as is hypophosphatemia. Hypermagnesemia should be looked for in cases of renal failure. Recently, airway colonization and predisposition to pneumonia have been reported in seriously ill patients treated with antacids or cimetidine (47).

9.3.9 Histamine-2-antagonists.

Intraluminal gastric pH can be increased by histamine-2-antagonists (H_2-antagonists) in an easier fashion than with antacids.

Administration is less time-consuming and the complication rate is much lower.

Priebe et al (33) compared cimetidine and antacid in a stress bleeding prophylaxis trial in 75 patients. Gastric pH was measured hourly and titrated above 3.5 in the antacid group, and cimetidine dosage was adjusted up to 2400 mg daily if pH was below 3.5 in the cimetidine group. Seven of 38 in the cimetidine group developed bleeding (18%); 2 had clinical bleeding and 5 had "chemical bleeding". None of the 37 antacid treated patients had hemorrhage. The authors conclude that cimetidine does not adequately protect seriously ill patients from acute upper-gastrointestinal tract bleeding. The failure of cimetidine is ascribed to the impairment of the secretory state of the gastric mucosa, decrease of intracellular buffering capacity, and inadequate reduction of intraluminal acidity. Seven out of eight patients who required 400 mg of cimetidine every four hours had gastric pH values below 3.5 on one or more occasions even at that dosage.

Zinner et al (44) found in 14% incidence of bleeding in cimetidine-treated patients as already mentioned above. In 34% of the patients treated with cimetidine, the gastric pH was not maintained above 4.0 (as was the aim in the design of this study) for longer than eight hours.

Van den Berg and van Blankenstein (48) saw more patients with bleeding in a cimetidine-treated group of patients on assisted ventilation with multiple risk factors (5 out of 10), than in a placebo-treated group (one of 14). Bleeding was evaluated by the ^{51}Cr-method. In a study by Luk et al (49) bleeding rate was also higher in the cimetidine-treated group than in the placebo-treated group. Bleeding was defined on clinical grounds and Hemoccult^{R} tests.

Cimetidine often elevates intragastric pH insufficiently, especially in severely stressed patients, even at high dosages. Martin et al (50) treated 39 critically ill patients with cimetidine, and in 11 of them (28%) pH could not be brought above 4.0. This failure of cimetidine (or antacids) to maintain gastric pH above 4.0 was found to be a sign of sepsis (51).

Stothert et al (52) found cimetidine at a 1200 mg daily dosage to give pH above 4 in only 47% of critically ill patients, while maximal dosage (2400 mg) gave pH above 4 in 74% of patients.

Side-effects of cimetidine are relatively rare. Fever, bone marrow suppression, and renal function impairment are sometimes seen. Mental confusion is seen more often, especially in the elderly. In 17% of critically ill patients mental symptoms were reported to be a consequence of cimetidine (53). Cimetidine has an inhibitory effect on hepatic drug metabolism. Interactions with other drugs has also been reported, including changes in absorption from the gut.

In contrast to the disappointing results of cimetidine in the prevention of stress bleeding mentioned above, there have been non-randomized studies that indicate effectiveness, such as those of Jones et al (54) and MacDougall et al (55). Jones et al studied patients following renal transplantation. They found no bleeding in 3 cimetidine-treated patients, whereas six of 33 patients (18%) who did not receive cimetidine developed hemorrhage. Bleeding was diagnosed on clinical grounds, and some of the patients underwent endoscopy. The lesions could not be called true stress ulcers, as many esophageal and duodenal lesions were seen in the untreated group. MacDougall et al compared antacids and cimetidine as prophylaxis for stress bleeding in patients with fulminant hepatic failure. Cimetidine appeared to have a better prophylactic effect against stress bleeding than antacids or no treatment. Antacids were given at four hour intervals. Prophylaxis failure was defined as the aspiration of fresh blood. Bleeding rates were 4%, 23% and 54% respectively. Gastric pH was not consistently controlled in this study.

Recently, an endoscopic study comparing cimetidine with placebo in patients in an intensive care unit has been reported (56). Though relatively small groups of patients were investigated, the results of the endoscopic findings are very suggestive of a beneficial effect of cimetidine in prophylaxis of stress ulcer and stress bleeding.

Prevention of acute gastrointestinal complications after severe head injury was studied by Halloran et al (57). Five of 26 cimetidine-treated patients (19%) and 18 of 24 placebo-treated

patients (75%) had hemorrhages, which were based on clinical findings and guaiac tests. They did not observe a difference in the incidence of mucosal lesions between the groups as far as endoscopies were performed.

Prevention of gastroduodenal lesions following thermal injury has been reported by McElwee and others (58), in which the efficacy of cimetidine (13 patients) was compared to that of antacids (14 patients). Duodenal disease was nearly eliminated and severity of gastric disease was markedly reduced when compared to that of untreated historical controls, in both treatment groups. Not all patients underwent endoscopy.

The role of ranitidine, a new H_2-antagonist, in the prophylaxis of true stress ulcers seems as controversial as that of cimetidine (13).

9.3.10 Histamine-2-antagonist plus antacid.

The use of cimetidine as the sole prophylactic agent remains controversial, although cimetidine may be effective in selected groups of patients with head injury (prevention of Cushing's ulcer) or thermal injury (prevention of Curling's ulcer), or severe liver disease (31). No well-done study has evaluated the relative efficacy of titrated-dose antacid versus the combination of cimetidine and antacid (59). The addition of cimetidine in patients on high-dose antacid and experiencing acid-base disturbances secondary to copious gastric secretions may be useful (59). On the other hand, if high dosages of antacids are not sufficient in maintaining pH above a certain value, the addition of cimetidine is not likely to raise intragastric pH, as was shown by Martin et al (50,51) and Stothert et al (52) in severely stressed patients.

9.3.11 Sucralfate.

Sucralfate is a complex of sulfated sucrose and aluminium

hydroxide, that is only minimally absorbed from the gastric tract. It produces an adherent complex with proteinaceous exsudate of ulcers. In vitro, a sucralfate-albumin film is a barrier to the diffusion of hydrogen ion. Sucralfate binds bile salts and inhibits pepsin.

Sucralfate was found to be as effective as antacid in the prevention of stress bleeding in a study of Borrero et al (60). Antacids were titrated hourly to maintain gastric pH above 3.5. Gastroccult^{R} paper tests were used for detecting occult blood. There was no gross bleeding in any of the patients. Three of the 48 sucralfate-treated patients and 2 of the 52 antacid-treated patients had positive Gastroccult^{R} tests, i.e. 6% and 4% respectively. Its advantage over antacids is a reduction in nursing time by simpler administration and testing gastric pH seems unnecessary. Only "chemical bleedings" were seen in this trial. Endoscoppy was performed in only two patients who bled and minor degrees of stress ulceration were seen. To which treatment group these two patients belonged was not mentioned.

Recently (61) cytoprotective properties mediated by stimulation of endogenous prostaglandins have been ascribed to sucralfate.

9.3.12 Pirenzepine.

Pirenzepine is a selective anticholinergic agent with affinity for specific muscarinic receptor sites. It inhibits in this way gastric secretion. Gastric mucosal microcirculation is maintained at an heightened level in the restraint ulcer model in rats (62). Pirenzepine probably has a place in prophylaxis of Cushing's ulcer (63) and the incidence of stress lesions and bleeding was reduced in a small group of intensive care patients given pirenzepine (64). Stress ulcer and stress bleeding prophylaxis with pirenzepine in critically ill patients needs further investigation. Cytoprotective effects have been ascribed to pirenzepine (65). This form of cytoprotection is probably not mediated by prostaglandins.

9.3.13 Pirenzepine plus ranitidine.

In a recent study (66) critically ill patients received either pirenzepine or ranitidine. Intragastric pH could be maintained above 4 in only 6% and 22%, even at maximum dosages of pirenzepine (90 mg/day) and ranitidine (600 mg/day), respectively. Those patients in whom pH could not be maintained above 4, subsequently received pirenzepine plus ranitidine. In 11 of 15 patients (73%) pH correction could be achieved in this way. No clinical bleeding was seen. This study shows poor effects of pirenzepine as well as of ranitidine. Combination therapy provided better, though suboptimal, effects on intragastric pH.

9.3.14 Prostaglandins.

Prostaglandins are theoretically attractive for stress ulcer and stress bleeding prophylaxis because of their cytoprotective effects. Our trial could not show a clear-cut prophylactic effect using dosages at which cytoprotection is gained, without an effect on gastric acid secretion (see chapter 5 of this thesis).

Recently Skillman et al (67) compared the prophylactic effect of 15(R)-15-methyl PGE_2 with that of antacids, using Hemoccult as a slide test for occult blood in gastric aspirates. Three of 22 patients in the antacid group bled (14%) and 12 of 24 patients in the prostaglandin group bled (50%). As far as from this report can be gathered, only "chemical bleedings" were diagnosed. Endoscopies are not mentioned. Gastric pH was mostly above 3.0 in the prostaglandin-treated patients with hemorrhage, whereas in the antacid-treated patients with bleeding pH was between 7 and 8 in two patients and between 4 and 6 in a third patient. The authors suggest prostaglandin-analogues that do not require conversion from an inactive to an active form by acid may possibly give better results, as 15(R)-15-methyl PGE_2 is epimerized in acid medium (pH below 3.0) to 15(S)-15-methyl PGE_2, which has antisecretory properties.

To day, despite numerous reports of cytoprotective treatment in animals, there are probably very few clinical applications for prostaglandins in the prevention of stress ulcer.

9.3.15 Nutrition.

Parenteral nutrition, especially hyperalimentation, was found to augment gastric mucosal regeneration after surgery, allowing for more physiological secretory patterns and the maintenance of the protective gastric mucosal mechanisms (68), as evidenced by reduced exfoliation of cells and reduced incidence of bleeding.

Preliminary data indicate enteral nutrition is important in the prophylaxis of stress bleeding (69) and may be better than antacids or cimetidine.

Commercial milk preparations contain substantial amounts of prostaglandins and milk has been shown to be effective in the prevention of stress-induced gastric ulceration in the rat (70). Therefore, milk may be prefered when enteral nutrition will be administered.

9.4 CONCLUSIONS

The use of antacids, cimetidine and many other drugs in critically ill patients to prevent stress bleeding has no solid scientific foundation, as most studies on this subject used peroxidase tests (33,43,44,60,67), which are not reliable for detecting blood in gastric juice.

If only clinically manifest bleedings are taken into account, published studies cannot be used to recommend antacids or cimetidine. Hastings et al (43) studying 100 patients found only one with hemorrhage which could be diagnosed on clinical grounds. This patient was in the antacid group. Fiddian-Green et al (40) saw massive bleeding in seven out of 103 patients in an intensive care unit. These seven patients were receiving antacids. Pinilla et al (46) did not see

a significant difference in the number of patients with visible bleeding comparing antacids with no specific prophylaxis. Cimetidine seemed to prevent bleeding in renal transplant patients in a clinical trial by Jones et al (54), but these patients were often found to have esophageal and duodenal lesions. In hepatic failure cimetidine seems to be better than antacids or no treatment, but in the study of MacDougall et al (55) there was no good control of gastric pH with antacids. The studies of Jones et al (54) and MacDougall et al (55) were non-randomized trials. Priebe et al (33) found clinical bleeding in the cimetidine group and not in the antacid group.

On the basis of endoscopic criteria four studies merit special notice. First, Spilker et al (36) found evidence of stress ulcer prophylaxis in secretin-treated patients. The use of this hormone in intensive care patients needs further investigation. In another study (38) cholestyramine gave better protection against stress lesions than antacids, as was shown by endoscopy. No stress lesions were seen in patients treated with both cholestyramine and antacids. However, this treatment has not gained clinical application. Peura and Johnson (56) found beneficial effects of cimetidine regarding gastroduodenal mucosal lesions and bleeding severity in small groups of patients. Mattes et al (64) saw a reduction in the incidence of stress lesions and stress bleeding in pirenzepine-treated intensive care patients, which is a promising feature. Expented clinical trials are indicated as pirenzepine has a rational for use in stress conditions, as it probably preserves gastric microcirculation.

^{51}Cr-labeling of erythrocytes enables reliable measurement of blood in gastric juice. Van den Berg and van Blankenstein (48) used this quantitative determination as a criterion of hemorrhage in their stress bleeding prophylaxis study. They found more cases of bleeding in the cimetidine group than in the placebo group. Chapter 5 of this thesis describes a trial with PGE_2, and no clear-cut effect on the prevention of stress bleeding could be shown, using the ^{51}Cr-method as a criterion of bleeding.

In summary, we do not know which pharmacologic agent should be given in the prevention of stress ulcers and stress bleeding.

Reactivation of a chronic peptic ulcer can be prevented by antacids or H_2-antagonists, and either of these should probably be given to patients with a history of peptic ulcer admitted to the intensive care. Curling's ulcer and Cushing's ulcer also can be prevented by antacids or H_2-antagonists. Prophylaxis of stress ulcers and stress bleeding consists of vigorous treatment of risk factors, giving optimal parenteral nutrition, and starting enteral feeding as soon as gastric decompression is no longer needed.

9.5 REFERENCES

1. Ritchie WP. Stress ulcer and erosive gastritis. World J Surg 1981;5:135-137.
2. Moody FG, Cheung LY. Stress ulcers: their pathogenesis, diagnosis, and treatment. Surg Clin North Am 1976;56:1469-1478.
3. Cheung LY. Treatment of established stress ulcer disease. World J Surg 1981;5:235-240.
4. Marrone GC, Silen W. Pathogenesis, diagnosis and treatment of acute gastric mucosal lesions. Clin Gastroenterol 1984;13:635-650.
5. Ponsky JL, Hoffman M, Swayngim DS. Saline irrigation in gastric hemorrhage: the effect of temperature. J Surg Res 1980;28:204-205.
6. Lucas CE, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt AJ. Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 1971;102:266-273.
7. Kiselow MC, Wagner M. Intragastric instillation of levarterenol: a method for control of upper gastrointestinal tract hemorrhage. Arch Surg 1973;107:387-389.
8. Gilbert DA, Saunders DR. Iced saline lavage does not slow bleeding from experimental canine gastric ulcers. Dig Dis Sci 1981;26:1065-1068.
9. Simonian SJ, Curtis LE. Treatment of hemorrhagic gastritis by antacid. Ann Surg 1976;184:429-434.
10. Robert A, Kauffman GL. Stress ulcers. In: Gastrointestinal Disease. Sleisenger MH, Fordtran JS (eds.). Saunders, Philadelphia 1983,pp.612-625.
11. Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation: a possible contributor to prolonged gastroduodenal mucosal hemorrhage. Gastroenterology 1978;74:38-43.
12. Freston JW. Cimetidine: developments, pharmacology, and efficacy. Ann Int Med 1982;97:573-580.
13. Zeldis JB, Friedman LS, Isselbacher KJ. Ranitidine: a new

H_2-receptor antagonist. N Engl J Med 1983;309:1368-1373.

14. Pickard RG, Sanderson I, South M, Kirkham JS, Northfield TC. Controlled trial of cimetidine in acute upper gastrointestinal bleeding. Br Med J 1979;1:661-662.
15. Dawson J and Cockel R. Ranitidine in acute upper gastrointestinal haemorrhage. Br Med J 1982;2:476-477.
16. Welch R, Douglas A, Cohen S, Lorber S, Melnyk C, Bliss C, Zuckerman G, Crossley R, Christiansen P, Kern F. Effect of cimetidine on upper gastrointestinal hemorrhage. Gastroenterology 1981;80:1313 (abstract).
17. Terés J, Bordas JM, Rimola A, Bru C, Rodes J. Cimetidine in acute gastric mucosal bleeding: results of a double-blind randomized trial. Dig Dis Sci 1980;25:92-96.
18. Barer D, Olgilvie A, Henry D, Dronfield M, Coggon D, French S, Ellis S, Atkinson M, Langman M. Cimetidine and tranexamic acid in the treatment of acute upper gastrointestinal tract bleeding. N Engl J Med 1983;308:1571-1575.
19. Kayasseh L, Keller U, Gyr K, Stalder GA, Wall M. Somatostatin and cimetidine in peptic-ulcer haemorrhage. A randomized controlled trial. Lancet 1980;I:844-846.
20. Limberg B, Kommerell B. Somatostatin for cimetidine-resistant gastroduodenal hemorrhage. (Letter to the Editor) Lancet 1980; II:916-917.
21. Somerville HW, Davies JG, Hawkey CJ, Henry DA, Hine KR, Langman MJS. Somatostatin in treatment of haematemesis and melaena. Lancet 1985;I:130-132.
22. Groeger JS, Dazza SJ, Carlon GC, Turnbull AD, Pierri MK, Howland WS. Prostaglandin therapy in a case of refractory stress ulcer bleeding. Crit Care Med 1982;10:486-487.
23. Weiss JB, Peskin GW, Isenberg JI. Treatment of hemorrhagic gastritis with 15(R)-15 methyl prostaglandin E_2: report of a case. Gastroenterology 1982,82:558-560.
24. Athanasoulis CA, Baum S, Waltman AC, Ring EJ, Imbembo A, Vander Salm TJ. Control of acute gastric mucosal hemorrhage. Intra-arterial infusion of posterior pituitary extract. N Engl J

Med 1974;290:597-603.

25. Peterson WL. Gastrointestinal bleeding. In: Gastrointestinal Disease. Sleisenger MH, Fordtran JS (eds.). Saunders, Philadelphia: 1983:pp.177-207.
26. Lieberman DA, Keller FS, Katon RM, Rosch J. Arterial embolization for massive upper gastrointestinal tract bleeding in poor surgical candidates. Gastroenterology 1984;86:876-885.
27. Geller SC, Athanasoulis CA. Vascular procedures: the intestinal tract. Clin Gastroenterol 1985;14:295-312.
28. Richardson JD, Aust JB. Gastric devascularization: a useful salvage procedure for massive hemorrhagic gastritis. Ann Surg 1977;185:649-655.
29. Kivilaakso E, Silen W. Pathogenesis of experimental gastric-mucosal injury. N Engl J Med 1979;301:364-369.
30. Kim YS, Kerr RJ, Lipkin M. Cell proliferation during the development of stress erosions in the mouse stomach. Nature 1967;215:1180-1181.
31. Priebe HJ and Skillman JJ. Methods of prophylaxis in stress ulcer disease. World J Surg 1981;5:223-233.
32. Takeuchi K, Johnson LR. Pentagastrin protects against stress ulceration in rats. Gastroenterology 1979;76:327-334.
33. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding: a randomized trial in 75 critically ill patients. N Engl J Med 1980;302:426-430.
34. Rees WDW and Turnberg LA. Biochemical aspects of gastric secretion. Clin Gastroenterol 1981;10:521-554.
35. Lankisch PG. Trophic effects of gastrointestinal hormones. Clin Gastroenterol 1980;9:773-784.
36. Spilker G, Theisinger W, Bader M, Seidel G. Sécrétine retard pour la prophylaxie des ulcères de stress en chirurgie. Nouv Press Med 1982;11:267-269.
37. Hamza KN, DenBesten L. Bile salts producing stress ulcers during experimental shock. Surgery 1972;71:161-167.
38. Schumpelick V, Grossner D. Erste klinische Erfahrungen mit

Cholestyramin zur Stressulkus-Prophylaxe. Münch Med Wschr 1977;41:1329-1332.

39. Ritchie WP, Shearburn EW. Influence of isoproterenol and cholestyramine on acute gastric mucosal ulcerogenesis. Gastroenterology 1977;73:62-65.
40. Fiddian-Green RG, McCough E, Pittenger G, Rothman E. Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. Gastroenterology 1983;85:613-620.
41. Menguy R. The role of gastric mucosal energy metabolism in the etiology of stress ulceration. World J Surg 1981;5:175-180.
42. Ritchie WP. Acute gastric mucosal damage induced by bile salts, acid, and ischemia. Gastroenterology 1975;68:699-707.
43. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled, randomized trial in 100 critically ill patients. N Engl J Med 1978;298:1041-1045.
44. Zinner MJ, Zuidema GD, Smith PL, Mignosa M. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet 1981;153:214-220.
45. Khan F, Parekh A, Patel S, Chitkara R, Rehman M, Goyal R. Results of gastric neutralization with hourly antacids and cimetidine in 320 intubated patients with respiratory failure. Chest 1981;79:409-412.
46. Pinilla JC, Oleniuk FH, Reed D, Malik B, Laverty WH. Does antacid prophylaxis prevent upper gastrointestinal bleeding in critically ill patients ? Crit Care Med 1985;13:646-650.
47. Du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1982;I:242-245.
48. Van den Berg B, van Blankenstein M. Prevention of stress-induced upper gastrointestinal bleeding by cimetidine in patients on assisted ventilation. Digestion 1985;31:1-8.
49. Luk GD, Summer WR, Messersmith JF. Cimetidine and antacid in

prophylaxis of acute gastrointestinal bleeding: a randomized, double-blind, controlled study. Gastroenterology 1982;82:1121 (Abstract).

50. Martin LF, Staloch DK, Simonowitz DA, Dellinger EP, Max MH. Failure of cimetidine prophylaxis in the critically ill. Arch Surg 1979;114:492-496.

51. Martin LF, Max MH, Polk HC. Failure of gastric pH control by antacids or cimetidine in the critically ill: a valid sign of sepsis. Surgery 1980;88:59-68.

52. Stothert JC, Simonowitz DA, Dellinger EP, Farley M, Edwards WA, Blair AD, Cutler R, Carrico J. Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. Ann Surg 1980;192:169-174.

53. McGuigan JE. A consideration of the adverse effects of cimetidine. Gastroenterology 1981;80:181-192.

54. Jones RH, Rudge CJ, Bewick M, Parsons V, Weston MJ. Cimetidine: Prophylaxis against upper gastrointestinal haemorrhage after renal transplantation. Br Med J 1978;1:398-400.

55. MacDougall BRD, Bailey RJ, Williams R. H_2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure: two controlled trials. Lancet 1977;I:617-619.

56. Peura DA, Johnson LF. Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an intensive care unit. Ann Int Med 1985;103:173-177.

57. Halloran LG, Zfass AM, Gayle WE, Wheeler CB, Miller JD. Prevention of acute gastrointestinal complications after severe head injury: a controlled trial of cimetidine prophylaxis. Am J Surg 1980;139:44-48.

58. McElwee HP, Sirinek KR, Levine BA. Cimetidine affords protection equal to antacids in prevention of stress ulceration following thermal injury. Surgery 1979;86:620-626.

59. Greene WL, Bollinger RR. Cimetidine for stress-ulcer prophylaxis. Crit Care Med 1984;12:571-575.

60. Borrero E, Margolis IB, Bank S, Shulman N, Chardavoyne R. Antacid

versus sucralfate in preventing acute gastrointestinal bleeding. Am J Surg 1984;148:809-812.

61. Ligumsky M, Karmeli F, Rachmilewitz D. Sucralfate stimulation of gastric PGE_2 synthesis: possible mechanism to explain its effective cytoprotective properties. Gastroenterology 1984;86:1164 (Abstract).

62. Oda M, Nakamura N, Yonei Y, Tsukada N, Komatsu H, Kaneko K, Akaiwa Y, Ichikawa E, Okazaki I, Tsuchiya M. Effects of the muscarinic receptor antagonist pirenzepine on the gastric mucosal microcirculation: its possible action sites in the stomach. Symposium Pirenzepine: new aspects in research and therapy. Proceedings: Bettarello (ed.). Excerpta Medica, Amsterdam 1985:pp.19-40.

63. Tritthart H, Schröttner O, Reschauer R. Stressinduzierte gastrointestinale Blutungen beim schwerem Schädelhirntrauma. Hefte zur Unfallheilkunde 1983;156:304-308.

64. Mattes P, Belohlavek D, Peros G, Kilian HG, Herfarth CH. Kontrollierte, prospektieve Studie über die Wirkung von Pirenzepin beim Stress-Ulkus. In: Die Behandlung des Ulcus pepticum mit Pirenzepin. Blum AL, Hammer R (eds.). Demeter Verlag Gräfelfing 1978:pp.239-242.

65. Del Soldato P, Daniotti S, Foschi D, Toti G, Rovati V. Curative and preventive cytoprotection of PGE_2, pirenzepine and ranitidine in rat ulcers. Drugs Exp Clin Res 1983;9:243-247.

66. More DG, Raper RF, Watson CJ, Shenfield GM. Combination therapy with ranitidine and pirenzepine for control of intragastric pH in the critically ill. Crit Care Med 1985;13:651-655.

67. Skillman JJ, Lisbon A, Long PC, Silen W. 15(R)-15-methyl prostaglandin E_2 does not prevent gastrointestinal bleeding in seriously ill patients. Am J Surg 1984;147:451-455.

68. Byrd HS, Lazarus HM, Torma MJ. Effects of parenteral alimentation on postoperative gastric function. Am J Surg 1975;130:688-693.

69. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med 1983;11:13-16.

70. Materia A, Joffe BM, Money SR, Rossi P, De Marco M, Basso N. Prostaglandins in commercial milk preparations. Their effect in the prevention of stress-induced gastric ulcer. Arch Surg 1984;119:290-292.

Chapter 10.

Discussion and conclusion

The stress ulcer syndrome is described in this thesis. This syndrome is seen in patients admitted to intensive care departments or being treated in field hospitals, in disaster areas, or battle fields. Acute mucosal lesions associated with burns (Curling's ulcers) and central nervous system disorders (Cushing's ulcers) appear to have a different pathophysiology and a different pathology to the real stress ulcers.
Peptic ulcers and gastric lesions following use of non-steroidal anti-inflammatory agents also differ from stress ulcers.

In chapter 2 the pathology of the stress ulcer is described. The true stress ulcer is usually found in the proximal part of the stomach, although it may rarely be seen in the distal part of the stomach or in the small or large bowel. Erosions are also included in the term stress ulcer. Histologically these are superficial defects which seldom reach the muscularis propria.

The literature on the pathophysiology of stress ulcers is reviewed in chapter 3. Until recently, the mucous layer of the gastric mucosa has been considered to be of major importance. The discovery that the stomach has the capacity to produce bicarbonate, lead to the concept of a mucous-bicarbonate barrier with a demonstrable pH gradient over the mucous layer. As prostaglandins increase both bicarbonate secretion and mucus production, it is probable that prostaglandins play an important role in the maintainance of the gastric mucosal barrier.

Many authors point out the importance of gastric acid for the development of stress ulcers. Gastric acid appears, however, to act more in a permissive than causal fashion. The central feature in the development of stress ulcers is systemic hypotension, which leads to mucosal ischemia. Ischemia in turn gives rise to decreased energy production within the cell and subsequently cell necrosis. Studies described by Menguy support this theory of the development of stress ulcers, and provide an explanation for the sparing of the gastric antrum.

Apart from hypotension or shock, additional risk factors are discussed in this chapter. These include renal insufficiency, jaundice, sepsis and peritonitis, respiratory insufficiency, major surgery and multiple trauma. The effects of bile and of corticosteroids on the stomach are also briefly reviewed.

The gastrointestinal effects of prostaglandins and cytoprotection are considered in chapter 4. Oral administration of the natural occurring prostaglandins appears to have little or no effects on gastric acid secretion. Administration of higher doses parenterally does decrease gastric acid secretion. Synthetic prostaglandins are capable of decreasing gastric acid secretion when given orally. This inhibition is mediated by direct effects of the prostaglandins on the parietal cells.

Stimulation of the vagus nerve and administration of gastrin results in an increased concentration of prostaglandins in the lumen of the stomach. Prostaglandins appear to have a modulating effect on gastric acid secretion, similar to their modulating effects on renal blood flow or in inflammation.

Cytoprotection was originally defined by Robert as the capacity of prostaglandins to protect the gastrointestinal epithelium against physical or chemical damage, which would otherwise lead to necrosis. This effect is not dependent on inhibition of gastric acid secretion. Subsequent experiments lead Robert to change this definition, as he found that the superficial epithelium was not protected, but only the underlying tissues. This suggests that the protective role of mucous and or other surface factors is limited, and that the cytoprotection

of prostaglandins is mediated by factors in the submucosa - either on a cellular level or via effects on the microcirculation. It remains an amazing observation that a small amount of prostaglandin, administered a few minutes before treatment, is capable of protecting the mucosa against such agressive agents as absolute alcohol or boiling water. Later on, it was shown that absolute alcohol did not affect the mucosal proliferative zone after pretreatment with prostaglandins. This zone produces within a few hours a new, normally functioning surface epithelial layer.

Adaptive cytoprotection is an interesting phenomenon which occurs after application of mildly irritating substances to the mucosa, following which the mucosa becomes resistant against necrotizing agents. This effect is a rapid one, which has been shown to be mediated by prostaglandins.

In animal experiments prostaglandins can prevent the development of various forms of stress ulcer. In humans the natural prostaglandin E_2 has been shown to prevent blood loss following aspirin or indomethacin administration. Later endoscopic studies showed that the synthetic prostaglandin E_2 prevented the development of gastric or duodenal lesions following aspirin ingestion. The healing of an existing peptic ulcer in the stomach or duodenum is facilitated by prostaglandins. Prolonged treatment with prostaglandins causes an increase in the thickness of the gastric mucosa, due to a decreased exfoliation of mucosal cells. All these findings suggested that prostaglandins might be useful in the prevention of stress ulcers in humans.

In chapter 5 a clinical study is described which was designed to examine the possible beneficial clinical effects of prostaglandins in intensive care patients. In general, intensive care patients either receive no specific prophylaxis for stress ulcers, or are given either a histamine-2-antagonist (cimetidine or ranitidine), antacids or the combination of a histamine-2-antagonist and antacids. The frequency of stress bleeding during the use of cimetidine has been found to be approximately the same as during the use of placebo, as e.g. shown in the studies of Hastings et al, Priebe et al and Zinner et al. This drug is easy to administer, but is of little practical benefit in

stress ulcers. Administration of antacids without frequent examination of the pH of the stomach also appears to be of little benefit, while hourly titration of the gastric contents with antacids to a pH greater than 3.5 is very difficult to realize in practice. Antacids have many side-effects and they often cannot be administered because gastric suction is necessary.

Prostaglandins are easy to administer and do not have side-effects when given in low dosage. To determine whether prostaglandins were indeed of practical benefit in the prevention of stress ulcers and stress bleed, a prospective, double-blind, placebo-controlled study was started. Prostaglandin E_2 (PGE_2) which occurs naturally in the stomach, was chosen. The dosage was selected to be cytoprotective without reducing gastric acid secretion. For an acceptable evaluation a minimum of 3 observation days was considered necessary, while the study continued maximally for 7 days. Ninety patients with two or more risk factors (major operations, multiple trauma, respiratory insufficiency, renal insufficiency, jaundice, hypotension, peritonitis or sepsis) were randomized for treatment with either PGE_2 0.5 mg or placebo given every 4 hours intragastrically. Blood loss in the gastric aspirates was measured quantitatively by means of the ^{51}Cr labelled erythrocyte method. This method was chosen because we had doubts about the reliability of the qualitative tests for blood based on peroxidase reactions. In previous studies on the prophylaxis of stress bleeding in our hospital, we had found that patients fell into two groups: patients with less than 5 ml of blood loss per 24 hours and those with more than 15 ml of blood loss per 24 hours. We therefore chose a blood loss of 15 ml or more per 24 hours as evidence of mucosal damage and this was chosen as the lower limit for the diagnosis of hemorrhage. To compare our results with those of the literature, the gastric aspirates were also examined for the presence of blood by means of a peroxidase reaction, namely the orthotolidine test. The pH of the gastric aspirates were measured and samples were kept at -20°C for determination of the DNA concentration. Of the patients admitted to the study, 33 were not evaluable. The first 3 days were often not completed due to transferral to another ward or

due to death, or because the gastric tube was removed. Oral feeding was not withheld from the patients because of the trial only. Of the 57 patients who were evaluable, 29 received PGE_2 and 28 placebo. Hemorrhage occurred in 9 of the PGE_2 group (31%) and in 13 of the placebo group (46%). This difference is not statistically significant. In all instances of hemorrhage where gastroscopy and/or postmortem examination was performed, lesions were found, mainly in the stomach, but also in esophagus. This provides evidence for the reliability of the ^{51}Cr method in demonstrating upper gastrointestinal tract hemorrhage. However we should point out that we cannot be absolutely certain at all if blood in gastric aspirates is due to stress bleeding, as lesions were found in the esophagus and duodenum.

The patients with stress bleeding had on average more risk factors than patients without bleeding, so that the number of risk factors does appear to be of prognostic importance. As could be expected, the number of risk factors also correlated with the mortality. Upper gastrointestinal bleeding was, however, rarely an important factor in mortality, a finding which diminishes the importance of stress bleeding prophylaxis.

The question is why PGE_2 in this dosage and administered in this fashion does not prevent stress bleeding. The dosage was probably adequate, as similar dosages promote healing of duodenal ulcers and prevent blood loss following aspirin administration. Higher dosages would have led to diarrhea and abdominal cramps. The administration by means of dilution of an ampula of PGE_2 in 20 ml of water and subsequent flushing of the nasogastric tube with 20 ml of water guaranteed that the drug was administered into the stomach. However the duration of exposition of the stomach and the portion of the stomach exposed to the PGE_2 is not known. It is possible that mainly the antrum and the posterior wall of the stomach were reached, and that the body and fundus of the stomach were not exposed sufficiently. Although there was no statistical significant difference in bleeding frequency, there was a difference. Theoretically, investigation of a larger number of patients could lead to a statistical significant difference in favour of PGE_2. Continuation of the study however did

not seem indicated as we were attempting to obtain a drug which effects were not only statistically siginificant but also clinically significant.

In chapter 6 the orthotolidine test, which is based on a peroxidase reaction, was found to be unsuitable for the determination or the detection of blood in gastric aspirates. In view of these findings the results of clinical studies on stress bleeding prophylaxis, which had been based on a peroxidase test, must be considered to be of doubtful significance.

In chapter 7 a new method for determining blood in gastric aspirates is described, which is based on the determination of the concentration of haem in gastric juice. Treatment of haem by heating in the presence of a reducing acid solution results in the formation of fluorescing protoporphyrin. This method is, in contrast to the peroxidase test, reliable and quantitative and does not have the disadvantages of the ^{51}Cr-method. This method is probably a suitable tool for use in future studies of stress bleeding.

In chapter 8 determination of DNA in gastric juice is described. No correlation could be found between DNA contents in gastric aspirates and PGE_2 administration or physiological stress.

In chapter 9 the treatment and prevention of stress bleeding, as described in the literature, is reviewed. Drug treatment is of little value once bleeding has started. Antacid administration is of value with regard to preventing clot lysis, and vasopressin may have a beneficial effect if it is given selectively intra-arterially. The effects of transcatheter embolization need to be studied. Operative treatment is associated with a high mortality.

As results of treating bleeding stress ulcers are poor, the rational approach would be to try to prevent ulcers. Some preventive effect has been shown with varying therapies, without widespread clinical application following. It is an intriguing finding that the powerful gastric acid secretion stimulator, gastrin, can prevent the development of stress ulcers in rats. Histamine has also been shown to have this effect. In this chapter the clinical studies on stress bleeding prophylaxis using antacids or cimetidine are discussed. The

weak points in these studies are noted: the problems associated with demonstrating blood by means of peroxidase reactions on the one hand, and the insufficient increase of gastric pH by means of cimetidine on the other hand. Pirenzepine is theoretically a better agent for stress ulcer prophylaxis, as it has an effect on the mucosal microcirculation. Further clinical studies using this drug need to be performed. At present we do not know which treatment is indicated for the prevention of stress ulcers. Antacids and H_2-antagonists have been shown to be effective in preventing Cushing's ulcer and Curling's ulcer, and patients admitted to an intensive care with a history of peptic ulcer would probably also benefit from these drugs. Prevention of stress ulcers and stress bleeds depends mainly on the active treatment of the risk factors and the administration of optimal parenteral nutrition and starting enteral feeding as soon as gastric suction is no longer required.

Samenvatting

In dit proefschrift is het stress ulcus syndroom beschreven. Dit wordt gezien bij patiënten op afdelingen voor intensive care en in de veldhospitalen bij oorlogs- en rampgebieden. Acute slijmvlieslaesies bij brandwonden (Curling's ulcers) en bij aandoeningen van het centrale zenuwstelsel (Cushing's ulcers) lijken een aparte pathofysiologie te hebben en een van het echte stress ulcus onderscheiden pathologie. Evenzo het ulcus pepticum en de maaglaesies bij gebruik van niet-steroïde anti-inflammatoire middelen.

In hoofdstuk 2 wordt de pathologie van het stress ulcus besproken. Het stress ulcus in eigenlijke zin is meestal gelocaliseerd in het proximale deel van de maag; zelden in het distale deel van de maag en in de dunne en dikke darm. Tot het begrip stress ulcus worden ook erosies gerekend, en het gaat histologisch om oppervlakkige laesies die zelden de muscularis propria bereiken.

In hoofdstuk 3 wordt de pathofysiologie beschreven aan de hand van literatuurgegevens. Het belang van de mucuslaag op het maagslijmvlies lijkt tot voor kort teveel te zijn benadrukt. De recente ontdekking van het vermogen van de maag om bicarbonaat te produceren, leidde tot het concept van de mucus-bicarbonaatbarrière, met een aangetoonde pH-gradiënt over de mucuslaag. Daar prostaglandines zowel de bicarbonaatsecretie als de mucusproductie kunnen vergroten, lijken zij bij de maagslijmvliesbarrière van grote betekenis.

De rol van het maagzuur bij het ontstaan van stress ulcera wordt door velen sterk benadrukt. Het maagzuur lijkt echter in dit opzicht meer "permissive" dan oorzakelijk.

Centraal bij het ontstaan van het stress ulcus is de systemische hypotensie, die tot mucosale ischaemie van de maag leidt. Ischaemie geeft intracellulair energietekort en vervolgens celnecrose. De studies van Menguy geven een goede verklaring voor het ontstaan van

stress ulcera op deze wijze, en maken ook het sparen van het antrum van de maag begrijpelijk.

Behalve hypotensie, c.q. shock, worden in dit hoofdstuk ook de andere risicofactoren besproken: nierinsufficiëntie, geelzucht, sepsis en peritonitis, respiratoire insufficiëntie, grote operaties en multipele traumata. In het kort komen de effecten op de maag van gal en van corticosteroïden aan de orde.

In hoofdstuk 4 worden de gastro-intestinale effecten van prostaglandines en de cytoprotectie besproken. De natuurlijk voorkomende prostaglandines hebben bij orale toediening geen of heel weinig remmende werking op de maagzuursecretie; bij parenterale toediening, in hoge dosering, wel. Synthetische prostaglandines kunnen bij toediening per os wel een goede zuursecretieremming geven. De zuursecretie wordt geïnhibeerd door een direct effect op de pariëtale cel.

Na vagusstimulatie en na toediening van gastrine worden prostaglandines in verhoogde concentratie in het maaglumen gevonden. Prostaglandines lijken een modulerende werking te hebben op de maagzuursecretie, zoals ze ook modulerend werken bij de nierdoorbloeding en bij ontstekingsprocessen.

Cytoprotectie werd oorspronkelijk door A. Robert gedefinieerd als het vermogen van prostaglandines het gastro-intestinale epitheel te beschermen tegen agentia, die anders necrose zouden geven. Dit effect is niet afhankelijk van maagzuursecretieremming. Latere onderzoekingen brachten Robert ertoe bovenstaande definitie te wijzigen, daar hij vaststelde dat het oppervlakte-epitheel niet wordt beschermd, maar wel het weefsel daaronder. Dit wijst erop dat de beschermende rol van mucus en/of andere oppervlaktefactoren beperkt is, en dat prostaglandines cytoprotectief werken via factoren in de submucosa: dus op cellulair niveau of microcirculatoir. Het blijft een wonderlijke gebeurtenis dat een geringe hoeveelheid prostaglandine, enige minuten tevoren toegediend, het slijmvlies beschermt tegen zulke agressieve agentia als absolute alcohol en kokend water. Later werd aangetoond dat absolute alcohol de mucosale proliferatieve zone niet aantast na voorbehandeling met prostaglandines. Deze zone zorgt dan

binnen enige uren voor een nieuwe, normaal functionerende oppervlakte-epitheellaag.

Adaptieve cytoprotectie is een interessant fenomeen, dat optreedt na toediening aan het slijmvlies van licht irriterende stoffen, waardoor het slijmvlies bestand is tegen necrotiserende agentia. Dit effect treedt ook snel in en het is aangetoond dat het door prostaglandines wordt gemedieerd.

Dierproeven lieten zien dat prostaglandines diverse vormen van stress ulcera kunnen voorkomen. Bij de mens bleek het natuurlijke prostaglandine E_2 bloedverlies t.g.v. aspirine en indometacine te voorkomen. Later bleek uit endoscopische studies dat synthetische prostaglandine E_2 ook werkelijk laesies in maag en duodenum t.g.v. aspirine voorkomt. Ook de genezing van een bestaand ulcus pepticum in maag of duodenum wordt bevorderd door prostaglandines. Langere-termijnbehandeling met prostaglandines geeft toename van de dikte van de maagmucosa door verminderde exfoliatie van mucuscellen.

Alle bovenstaande gegevens wijzen op een mogelijk preventief effect van prostaglandine tegen stress ulcus bij de mens.

In hoofdstuk 5 wordt het eigen klinisch onderzoek beschreven dat erop gericht was bovenstaand gunstig klinisch effect bij intensive care patiënten na te gaan. In de praktijk wordt tot nog toe aan intensive care patiënten òf geen specifieke op stress ulcus prophylaxe gerichte medicatie gegeven òf men geeft een histamine-2-antagonist (cimetidine of ranitidine), òf alleen antacida, danwel de combinatie van histamine-2-antagonist en antacida.

De frequentie van stress bloeding is bij gebruik van cimetidine ongeveer in dezelfde orde van grootte als bij placebo, zoals blijkt uit de studies van Hastings et al, Priebe et al en Zinner et al. De toediening van dit middel is wel eenvoudig, maar de toepassing ervan als prophylacticum heeft geen goede wetenschappelijke basis. Antacidatoediening zonder frequente controle van de pH van het maagsap lijkt weinig zinvol, terwijl elk uur het maagsap titreren met antacida tot een pH $\geqslant 3{,}5$ in de praktijk vrijwel onuitvoerbaar is. Antacida hebben veel bijwerkingen en vaak is toepassing niet eens mogelijk omdat de maag moet worden gedecomprimeerd.

Prostaglandines zijn gemakkelijk toe te dienen en hebben bij lage dosering geen bijwerkingen. Om na te gaan of prostaglandine ook van praktisch nut is in de preventie van stress ulcus en stress bloeding, werd een prospectief, dubbel-blind, placebo-gecontroleerd onderzoek opgezet. Gekozen werd voor prostaglandine E_2 (PGE_2), dat natuurlijk in de maag voorkomt en daarom geen schadelijke bijwerkingen kan hebben. De dosering werd zodanig gekozen dat er geen zuursecretieremming optreedt, maar wel cytoprotectie. Voor een redelijke beoordeling werd een minimum van 3 observatiedagen nodig geacht, terwijl de studie maximaal 7 dagen liep. Negentig patiënten met 2 of meer risicofactoren (grote operatie, multipele traumata, respiratoire insufficiëntie, nierinsufficiëntie, geelzucht, hypotensie, peritonitis, sepsis) werden gerandomiseerd voor behandeling met òf PGE_2 0,5 mg òf placebo, elke 4 uur intragastrisch toegediend. Bloedverlies in maagsap werd kwantitatief bepaald met de ^{51}Cr-methode. Voor deze methode werd gekozen omdat wij twijfels hadden over de betrouwbaarheid van de op peroxidasereactie gebaseerde teststrookjes. In voorgaand onderzoek over stress bloeding prophylaxe in ons ziekenhuis werd gezien dat de meeste patiënten <5 ml bloedverlies/24 uur hadden, en er was een andere groep die $\geqslant 15$ ml bloedverlies/24 uur vertoonde. Daarom werd $\geqslant 15$ ml bloedverlies/24 uur beschouwd als uiting van mucosale beschadiging en werd deze grens aangehouden voor de diagnose bloeding. Volledigheidshalve werd het maagsap ook onderzocht op bloed m.b.v. een op peroxidase-reactie gebaseerde teststrook, namelijk de ortho-toluïdinetest. Ook werd de pH van het maagsap gemeten en er werden monsters bewaard voor latere bepaling van het DNA-gehalte. Uiteindelijk waren 33 patiënten niet evalueerbaar. Vaak werden de eerste 3 dagen niet vol gemaakt door overplaatsing en door overlijden, of omdat de maagsonde werd verwijderd. Voeding per os werd niet aan de patiënt onthouden alleen terwille van de trial. Van de 57 evalueerbare patiënten kregen er 29 PGE_2 en 28 placebo. Bloeding trad op bij 9 van de PGE_2 groep (31%) en bij 13 van de placebogroep (46%). Dit verschil is statistisch niet significant.

In alle gevallen van bloeding waarbij gastroscopie en/of obductie werd verricht, werden ook laesies gevonden, meestal in de maag, maar

ook in slokdarm en maag. Dit geeft aan dat de ^{51}Cr-methode betrouwbaar is en geschikt voor het vaststellen van hoge tractus digestivusbloedingen. Tevens moet worden opgemerkt dat we niet zonder meer van stressbloeding kunnen spreken als er bloed in het maagsap wordt gevonden, daar er ook relatief vaak laesies in de slokdarm en het duodenum werden gevonden.

De patiënten met bloeding hadden gemiddeld meer risicofactoren dan de patiënten zonder bloeding, zodat aan het aantal risicofactoren een prognostische betekenis kan worden toegekend ten aanzien van een eventuele bloeding. Zoals kon worden verwacht, was het aantal risicofactoren ook gecorreleerd met de mortaliteit. Een bloeding was echter zelden een belangrijke factor bij het overlijden.

De vraag is waarom PGE_2 in deze dosering en op deze wijze toegediend niet preventief werkt met betrekking tot stress bloeding. De dosering moet voldoende zijn geweest, daar bij dergelijke doseringen de genezing van ulcera duodeni werd bespoedigd en bloedverlies bij aspirinegebruik werd voorkomen. Hogere doseringen zouden overigens leiden tot diarrhoe en buikkrampen. De toediening: oplossen van een ampul PGE_2 in 20 ml water en de maagslang naspoelen met 20 ml water, garandeert wel dat het middel in de maag komt. Echter, hoe lang het daar blijft en welk deel van de maag wordt bereikt is niet zonder meer te zeggen. Overwogen moet worden dat het voornamelijk het antrum en de achterzijde van de maag wordt bereikt, en mogelijk corpus en fundus in onvoldoende mate. Hoewel er geen statistisch significant verschil in bloedingsfrequentie werd gezien, was er toch wel een verschil. Theoretisch zou onderzoek van een groter aantal patienten wel een statistisch verschil ten gunste van PGE_2 op kunnen leveren. Voortzetting van de studie leek echter niet juist, daar we zoeken naar een effectief middel en omdat klinische relevantie belangrijker is dan statistische significantie.

In hoofdstuk 6 wordt de ortho-toluïdine test, die gebaseerd is op een peroxidasereactie, als ongeschikt voor de bepaling van bloed in maagsap beschreven. Op grond hiervan zijn de resultaten van de klinische onderzoekingen over stress bloeding prophylaxe, die gebaseerd waren op een peroxidase test, zeer twijfelachtig geworden.

In hoofdstuk 7 wordt een nieuwe bepaling van bloed in maagsap beschreven, die berust op bepaling van de haemconcentratie van het maagsap. Deze methode is, in tegenstelling tot de peroxidasetest, betrouwbaar en bovendien kwantitatief, en heeft niet de nadelen van de ^{51}Cr-methode. In toekomstige trials over stress bloeding kan de haembepaling goede diensten bewijzen.

Hoofdstuk 8 beschrijft de onderzoekingen betreffende DNA in maagsap. Uit de gevonden waarden kunnen geen conclusies worden getrokken met betrekking tot een effect van PGE_2 of de ernst van de fysiologische stress.

In hoofdstuk 9 wordt, aan de hand van literatuuronderzoek, de behandeling en vervolgens de preventie van stress bloeding beschreven.

Bij een eenmaal opgetreden bloeding zijn medicamenten van beperkte waarde. Wel is toediening van van antacida zinvol met het oog op de stolling en vasopressine is van nut indien het selectief intra-arterieel wordt toegediend. Het resultaat van transcatheterembolisatie dient te worden nagegaan, alvorens tot operatie wordt besloten, daar operatieve behandeling met een hoge mortaliteit gepaard gaat.

Daar de behandelingsresultaten van bloedende stress ulcera slecht zijn, is het rationeel te proberen ulcera te voorkomen. Van verschillende middelen is enig preventief effect aangetoond, zonder dat klinische toepassing volgde. Het is een intrigerend gegeven dat een krachtige maagzuursecretie bevorderende stof, het gastrine, stress ulcus bij de rat kan voorkomen. Ook histamine kan dit. In dit hoofdstuk worden de klinische studies over stress bloeding prophylaxe met behulp van antacida en cimetidine besproken. De zwakke punten daarin worden aangegeven: enerzijds de onbetrouwbare meting van bloed met op peroxidase reactie gebaseerde testmethoden en anderzijds de vaak onvoldoende verhoging van de pH van het maagsap bij gebruik van cimetidine.

Wellicht is pirenzepine geschikt voor stress ulcus prophylaxe, daar het iets doet aan de mucosale microcirculatie. Verdere klinische onderzoekingen met dit middel lijken aangewezen.

Wij weten niet welk middel zinvol is bij de preventie van stress ulcus. Wel zijn voor de preventie van Cushing's ulcer en Curling's ulcer zowel antacida als H_2-antagonisten effectief, en patiënten op een intensive care met een anamnese van ulcus pepticum zijn met deze middelen wellicht ook gebaat. Preventie van stress ulcus en stress bloeding bestaat voornamelijk uit actieve behandeling van risicofactoren, en het geven van optimale parenterale voeding. Enterale voeding dient gegeven te worden zodra maagontlediging niet langer nodig is.

Verantwoording

Het in dit proefschrift beschreven onderzoek werd verricht op de afdeling Inwendige Geneeskunde II van het Academisch Ziekenhuis Dijkzigt te Rotterdam. Velen hebben daaraan meegewerkt, ook die van andere afdelingen. M. van Blankenstein initieerde de PGE_2 trial. Hij en Prof. J.H.P. Wilson gaven mij steeds waardevolle adviezen. B. van den Berg van de afdeling Beademing had reeds dergelijk onderzoek over stress bloeding gedaan, zodat er een kader was waarin de nieuwe trial paste. De artsen en verpleegkundigen van de afdeling Beademing (3 Zuid I.C.; hoofd: Prof.dr. C. Hilvering) en van de chirurgische Intensive Care (10 Zuid I.C.; hoofd: Dr. H.A. Bruining) waren mij steeds behulpzaam. De verpleging diende nauwgezet de medicatie toe en heeft met veel geduld de talloze zakjes maagsap verzameld en bewaard.

Op de afdeling Nucleaire Geneeskunde (hoofd: Drs. W.H. Bakker) werd ik ingevoerd in de techniek van het labelen van erythrocyten. Agnes de Lange-Macdaniël bood mij vaak de helpende hand.

P.J.M. Schmitz gaf advies voor statistische beoordeling.

Het Centraal Klinisch Chemisch Laboratorium (hoofd: Dr. B.G. Blijenberg) was bereid de zoutzuurbepaling van de vele maagsapmonsters uit te voeren. De analisten, onder wie G.C. Verheij, wisten in korte tijd de uitslagen te leveren.

Op het Laboratorium Interne II was ik te gast voor specieel onderzoek van maagsap. De biochemici Dr. W.H.O. van den Berg en Dr. F.W.M. de Rooij hebben mij op prettige wijze begeleid. Datzelfde geldt voor de analisten, die ook een deel van het werk deden; van hen wil ik Rita Koole-Lesuis en Trinet Rietveld met name noemen.

Nienke Essed, patholoog-anatome, verstrekte mij fotomateriaal.

De patienten en hun familie, die toestemming gaven voor het klinisch onderzoek, ben ik erkentelijk.

De firma Upjohn (Kalamazoo) leverde de ampullen met prostaglandine en placebo voor dit onderzoek.

Ellis van der Waarde-Masthoff wil ik bijzonder danken voor het accuraat uittypen op de tekstverwerker van mijn manuscripten.

Mijn promotor, Prof. J.H.P. Wilson, heeft mij op zeer prettige wijze begeleid en talrijke praktische tips gegeven.

Tenslotte vooral dank aan mijn vrouw Marjolein, die ondanks de zorg voor jonge kinderen, een sfeer verschafte die het mogelijk maakte dit proefschrift tot stand te brengen.

Curriculum vitae.

De schrijver van dit proefschrift werd op 2 oktober 1948 te Barneveld geboren. Na het behalen van het diploma HBS-B aan het Christelijk Streeklyceum te Ede in 1968, studeerde hij farmacie aan de Rijksuniversiteit te Utrecht, waar hij in 1971 slaagde voor het kandidaatsexamen. Daarna werd de studie geneeskunde aangevangen, ook te Utrecht. Het doctoraal diploma werd in 1976 uitgereikt met de toevoeging "met genoegen". Op 23 maart 1977 werd het artsexamen afgelegd. Op 1 mei 1977 begon hij aan de opleiding tot internist in het Havenziekenhuis te Rotterdam (opleider: Dr. P.C. Stuiver), die in 1979 werd voortgezet in het Gemeenteziekenhuis te Dordrecht (opleider: Dr. B.A. de Planque). In het kader van het vrije jaar van de opleiding, ging hij in 1981 naar het Academisch Ziekenhuis Dijkzigt te Rotterdam, afdeling Inwendige Geneeskunde II (hoofd: Prof.dr. M. Frenkel), teneinde het in dit proefschrift beschreven onderzoek te verrichten en zich te bekwamen in de gastro-enterologie. Op 1 mei 1982 werd hij in het specialistenregister ingeschreven. Het klinisch onderzoek werd in september 1983 afgesloten. Daarna volgde een waarneming in de Stichting Oosterschelde Ziekenhuizen te Goes. Sinds 1 juli 1984 is hij werkzaam als internist, in het bijzonder voor de gastro-enterologie, in het St. Clara Ziekenhuis te Rotterdam.